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The Study of Correlation between Diurnal Blood Pressure with Nocturnal Oxygen Desaturation and Nitrite Production in Subjects with Obstructive Sleep Apnea (OSA)

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Abstract

Background: Endothelial dysfunction is often present in subjects with obstructive sleep apnea (OSA) on walking up. Although the intermittent hypoxia has been suggested as a main cause of endothelial dysfunction in these subjects, the precise mechanism of this event is still unclear. The aim of this study was to demonstrate the correlation between the level of hypoxia during sleep with arterial blood pressure and plasma concentration of nitrite.

Methods: Non-smoker subjects were included in a cross-sectional study. They underwent systolic and diastolic blood pressure (SBP and DBP) measured at bed before sleep and on walking up, overnight polysomnography (PSG), and measurement of nitrite in plasma from peripheral blood at walking up.

Results: Sixty-five subjects with mean age of 58 ± 12 years were included in this study. The male-female ratio was 0.9 and BMI was 23.3 ± 3.4 kg/m^2. The mean of systolic BP and diastolic BP post-PSG of subjects with SpO_2<93% was significantly higher than subjects with SpO_2 ≥ 93% (P<0.05 and P<0.01; respectively). The mean SpO_2 and nadir SpO_2 of subjects with SpO_2<93% were significantly lower than subjects with SpO_2 ≥ 93% (90 ± 4% vs. 94 ± 2% and 73 ± 9% vs. 88 ± 8%; P<0.05 and P<0.01; respectively). The level of apnea-hypopnea index in subjects with SpO_2<93% was significantly higher than that in subjects with SpO_2 ≥ 93% (P<0.01). The concentration of NO_2- in peripheral blood of subjects with SpO_2<93% was significantly lower than that in subjects with SpO_2 ≥ 93% (P<0.01). There were the significant correlations between nadir SpO_2 and NO_2- with SBP and DBP on walking up.

Conclusion: Endothelial dysfunction is a crucial event in subjects with OSA, especially for whom with obstructive sleep apnea. This event might be linked to the diurnal increase of peripheral blood pressure. The concentration of NO_2- in plasma measuring on walking up might be a relevant marker of endothelial dysfunction during sleep.

Keywords: Endothelial dysfunction; Blood pressure; Apnea-hypopnea index; OSA; NO_2-; Nadir SpO_2

Introduction

The endothelium has an important role in the modulation of vasodilation-vasoconstriction balance. In human, the intact of endothelium guarantees the quality of the macro-circulation and micro-circulation. The endothelium is known as a secreting organ by producing abundant mediators to control homeostasis, inflammation, cell proliferation, and vascular tonus. Endothelium has an essential role in the regulation of vascular tone, blood viscosity, anticoagulant function, angiogenesis, and local or systemic circulation pressure. The normal endothelial function is a key player in the maintenance of vascular health. In human, endothelium forms the inner lining of blood vessels and serves as a physical barrier [1].

Currently, endothelial dysfunction is defined as an imbalance between vasorelaxation (mediated mainly by nitric oxide pathway) and vasoconstriction (induced by endothelin-1 and its receptors), between anti-coagulant and pro-coagulant substances, or between growth-inhibiting and growth–promoting mediators [2]. It has been demonstrated that endothelial dysfunction is one of the earliest manifestations of vascular disease and atherosclerosis [3]. The last one is a potential risk factor for high blood pressure in adult. However, endothelial dysfunction is also associated with different forms of vascular diseases, such as systemic or regional arterial hypertension [2,4] and coronary arterial or peripheral vascular diseases [5-8]. Inversely, there are several pathological circumstances that might induce endothelial dysfunction. These include cigarette smoking, hypertension, chronic heart or kidney failure, diabetes, and severe infection [9-16]. The mechanism for which each pathological condition induces endothelial dysfunction has been described by previous studies [17]. In addition, an increasing body of evidence suggests that oxidative stress is involved significantly in the pathogenesis of endothelial dysfunction [18-20].

In subjects with nocturnal hypoventilation or obstructive sleep apnea (OSA), it has been suggested that endothelial dysfunction is usually present during sleep and on walking up. The intermittent hypoxia during sleep, due to sleep disorders, has been suggested as a major cause of endothelial dysfunction. Previous studies showed

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that intermittent hypoxia during sleep might increase the production of reactive oxygen species (ROS) and proinflammatory mediators, leading to endothelial dysfunction and cardiovascular diseases. The aim of this study was to demonstrate the correlation between the level of hypoxia during sleep with endothelial dysfunction, evaluated by brachial arterial blood pressure, and the concentration of nitrite (end product of nitric oxide) in peripheral blood in adult.

Materials and Methods

Study subjects

Non-smoker subjects, who came to the Clinical Research Center of Lam Dong Medical College for screening of obstructive sleep apnea (OSA), were included in this cross-sectional study after signing an Institutional Review Board-approved consent form. Subjects with acute or chronic cardiovascular diseases (acute myocardial infarction, severe coronary disease, chronic heart failure, or high blood pressure), acute or chronic respiratory disease (exacerbation of COPD or asthma crisis), or with other chronic diseases (chronic kidney failure, diabetes, systemic immunological disorders) were excluded in the present study.

All study subjects were examined for health status and completed the screening questionnaire of sleep quality and events. They underwent blood pressure measured at bed before sleep and on walking up, overnight polysomnography (PSG), and measurement of nitrite in plasma from peripheral blood at walking up.

Methods

Measuring intermittent hypoxia (IH) by polysomnography (PSG): In-laboratory overnight PSG was performed for each study subject using Alice PSG (Philips, USA) as recommended by American Academy of Sleep Medicine [21]. The recording time was from 10 pm to 6 am of the day after. The recorded parameters were electroencephalography (EEG); chin electromyography (EMG); electrocardiography (ECG); air flows; thorax-abdomen movements; sleeping posture; apnea-hypopnea index (times/minutes); type of apnea (central apnea, obstructive apnea, or mixed apnea); mean oxygen saturation (SpO_2), mean SpO_2 with desaturation, and minimum SpO_2 (nadir SpO_2). Subjects with OSA were defined by apnea-hyponea index (AHI) ≥ 5/hour and classified as mild (AHI=5-15), moderate (AHI=16-30), and severe (AHI>30) OSA.

Measuring blood pressure pre- and post-polysomnography by sphygmanometer: The blood pressure (BP) measured before sleep and on walking up was realized in all study subjects with the standard procedure recommended by American Heart Association (AHA) [22]. BP was measured by mercury sphygmanometer with the auscultatory (Korotkoff's sound) technique as described by the following method: patient seated comfortably with back supported, legs uncrossed, and upper arm bared; patient's arm was supported at heart level with cuff bladder encircled 80 percent or more of the circumference; cuff bladder was deflated at 2 to 3 mm per second; first and last audible sounds were recorded as systolic and diastolic pressure, respectively; measurements was given to the nearest 2 mm Hg; neither the study subject nor the person taking the measurement could talk during the procedure.

Measuring nitrite (NO_2-) concentration in peripheral blood: Nitrite (NO_2-) is a stable and end product of nitric oxide (NO). The concentration of NO_2- was used to quantify NO production in all study subjects by using Nitric Oxide Measurement System (Lazar Research Laboratories; Inc. Arrowstraight; CA, USA). This system used the micro ion selective electrodes to measure NO_2- in conjunction with an Ion Analyzer Program.

Sample preparation: Peripheral blood of study subjects was collected on walking up, centrifuged, filtered, and analyzed after ultrafiltration.

Electrode preparation: Before using, grasped the black outer body with one hand and unscrewed the cap at the top of the electrode with the other hand; removed the inner pH glass electrode from the outer body; rinsed the glass electrode with deionized water to remove any KCl crystals. Filled the outer body with 2 mL of Electrode Filling Solution using the plastic syringe; inserted the inner glass electrode back into the outer black body, and screwed on the large cap until finger tight. Connected the electrode to Model 6230N ion analyzer with the BNC connector cable on NO_2- electrode.

Setting up NO_2- flow through cell assembly: NO_2- electrode was rinsed with deionized water and carefully insert into acrylic flow cell; adjusted electrode height about 1 mm or less above cell cavity bottom; tightened locknut to secure NO_2- electrode inside flow cell. Micro bore tubing was connected from injection port on front panel of Arrow Straight Instrument input port of NO_2- flow cell assembly by using plastic fittings; micro bore tubing was connected from NO_2- flow cell output port to micro bore tubing into waste bottle. Then, filled syringe with deionized water and insert into NO_2- injection port; injected at least 30 mL of deionized water into NO_2- flow cell assembly while holding the flow cell assembly in vertical position with input port at the bottom and output port at the top.

Measuring NO_2- concentration of samples: Injected 90 microliters of study sample into clean 96 well plate by using a micro syringe; added 10 microliters of nitrogen oxide buffer solution and stirred briefly; taken micro syringe and drew up standard and carefully injected into the NO_2- injection port so that solution flowed through the flow cell completely displacing the deionized water which was in the flow cell previously. Checked the radio button next to measure NO_2- for reading NO_2- concentration. When electrode reading stabilized the concentration value of NO_2- in micro molar units will appear in the current reading window. All the concentration value was recorded for statistical analyses.

Statistical analysis

Data were analyzed using IBM SPSS 22.0 software (Chicago, Illinois, USA). Values were expressed as mean ± standard deviation and percentage for qualitative variables. Normal distribution was tested by using the Skewness-Kurtosis test. Comparison between the subjects with SpO_2 <93% and ≥ 93% was done by using Student's t-test. The regression analysis was used to measure the correlation between continuous variables, with the correlation coefficient R of Pearson for normal distribution variables and of Spearman for non-normal distribution variables.

Results

Anthropometric characteristics

From January to April 2017, 65 subjects were included in the present study. The mean age was 58 ± 12 years (44-89 years; Table 1). The male-female ratio was 0.9. The mean BMI of study subjects was 23.3 ± 3.4 kg/m^2 (13.9-31.1 kg/m^2; Table 1). The mean neck and abdomen circumstances of study subjects were 38 ± 3 cm (28-40 cm) and 89 ± 17 cm (59-130 cm), respectively (Table 1).

Parameters	Study subjects (N=65)	
	Mean ± SD	Min-Max
Age, *years*	58 ± 12	44-89
Male/Female, *ratio*	0.9	-
Height, *cm*	160 ± 7	150-170
Weight, *kg*	60 ± 10	30-75
BMI, *kg/m²*	23.3 ± 3.4	13.9-31.1
Neck circumstance, *cm*	38 ± 3	28-40
Abdomen circumstance, *cm*	89 ± 17	59-130

BMI: body mass index.

Table 1: Anthropometric characteristics of study subjects.

Parameters	Study subjects (n=65)	
	Mean ± SD	Min-Max
Blood pressure		
Pre-PSG		
Systolic-Blood pressure, *mmHg*	132 ± 8	100-140
Diastolic-Blood pressure, *mmHg*	81 ± 9	70-90
Post-PSG		
Systolic-Blood pressure, *mmHg*	139 ± 15	100-150
Diastolic-Blood pressure, *mmHg*	84 ± 12	60-110
Heart rate		
Pre-PSG		
Mean heart rate, *beats/min*	77 ± 14	55-94
During PSG		
Mean heart rate, *beats/min*	72 ± 16	52-106
Mean minimum heart rate, *beats/min*	68 ± 19	52-78
Mean maximum heart rate, *beats/min*	107 ± 29	70-169
SpO_2		
Pre-PSG		
Mean SpO_2, *%*	95 ± 3	92-98
During PSG		
Mean SpO_2, *%*	91 ± 3	86-94
Mean SpO_2 <93%	84 ± 8	68-94
Nadir SpO_2, *%*	81 ± 8	64-93
AHI, *times/hour*	13 ± 11	1-33
NO_2-, *µmol/L*	42.6 ± 5.7	25.2-48.4

PSG: Polysomnography; AHI: Apnea-Hypopnea Index.

Table 2: Hemodynamic and PSG characteristic and NO_2- concentration of study subjects.

Hemodynamic and PSG characteristic and NO_2- concentration of study subjects

The result of present study showed that the levels of mean blood pressure (BP) pre- and post-polysomnography (PSG) were in the normal limitation (132 ± 8 mmHg/81 ± 9 mmHg and 139 ± 15 mmHg/84 ± 12 mmHg; respectively; Table 2). The mean heart rate pre-PSG was 77 ± 14 beats/min (55-94 beats/min; Table 2). The mean hear rate during PSG was 72 ± 16 beats/min with the mean minimum and maximum heart rates were 68 ± 19 (52-78) beats/min and 107 ± 29 (70-169) beats/min (Table 2).

The mean SpO_2 pre-PSG was 95 ± 3% (92-98%). The mean SpO_2 , mean SpO_2 <93%, and nadir SpO_2 during sleep were 91 ± 3%, 84 ± 8%, and 81 ± 8%; respectively (Table 2). The mean apnea-hypopnea index was 13 ± 11 times/hour (non-OSA: 7.7%, mild OSA: 38.4%, moderate OSA: 35.4%, and severe OSA: 18.5%). The concentration of NO2- was 42.6 ± 5.7 (25.2-48.4) µmol/L.

Hemodynamic and PSG characteristic and NO2- concentration of subjects with oxygen desaturation during sleep (SpO_2 <93%)

The levels of mean systolic BP (SBP) and diastolic BP (DBP) pre- and post-PSG of subjects with SpO_2 <93% were 134 ± 5 (100-140) mmHg/84 ± 6 (70-90) mmHg and 145 ± 6 (100-150) mmHg/95 ± 10 (80-110) mmHg; respectively (Table 3). The mean heart rate pre-PSG of these subjects was 83 ± 12 beats/min (62-94 beats/min; Table 3). The mean hear rate during PSG was 78 ± 18 beats/min with the mean minimum and maximum heart rates were 72 ± 11 (54-86) beats/min and 118 ± 24 (88-169) beats/min (Table 3).

The mean SpO2 pre-PSG was 95 ± 4% (91-98%). The mean SpO_2 , mean SpO2 <93%, and nadir SpO_2 during sleep were 90 ± 4%, 82 ± 9%, and 72 ± 9%; respectively. The mean apnea-hypopnea index was 19 ± 14 times/hour. The concentration of NO_2- was 36.8 ± 4.3 (25.2-44.1) µmol/L (Table 3).

Comparison of hemodynamic and PSG characteristic and NO_2- concentration of study subjects classified by SpO_2

The level of mean BP pre-PSG of subjects with SpO_2 ≥ 93% and SpO_2 <93% was not significantly different between two groups (128 ± 12 mmHg/79 ± 8 mmHg *vs.* 134 ± 5 mmHg/84 ± 6 mmHg; P>0.05; Table 4). The mean of SBP and DBP post-PSG of subjects with SpO2 <93% was significantly higher than that in subjects with SpO_2 ≥ 93% (145 ± 6 mmHg/95 ± 10 mmHg *vs.* 135 ± 12 mmHg/82 ± 15 mmHg; P<0.05 and P<0.01; respectively; Table 4).

There were no significant differences of heart rate pre-PSG and during-PSG of between study subjects with SpO_2 ≥ 93% and SpO_2 <93% (P>0.05; Table 4). There was no significant difference of SpO_2 pre-PSG between these two groups (P>0.05; Table 4). The levels of mean SpO_2

Parameters	Subjects with SpO_2<93% during PSG (N=32)	
	Mean ± SD	Min-Max
Blood pressure		
Pre-PSG		
Systolic-Blood pressure, *mmHg*	134 ± 5	100-140
Diastolic-Blood pressure, *mmHg*	84 ± 6	70-90
Post-PSG		
Systolic-Blood pressure, *mmHg*	145 ± 6	100-150
Diastolic-Blood pressure, *mmHg*	95 ± 10	80-110
Heart rate		
Pre-PSG		
Mean heart rate, *beats/min*	83 ± 12	62-94
During PSG		
Mean heart rate, *beats/min*	78 ± 18	52-106
Mean minimum heart rate, *beats/min*	72 ± 11	54-86
Mean maximum heart rate, *beats/min*	118 ± 24	88-169
SpO_2		
Pre-PSG		
Mean SpO_2, *%*	95 ± 4	91-98
During PSG		
Mean SpO_2, *%*	90 ± 4	85-93
Mean SpO_2 <93%	82 ± 9	68-91
Nadir SpO_2, *%*	72 ± 9	64-89
AHI, *times/hour*	19 ± 14	6-33
NO_2-, *µmol/L*	36.8 ± 4.3	25.2-44.1

Table 3: Hemodynamic and PSG characteristic and NO_2- concentration of subjects with SpO_2<93%.

and nadir SpO_2 of subjects with SpO_2 <93% were significantly lower than that in subjects with SpO_2 ≥ 93% (90 ± 4% *vs.* 94 ± 2% and 73 ± 9% *vs.* 88 ± 8%; P<0.05 and P<0.01; respectively; Table 4). The level of AHI in subjects with SpO_2 <93% was significantly higher than that in subjects with SpO_2 ≥ 93% (19 ± 14 *vs.* 8 ± 5 times/hour; P<0.01; Table 4).

Parameters	SpO_2 during PSG ≥ 93%	SpO_2 during-PSG<93%	P
	N=33	N=32	
Blood pressure			
Pre-PSG			
SBP, *mmHg*	128 ± 12	134 ± 5	NS
DBP, *mmHg*	79 ± 8	84 ± 6	NS
Post-PSG			
SBP, *mmHg*	135 ± 12	145 ± 6	<0.05
DBP, *mmHg*	82 ± 15	95 ± 10	<0.01
Heart rate			
Pre-PSG			
HR, *beats/min*	77 ± 13	83 ± 12	NS
During PSG			
HR, *beats/min*	74 ± 14	78 ± 18	NS
Min HR, *beats/min*	66 ± 16	72 ± 11	NS
Max HR, *beats/min*	104 ± 29	118 ± 24	NS
SpO_2			
Pre-PSG			
SpO_2, *%*	95 ± 3	95 ± 4	NS
During PSG			
SpO_2, *%*	94 ± 2	90 ± 4	<0.05
Nadir SpO_2, %	88 ± 8	72 ± 9	<0.01
AHI, *times/hour*	8 ± 5	19 ± 14	<0.01
NO_2-, *µmol/L*	42.3 ± 4.5	31.6 ± 3.7	<0.01

Table 4: Hemodynamic and PSG characteristic and NO_2- concentration of study subjects classified by SpO_2.

The concentration of NO_2- in peripheral blood of subjects with SpO_2 <93% was significantly lower than that in subjects with SpO_2 ≥ 93% (31.6 ± 3.7 µmol/L *vs.* 42.3 ± 4.5 µmol/L; Table 4).

Correlation between blood pressure (BP) and other parameters of study subjects

There were no significant correlations between SpO_2 during-PSG and apnea-hypopnea index (AHI) with systolic blood pressure (SBP) and diastolic blood pressure (DBP) on walking up in study subjects (R=0.125, P=0.245; R=0.098, P=0.013; R=0.087, P=0.075; R=0.092, P=0.058; respectively).

There were the significant negative correlations between nadir SpO_2 during sleep, SBP and DBP on walking up (R=-0.642, P=0.0004 and R=-0.576, P=0.0052; respectively; Figure 1). The concentration of NO_2- in peripheral blood was significantly correlated with SBP and DBP of study subjects (R=-0.723, P=0.0054 and R=-0.795, P=0.0006; respectively; Figure 1).

Discussion

The result of present study showed that all study subjects had normal hemodynamic parameters evaluated by blood pressure and heart rate at pre-, during, and post-polysomnography (PSG) or on walking up (Table 2). In comparison with oxygen saturation (SpO_2) pre-PSG, the study subjects had a slight desaturation during sleep. It might be due to the hypoventilation during sleep in these subjects. Moreover, the study subjects also had a mild obstructive sleep apnea (OSA) defined by apnea-hypopnea index less than 15 times/hour [21]. Our studies also showed that oxygen desaturation was usually associated with OSA and due to the intermittent hypoxia during apnea episodes, especially in subjects with high blood pressure [22,23].

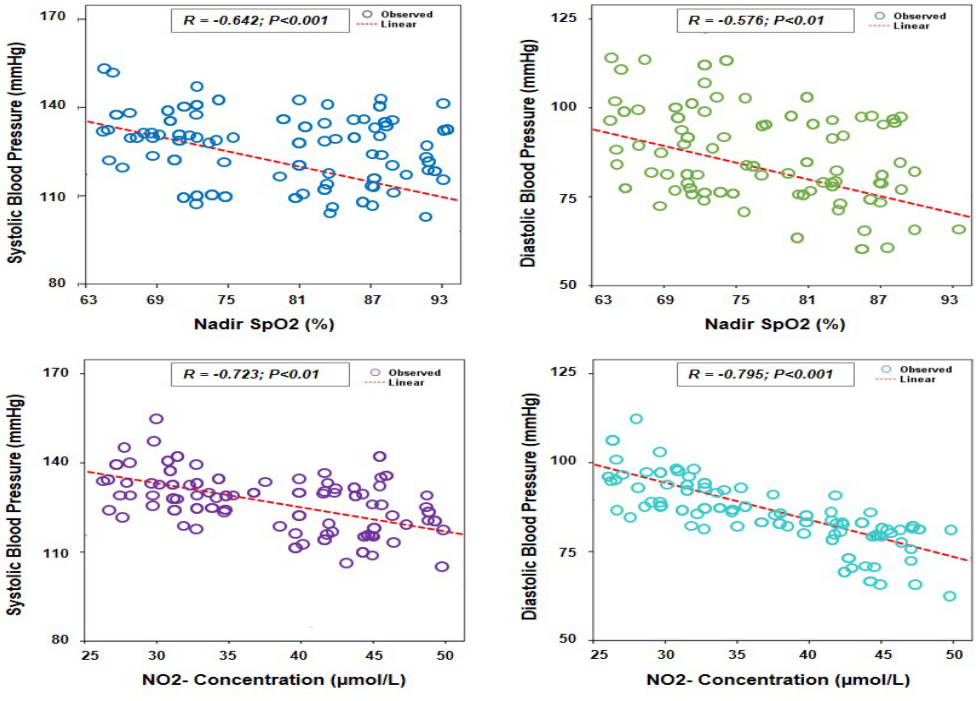

Figure 1: Correlation between Nadir SpO_2 and NO_2- concentration with blood pressure.

However, in the present study, the analysis of sub-groups with cut-off point of SpO_2 at 93% during sleep found out the BP on walking up of subjects with SpO_2 <93% was significantly higher than that in subjects with SpO_2 ≥ 93% (Table 4). Moreover, subjects with SpO_2 <93% had the AHI significantly higher than who with SpO_2 ≥ 93%. Interestingly, the nadir SpO_2 in subjects with mean SpO2 <93% at night was also significantly lower than subjects with SpO_2 ≥ 93%. Take it together, this result suggests that the significant increase of blood pressure might be due the OSA-induced hypoxia. In addition, there were the significant correlations between nadir SpO_2 during-PSG in study subjects with systolic and diastolic blood pressure (Figure 1).

Although the increase of blood pressure on walking up in subjects with OSA has been demonstrated previously [24,25]. However, the exact mechanism by which the vascular tonus has been increased, marked by high blood pressure, in subjects with OSA-induced intermittent hypoxia is not clearly understood. It has been suggested that the increased blood pressure on walking up might be related to disturbance of sympathetic and para-sympathetic nervous system with predominance of vasoconstriction [26,27]. The result of the present study revealed the NO_2- concentration in peripheral blood in subjects with oxygen desaturation (SpO_2 <93%) was significantly lower than that in subjects without oxygen desaturation (Table 4). Especially, the present study also showed that there were the significant and negative correlations between NO_2- concentration with systolic and diastolic blood pressure (Figure 1). We suggest that OSA-induced intermittent hypoxia might be a cause of endothelial dysfunction and by which, the production of nitric oxide (NO) from endothelial cells might be decreased. That could be the cause of increased peripheral blood pressure due to the impairment of NO-induced vasodilatation activity. However, with a small number of study subjects and descriptive study, we could not explain the exact mechanism that links between the impairment of NO production, detected by a low concentration of NO_2- in plasma, and oxygen desaturation. Our on-going study with the measurement of plasma steady state concentration of both NO_2- and NO_3- (nitrate), on walking up in subjects with OSA will clarify more clearly the role of nitric oxide end product (NOx) in endothelial dysfunction.

Conclusion

Endothelial dysfunction is an important nocturnal event in subjects with oxygen desaturation induced by obstructive sleep apnea. This phenomenon may be a main cause of diurnal increased blood pressure. The measurement of plasma end product of nitric oxide on walking up is a relevant method to evaluate endothelial dysfunction during sleep.

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Disclosure

The authors report no conflicts of interest in this work.

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