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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

The effects of arousal accompanying an apneic event on blood pressure and sympathetic nerve activity in severe obstructive sleep apnea

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Abstract
Purpose Arousal plays an important protective role against life-threatening events by terminating the apneic events. However, arousal might also be considered as a contributor to obstructive sleep apnea (OSA) pathogenesis since ventilatory overshoot due to arousal leads to irregular breathing. Patients with OSA who have greater upper airway compensation, expressed by relatively high proportion of apneic events without arousal, could have less adverse events or consequences. Thus, our hypothesis was that the proportion of apneic events with or without arousal affects daytime systemic blood pressure and nocturnal sympathetic activity.
Methods Subjects were consecutive 97 patients who had diagnostic polysomnography (PSG) and showed severe OSA (apnea-hypopnea index ≥ 30). The proportion of apnea-hypopneas with arousal among all apnea-hypopneas was calculated in each patient. Then, the association among the proportion of arousal accompanying apnea-hypopneas and a diagnosis of hypertension or heart rate variability during the PSG were investigated.
Results The proportion of apnea-hypopneas with arousal among all apnea-hypopneas was higher in hypertensive patients ($n = 47$) than that in normotensive patients ($n = 50$) (mean ± standard deviation; 80.0 ± 12.8% vs. 73.7 ± 13.0%, $p < 0.01$). However, heart rate variability was not associated with the proportion of apnea-hypopneas with arousal.
Conclusions Apnea-hypopneas terminated by arousal are more often present in those with current systemic hypertension but independent of sympathetic nerve activity, compared with those whose apnea-hypopnea events do not have as many arousals. One could target an elevation in arousal threshold as a pathway for reducing daytime blood pressure.

Keywords Obstructive sleep apnea · Arousal · Hypertension · Sympathetic nerve activity · Heart rate variability

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Abbreviations

OSA	Obstructive sleep apnea
PSG	Polysomnography
AHI	Apnea-hypopnea index
RIP	Respiratory inductance plethysmography
ODI3	3% oxygen desaturation index
SD	Standard deviation
BMI	Body mass index

ESS Epworth Sleepiness Score
MSNA Muscle sympathetic nerve activity

Introduction

The clinical outcomes of obstructive sleep apnea (OSA)-hypopnea are attributed to repeated oxygen desaturations and arousals during sleep which in turn lead to cardiovascular diseases, metabolic dysfunction, and cognitive dysfunction. Both oxygen desaturation and cortical arousal are included in the current scoring manual for the definition of hypopnea [1], thus, either desaturation or cortical arousal must be needed to score hypopnea. However, respiratory events terminated without cortical arousal can be seen in the polysomnography (PSG).

Arousal may play an important protective role by terminating apneic events. However, arousal causes ventilatory overshoot and could contribute to irregular breathing and an increasing apnea-hypopnea index (AHI) [2, 3]. In the case of apneic events without arousal, upper airway muscle compensation against the airway narrowing may be enough to restore breathing by itself before arousal occurs [4, 5]. Patients with OSA who have greater upper airway compensation, expressed by relatively high proportion of apneic events without arousal, may present less adverse events or consequences, since there would be less autonomic change such as heart rate increase and ventilatory overshoot caused by cortical arousal.

Accordingly, the current study aimed to determine whether the proportion of apneic events with or without arousal equally contributes to daytime systemic blood pressure and nocturnal sympathetic nerve activity assessed by the ratio of low-frequency and high-frequency domains over the whole sleep study.

Materials and methods

Subjects Ninety-seven consecutive patients who had diagnostic PSG and AHI ≥ 30 in the Center for Sleep Disorders, Tenri City Hospital were enrolled for analysis. At the first visit to our sleep clinic, anthropometric evaluation were performed on all patients including sitting blood pressure measurement by a physician using either a standard mercury sphygmomanometer or a calibrated and validated automated sphygmomanometer after 5 min of seated rest, and medical history was also asked such as hypertension. Blood pressure values were obtained by a single measurement. All patients had agreed that clinical data could be used for research and had completed a written informed consent. The Ethical Advisory Committee at Nara Medical University approved the study (No. 01519).

Diagnostic sleep study Data acquisition started from 9:00 PM and continued until 6:00 AM on the following morning. PSG was performed using a polygraph system (EEG7414; Nihon Kohden, Japan). EEG (C3-A2, C4-A1, O1-A2, O2-A1), bilateral EOG, submental EMG, ECG, and bilateral anterior tibial EMG were recorded. Airflow was monitored using an oronasal thermal sensor and/or nasal air pressure transducer. Thoracic and abdominal respiratory movements were monitored using RIP (Respitrace; Ambulatory Monitoring Inc., USA). Oxyhemoglobin saturation and pulse rate were monitored using pulse oximetry with a finger probe (OLV-3100; Nihon Kohden, Japan). All the signals were digitized and stored on a personal computer (PC). Diagnostic PSG was scored according to the rules of the *AASM manual for the scoring of sleep and associated events* Ver. 2.3 [1].

Scoring procedure of respiratory events with or without arousal During reviewing the diagnostic PSG, every apnea-hypopnea already scored was checked again whether accompanied with arousal or not, then the proportion of apnea-hypopnea events with arousal among all apnea-hypopnea events was calculated in each patient. The investigator was a registered polysomnographic technologist (RPSGT) blinded to blood pressure information. Figure 1 showed typical examples of apnea-hypopneas with or without arousal. Arousal scoring was performed according to *AASM manual for the scoring of sleep and associated events* Ver. 2.3 [1].

The evaluation of sympathetic nerve activity Using the ECG data (sampling rate was 200 Hz) for the total recording time of diagnostic PSG, heart rate variability analysis was performed with the software MemCalc/Chiram 3 (GMS Co., Ltd., Tokyo, Japan). Then, sympathetic nerve activation was estimated by low-frequency (0–0.05 Hz) power divided by high-frequency (0.20–0.35 Hz) power (LF/HF ratio) over the whole sleep study.

Statistical analysis The percentage of apnea-hypopnea events with arousal was compared between hypertensive and normotensive patients with the Mann-Whitney *U* test. Hypertensive patients were defined as those receiving anti-hypertensive agents or showing systolic or diastolic blood pressures ≥140 or 90 mmHg according to the guideline for the management of hypertension 2014 of the Japanese Society of Hypertension (JSH2014) and JNC7 [6]. Correlations between the percentage of apnea-hypopnea events with arousal and systolic and diastolic blood pressures, 3% oxygen desaturation index (ODI3), and LF/HF ratio were analyzed with Spearman's rank correlation. Anti-hypertensive agents decrease blood pressure, thus, the analyses of correlations between the percentage of apnea-hypopnea events with arousal and blood pressure values were performed with medication-free patients (n = 75). As arousal threshold varies with aging, statistical assessments were performed both in all patients (n = 97) and patients less than 65 years old (n = 80). Lastly, to determine whether the percentage of apnea-hypopnea events with arousal was independently

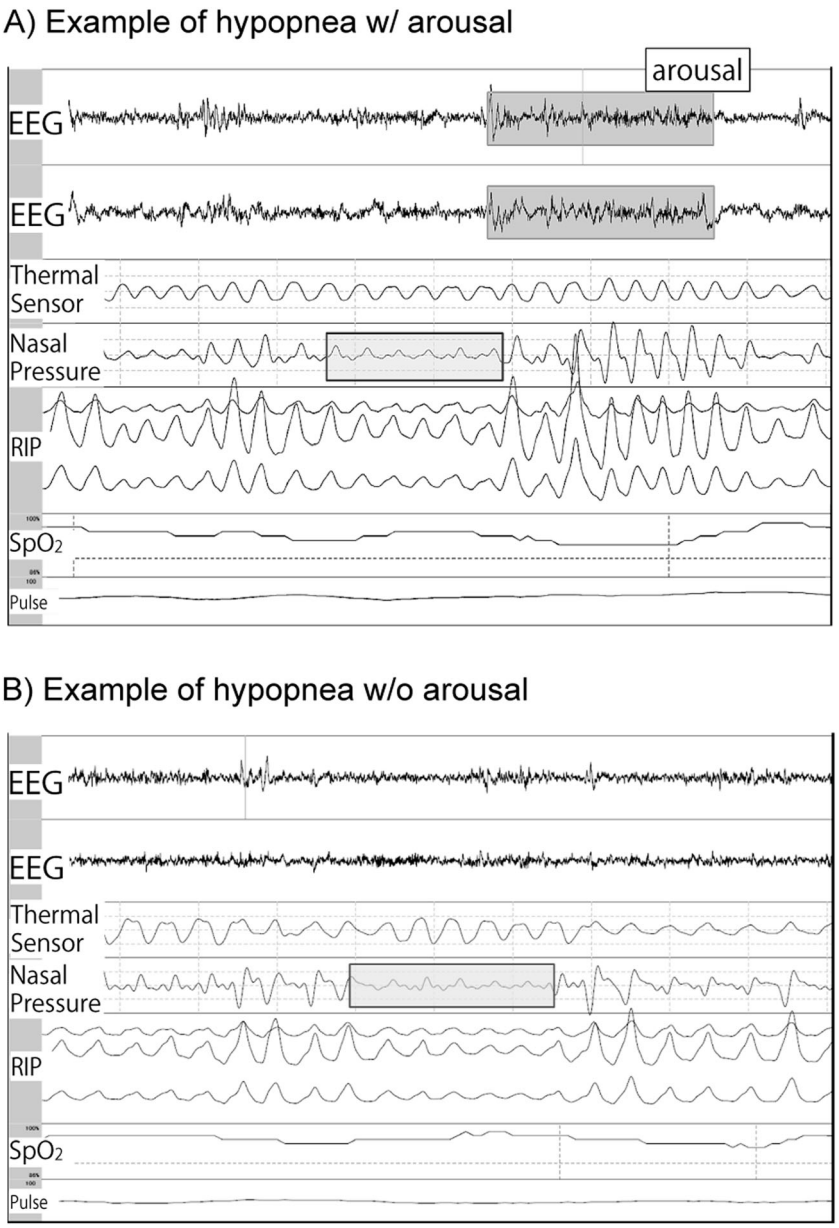

Fig. 1 Typical examples of hypopnea with (**a**) or without (**b**) arousal

associated with comorbidity of hypertension, logistic regression analyses were performed with comorbidity of hypertension as the dependent variable and with the percentage of apnea-hypopnea events with arousal and ODI3 as independent variables. Data are presented as mean ± standard deviation (SD). Statistical analysis was done with SPSS version 21.0 for Windows software (SPSS, Chicago, IL).

Results

Patient characteristics

As shown in Table 1, among 97 enrolled patients, 85 patients were male and the rest 12 patients were female. Age, body mass index (BMI), Epworth Sleepiness Score (ESS), AHI, ODI3, time spent with $SpO_2 < 90\%$, and respiratory arousal index were 51.3 ± 12.5 years old, 28.4 ± 5.6 kg/m^2, 10.0 ± 4.9, 53.6 ± 19.6/h, 38.3 ± 17.7/h, 10.8 ± 14.2%, and 41.5 ± 18.0/h, respectively. Forty-seven (48.5%) had a diagnosis of systemic hypertension.

The associations between the percentage of apnea-hypopnea events with arousal and daytime clinic blood pressure

Mean percentage of apnea-hypopnea events with arousal among all apnea-hypopnea events was 76.8 ± 13.2%. In patients with hypertension, the percentage of apnea-hypopnea events with arousal was significantly higher than that in normotensive

Table 1 Patient characteristics

n (male, female)	97 (male 85, female 12)
Age (years)	51.3 ± 12.5
BMI (kg/m^2)	28.4 ± 5.6
ESS	10.0 ± 4.9
AHI (/h)	53.6 ± 19.6
ODI3 (/h)	38.3 ± 17.7
Time spent with SpO_2 < 90% (%)	10.8 ± 14.2
Respiratory arousal index (/h)	41.5 ± 18.0

Data are presented as mean ± SD

BMI body mass index, *ESS* Epworth Sleepiness Scale, *AHI* apnea-hypopnea index, *ODI3* 3% oxygen desaturation index

patients in the analyses with whole patients and with patients less than 65 years old (80.0 ± 12.8 vs. 73.7 ± 13.0, p = 0.01, 80.8 ± 11.7% vs. 71.8 ± 12.5%, p < 0.01, respectively; Table 2). Although ODI3 was higher in patients with hypertension than that in normotensive patients in both groups, they were not statistically significant (Table 2). The percentage of apnea-hypopnea events with arousal was not correlated with ODI3 ($r = -0.015$, $p = 0.881$; data are not shown). Then, we performed logistic regression analyses to test whether the comorbid hypertension was independently associated with the percentage of apnea-hypopnea events with arousal. In the analyses using both whole patients and patients less than 65 years old, the percentage of apnea-hypopnea events with arousal independently contributed to the comorbid hypertension (odds ratio (95% CI); 1.042 (1.007–1.078) and 1.067 (1.023–1.112), respectively; Table 3). The odds ratios of 1.042 and 1.067 mean that a one-percentage point increase in the percentage of apnea-hypopnea events with arousal indicates 1.042 and 1.067 times higher presence of comorbid hypertension in whole patients and in patients less than 65 years old, respectively. And both systolic and diastolic blood pressures were significantly correlated with the percentage of apnea-hypopnea events with arousal (r = 0.350, p < 0.01, r = 0.367, p < 0.01, respectively; Fig. 2).

Nocturnal sympathetic nerve activity and the percentage of apnea-hypopnea events with arousal

As shown in Fig. 3, LF/HF ratio was not correlated with the percentage of apnea-hypopnea events with arousal in all patients and in patients less than 65 years old ($r = -0.016$, p = 0.876, $r = -0.102$, p = 0.366, respectively).

Discussion

Hypertensive OSA patients had more arousals with respiratory events than normotensive patients, and arousal status was significantly correlated with absolute values of both systolic and diastolic blood pressures. However, overnight LF/HF ratio, a marker for sympathetic nerve activity, was not correlated with the percentage of apnea-hypopnea events with arousal among all apnea-hypopnea events.

The proportion of arousal accompanying apnea-hypopneas was 76.8 ± 13.2%, which was comparable to that of former studies [7–13]. Thus, approximately 15% of apnea-hypopnea was terminated without arousal, in which ventilation was recovered before cortical arousal occurs. In this case, upper airway compensation against upper airway narrowing and increase in ventilatory drive restored breathing to normal before arousal occurred. Originally, arousal is considered as a favorable mechanism for protection against life-threatening events by terminating the apneic events; however, recent studies have indicated opposing effects of arousal, that is, arousal threshold is considered as one of the physiological traits consisting the pathogenesis of OSA [3–5]. In some patients with sleep-disordered breathing, such as obesity hypoventilation syndrome, arousal is needed to prevent severe hypoxia and

Table 2 Comparison of arousal accompanying apnea-hypopnea and oxygen desaturation between patients with and without hypertension

	Whole patients			Patients less than 65 years old		
Parameters	Patients with hypertension (n = 47)	Patients without hypertension (n = 50)	p value	Patients with hypertension (n = 40)	Patients without hypertension (n = 40)	p value
The percentage of apnea-hypopnea events with arousal	80.0 ± 12.8	73.7 ± 13.0	0.01	80.8 ± 11.7	71.8 ± 12.5	p < 0.01
ODI3	42.5 ± 19.2	34.4 ± 15.4	0.06 (N.S.)	43.0 ± 19.5	35.6 ± 16.1	0.15 (N.S.)
Time spent with SpO_2 < 90%	13.0 ± 17.4	8.7 ± 9.9	0.50 (N.S.)	14.4 ± 18.5	9.2 ± 10.8	0.44 (N.S.)

Analyses performed using two groups, which consisted of whole patients and of patients less than 65 years old

ODI3 3% oxygen desaturation index, *N.S.* not significant

Table 3 Logistic regression models for the prevalence of comorbid hypertension

Independent variable	B	SE	*p* value	OR	95%CI
Whole patients (*n* = 97)					
The percentage of apnea-hypopnea events with arousal	0.041	0.017	0.018	1.042	1.007–1.078
ODI3	0.029	0.013	0.022	1.030	1.004–1.056
Patients less than 65 years old (*n* = 80)					
The percentage of apnea-hypopnea events with arousal	0.064	0.021	0.03	1.067	1.023–1.112
ODI3	0.026	0.014	0.07	1.027	0.998–1.056

B unstandardized regression coefficient, *SE* standard error, *OR* odds ratio, *95%CI* 95% confidence interval, *ODI3* 3% oxygen desaturation index

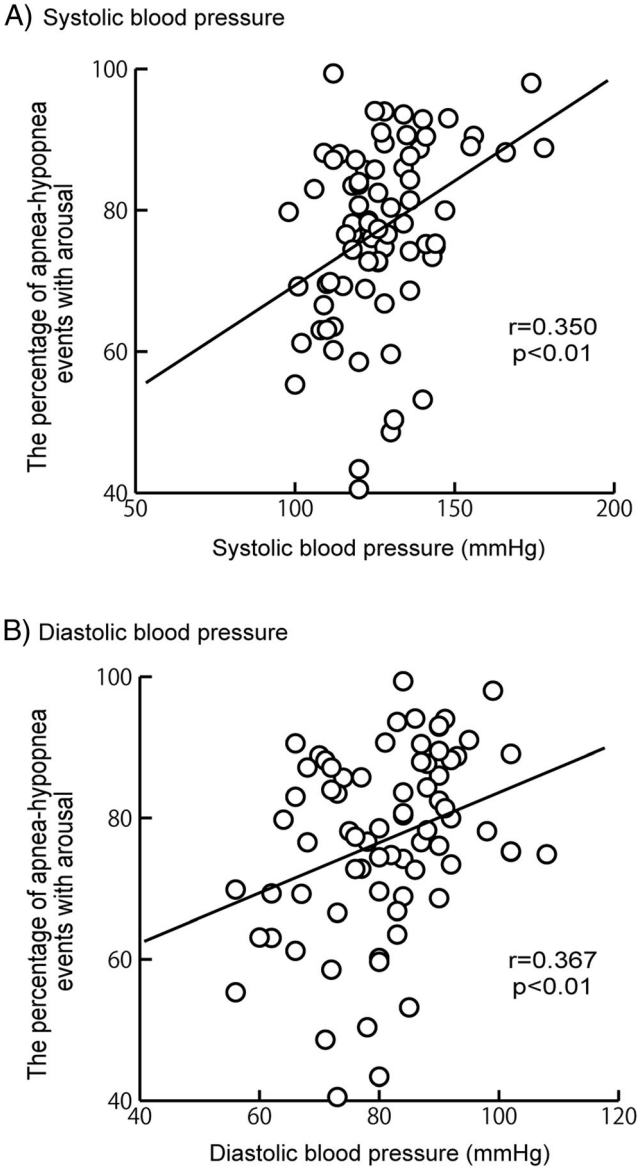

Fig. 2 Correlation between systolic (**a**) or diastolic (**b**) blood pressures and the percentage of apnea-hypopnea events with arousal. Absolute value of both systolic and diastolic blood pressures was significantly correlated with the percentage of apnea-hypopnea events with arousal. Analysis was performed with medication-free patients for hypertension (*n* = 75)

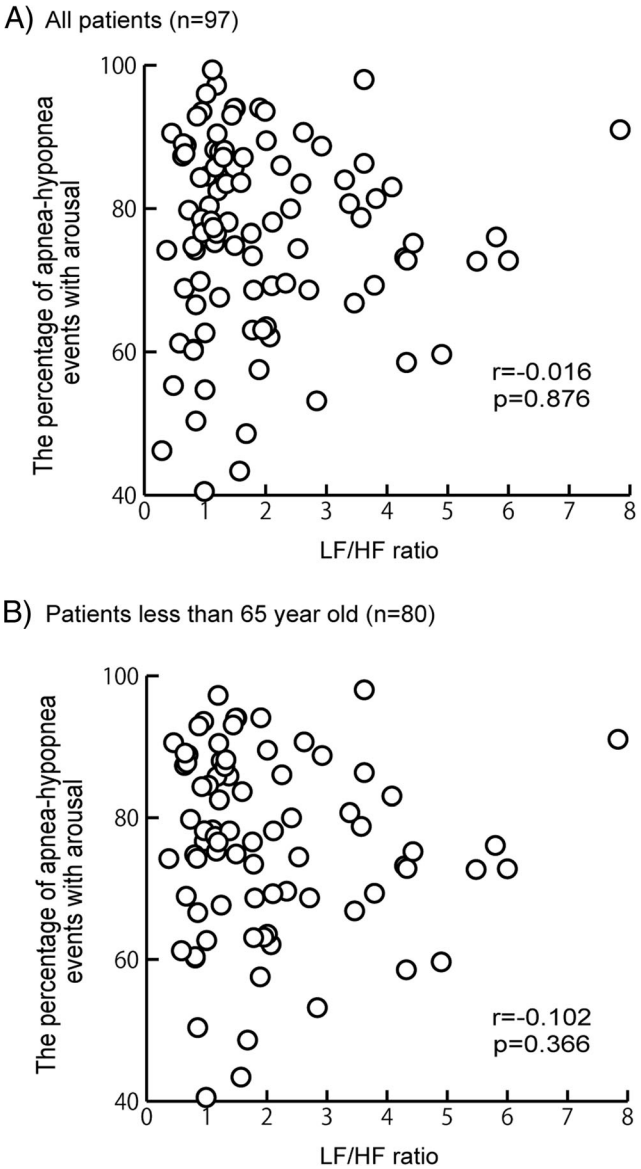

Fig. 3 Correlation between LF/HF ratio and the percentage of apnea-hypopnea events with arousal. The LF/HF ratio was not correlated with the percentage of apnea-hypopnea events with arousal in all patients (**a**) and patients less than 65 years old (**b**)

hypercapnia due to sleep hypoventilation; however, in the patients with OSA, ventilatory overshoot and/or heart rate increase caused by cortical arousal induce reentry to another apnea-hypopnea due to ventilatory instability and activation of the sympathetic nerve system. In the current study, patients who had higher proportion of arousal accompanying apnea-hypopnea events showed hypertension, which supports reported unfavorable effects of cortical arousal. As for mechanisms explaining this higher prevalence of comorbidity of hypertension, sleep fragmentation, repeated activation of the sympathetic nerve system, and intermittent hypoxia represented by ODI were considered; however, the current study did not demonstrate elevated sympathetic nerve activity in higher proportion of arousal accompanying apnea-hypopnea events, since the values of LF/HF ratio and the percentage of arousal accompanying apnea-hypopnea events were not correlated. Moreover, ODI3 somewhat had effects on systemic hypertension (Tables 2 and 3); however, the percentage of apnea-hypopnea events with arousal was a stronger contributor to comorbid hypertension.

Recent studies have demonstrated that arousal intensity was related to the respiratory and pharyngeal muscle response and heart rate increase [2, 13–15]. In the current study, we just looked at the presence of arousal according to the *AASM manual for the scoring of sleep and associated events*, not at arousal intensity either with visual or automatic processing scoring. This might explain no correlation between sympathetic nerve activation (LF/HF ratio) and the proportion of arousal accompanying apnea-hypopnea events. Accordingly, although we indicated that the presence of arousal was associated with hypertension, the exact mechanism for this finding could not be elucidated in the current study, and further study is needed to elucidate the exact mechanisms.

There are potential limitations. First, the causal relationship between accompanying arousal and systemic hypertension has been unknown, as the current study was performed with a cross-sectional setting. Second, as we mentioned above, arousal intensity was not investigated since objective assessment of arousal intensity has not been easy to perform so far. However, we could successfully indicate the unfavorable effect of the presence of cortical arousal with apnea-hypopnea, showing higher prevalence of hypertension which is one of the important comorbidities of OSA. Lastly, we adopted the LF/HF ratio using the ECG signal in the diagnostic PSG to assess sympathetic nerve activity. The debate still exists regarding the assessment of the sympathetic tone using heart rate variability; thus, we could not completely reject the relationship between the accompanying arousal and elevated sympathetic nerve activity. As it is difficult to access cardiac afferents, methods such as muscle sympathetic nerve activity (MSNA) might help to assess this possibility [16–19], but this was beyond the scope of the present large dataset.

In summary, we conclude that patients who show a higher proportion of arousal accompanying apnea-hypopnea events exhibit a higher prevalence of hypertension. An unfavorable effect of cortical arousal was shown in the current study. When we consider arousal threshold as one of the physiological traits for OSA pathogenesis, elevating the arousal threshold might be effective to prevent hypertension.

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Author contributions Drs. Uyama, Yamauchi, Yoshikawa, and Kimura have been responsible for the study concept and design and interpretation of the data. Drs. Uyama, Yamauchi, and Kimura have been responsible for drafting and revising the manuscript. Drs. Uyama, Yamauchi, Fujita, and Ohnishi have been responsible for data acquisition. Drs. Uyama, Yamauchi, and Fujita have been responsible for data analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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