Prevalence and Significance of Restless Legs Syndrome in Patients With Coronary Artery Disease

Shoichiro Yatsu, MD, PhD[a,b], Takatoshi Kasai, MD, PhD[a,c,d,*], Shoko Suda, MD, PhD[a,c], Hiroki Matsumoto, MD[a,c], Sayaki Ishiwata, MD[a,c], Nanako Shiroshita, BSc[c], Mitsue Kato[c], Fusae Kawana, BSc[c], Azusa Murata, MD, PhD[a], Megumi Shimizu, MD, PhD[a], Jun Shitara, MD[a], Takao Kato, MD, PhD[a], Masaru Hiki, MD, PhD[a], Eiryu Sai, MD, PhD[a,b], Katsumi Miyauchi, MD[a,b], and Hiroyuki Daida, MD[a]

Restless legs syndrome (RLS), characterized by leg restlessness and dysesthesia predominantly at night and at rest, disrupts sleep and quality of life. The reported prevalence of RLS is 2% to 5%. Although a relation between RLS and coronary artery disease has been suggested, the prevalence and clinical significance of RLS in coronary artery disease patients remain unknown. We enrolled coronary artery disease patients who underwent percutaneous coronary intervention. Patients with RLS were identified according to international criteria. Subjective sleepiness, sleep quality, and health-related quality of life were assessed using the Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, and Short Form-8, respectively. Among 326 patients with coronary artery disease, 26 (8.0%) had RLS. There were no significant differences in characteristics between patients with and without RLS. Sleep quality and quality of life were more disrupted in patients with RLS (Pittsburgh Sleep Quality Index score, 7.4 ± 2.4 vs 5.6 ± 2.5, p <0.001; physical component summary and mental component summary scores of Short Form-8, 39.6 ± 1.8 vs 43.5 ± 0.5, p = 0.042 and 45.2 ± 8.4 vs 48.4 ± 7.4, p = 0.037, respectively), despite no significant difference in Epworth Sleepiness Scale score (8.2 ± 5.1 vs 7.1 ± 4.8, p = 0.293). In multiple linear regression analyses, RLS was independently associated with Pittsburgh Sleep Quality Index (β = 0.174, p <0.001), physical component summary (β = −0.127, p = 0.029), and mental component summary (β = −0.113, p = 0.042) scores. In conclusion, in patients with coronary artery disease, the prevalence of RLS was relatively high compared to that reported in the general population. The presence of RLS was associated with disrupted sleep quality and health-related quality of life in coronary artery disease patients. **(Am J Cardiol 2019;123:1580−1586)**

Restless legs syndrome (RLS) is a sleep-related movement disorder in which patients feel unpleasant leg sensations and the urge to move their legs.[1] RLS symptoms are usually worse at rest or at night. Patients with RLS have disrupted daily lives and sleep due to the RLS symptoms.[1] In the general population, the reported prevalence of RLS differs by ethnicity (i.e., approximately 2% to 5% in Japan[2] and 5% to 10% in Western country[1]). Although the pathogenetic mechanism of RLS remains unknown, RLS has been suggested as a risk factor of cardiovascular disease possibly through the disruption of patient sleep and sympathetic nerve overactivity.[3] If RLS is associated with incident coronary artery disease, the prevalence of RLS in patients with coronary artery disease would be relatively higher compared with that in the general population. However, the prevalence and significance of RLS in patients with coronary artery disease has never been formally reported. Thus, the present study evaluates the prevalence and clinical importance of RLS in patients with coronary artery disease.

METHODS

This study was a prospective multicenter observational study. Consecutive patients who were hospitalized at Juntendo University Hospital and Juntendo Tokyo Koto Geriatric Medical Center to undergo percutaneous coronary revascularization for coronary artery disease between January 2015 and July 2016 were enrolled. The exclusion criteria were end-stage renal disease requiring hemodialysis, psychiatric disorders, degenerative disease

[a]Department of Cardiovascular Medicine, Juntendo University School of Medicine, Tokyo, Japan; [b]Department of Cardiovascular Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan; [c]Cardiovascular Respiratory Sleep Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan; and [d]Sleep and Sleep-Disordered Breathing Center, Juntendo University Hospital, Tokyo, Japan. Manuscript received December 10, 2018; revised manuscript received and accepted February 11, 2019.

Funding source: This study was partly supported by a Grant-in-Aid for Scientific Research (C), grant number 26507010; JSPS KAKENHI, grant number JP17K09527; a grant to the Intractable Respiratory Diseases and Pulmonary Hypertension Research Group, from the Ministry of Health, Labor and Welfare, H29-027, and by the MEXT∗-Supported Program for the Strategic Research Foundation at Private Universities, 2014 to 2018 (∗Ministry of Education, Culture, Sports, Science and Technology). These funding sources have no other roles in this study.

See page 1585 for disclosure information.

*Corresponding author: Tel: +81-3-3813-3111; fax: +81-3-5689-0627.
E-mail address: kasai-t@mx6.nisiq.net (T. Kasai).

0002-9149/
https://doi.org/10.1016/j.amjcard.2019.02.017

with neurological deficits, and known sleep-disordered breathing. The participants were divided into 2 groups according to the presence of RLS. The study protocol was approved by each hospital's Review Board and the study complied with the Declaration of Helsinki. Informed consent was obtained from all patients. All participants underwent a face-to-face interview with a trained physician to assess the presence of RLS. RLS was identified using the 2012 International RLS Study Group criteria.[4] RLS was diagnosed by a positive answer to all 5 of the following: (1) urge to move the legs usually but not always accompanied by or believed to be caused by uncomfortable and unpleasant sensations in the legs; (2) urge to move the legs and any accompanying unpleasant sensations that begin or worsen during periods of rest or inactivity such as lying down or sitting; (3) urge to move the legs and any accompanying unpleasant sensations that are partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues; (4) urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occurring or worsening in the evening or at night; and (5) the occurrence of the above features not solely accounted for as the symptoms primary to another medical or a behavioral condition.

Subjective sleep quality was assessed by the Pittsburgh Sleep Quality Index in all participants.[5,6] The Pittsburgh Sleep Quality Index is used to evaluate sleep quality and disturbances over a 1-month period based on self-reported information. The scale comprises 19 individual items and 7 component scores; the components include sleep duration, sleep disturbance, sleep latency, daytime dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and sleep medication use. The scores on each item of the index vary between 0 and 3. The total score of the 7 components ranged from 0 to 21, with higher scores indicating a worse sleep quality and total scores >5 indicating poor sleep quality.[5,7] The Pittsburgh Sleep Quality Index was translated into Japanese and validated;[7] we used this Japanese version of the Pittsburgh Sleep Quality Index in the present study.

Subjective sleepiness was evaluated by the Epworth Sleepiness Scale.[8] Subjects determine their chances of falling sleep in various active and passive situations, scoring the likelihood from 0 (no chance) to 3 (high chance). The Scale has been translated into Japanese and validated.[9] In this study, the Japanese version of Epworth Sleepiness Scale was used to evaluate the subjective sleepiness of all participants, with excessive daytime sleepiness defined as a score of >10 (range 0 to 24).

The health-related quality of life was evaluated by the Short Form (SF)-8 consisting of an 8-item questionnaire. The SF-8 was translated into Japanese and validated.[10,11] This scale comprises 8 subscales, including physical functioning, role limitations due to physical problems (role-physical), bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. Two aggregate scores, the physical component summary score and the mental component summary score, are derived from the 8 health domains. These scores are calculated by weighing each subscale.[11] Scoring is based on Japanese standards; the possible scores range from 0 to 100, with higher scores representing a better health-related quality of life.[11]

The baseline data of patients with and without RLS included age, gender, body mass index, atrial fibrillation, current smoker, hypertension, dyslipidemia, diabetes mellitus, acute coronary syndrome, systolic and diastolic blood pressure, heart rate, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride level, hemoglobin level, iron level, total iron binding capacity, ferritin level, albumin level, sodium level, potassium level, C-reactive protein level, hemoglobin A1c level, estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation with a Japanese coefficient from baseline serum creatinine levels,[12] plasma B-type natriuretic peptide level, left ventricular ejection fraction by echocardiogram with a modified Simpson method, and medication use were prospectively collected from each patient. Blood samples were collected during the early morning after overnight fasting. Nocturnal pulse oximetry was performed for 1 night in the hospitals using a finger pulse oximeter to examine the number of desaturations per hour, expressed as the oxygen desaturation index.

Data are expressed as mean ± SD or median (interquartile range) for continuous variables and numbers (%) for nominal variables. To compare baseline characteristics between the RLS and non-RLS groups, chi-square or Fisher's exact tests for categorical variables and Student's t or Mann-Whitney U tests for continuous variables were used. Simple and multiple linear regression analyses, including Pittsburgh Sleep Quality Index scores as the dependent variable and age, gender, body mass index, atrial fibrillation, current smoker, hypertension, dyslipidemia, diabetes mellitus, acute coronary syndrome, systolic and diastolic blood pressure, heart rate, ventricular ejection fraction, hemoglobin, iron, total iron binding capacity, ferritin, estimated glomerular filtration rate, sodium, potassium, C-reactive protein, plasma B-type natriuretic peptide, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, use of β blocker, vasodilator, angiotensin converting enzyme/angiotensin II receptor blocker, aldosterone blocker, diuretics, and 3% oxygen desaturation index as independent variables, were performed. Furthermore, simple and multiple linear regression analyses, including the component summary scores of the SF-8 as dependent variables and the same variables included in the regression analyses for Pittsburgh Sleep Quality Index scores as independent variables were also performed. The natural log-transformed values were used for C-reactive protein and plasma B-type natriuretic peptide as these values were skewed. Variables with $p < 0.10$ in univariable analysis were entered into a stepwise multiple linear regression analysis ($p < 0.10$ for inclusion and $p > 0.05$ for exclusion). A p value of < 0.05 was considered statistically significant unless otherwise indicated. All data were analyzed using JMP 12.0.1 MDSU (SAS Institute, Cary, North Carolina).

RESULTS

Among 451 patients who were hospitalized for percutaneous coronary revascularization, 355 eligible patients were enrolled. Data from 29 patients were excluded

because of missing baseline data; therefore, 326 patients were finally analyzed. Of these, 26 (8.0%) patients had RLS. The characteristics of the patients with and those without RLS are shown in Table 1. There was no significant difference between these 2 groups.

Patients with RLS had significantly higher Pittsburgh Sleep Quality Index scores than those without RLS (Figure 1), indicating that patients with RLS were more likely to have poor sleep quality than those without RLS (Figure 1). The variables with $p < 0.1$ in each simple linear regression analysis are shown in Table 2. In the stepwise multiple linear regression analysis (Table 2), RLS and Japanese version of Epworth Sleepiness Scale score were positively and potassium levels were negatively correlated with Pittsburgh Sleep Quality Index scores. As shown in Figure 2, no significant differences were observed in Japanese version of Epworth Sleepiness Scale score between patients with and without RLS and in the proportion of patients with excessive daytime sleepiness. Thus, there was no relation between Japanese version of Epworth Sleepiness Scale scores and RLS ($\beta = -0.059$, $p = 0.293$). Based on the health-related quality of life assessment using the SF-8, none of the 8 subscales differed significantly between patients with and without RLS. However, 2 component summary scores (i.e., physical and mental component summary scores) were significantly lower in patients with RLS compared to those without RLS (Figure 3). Variables with $p < 0.1$ in the simple linear regression analyses for physical and mental component summary scores are shown in Tables 3 and 4. The final model of the stepwise multiple linear regression analysis for physical component summary score included body mass index, ferritin, use of vasodilator, log plasma B-type natriuretic peptide level, and RLS (Table 3). Furthermore, the final model of the stepwise multiple linear regression analysis for mental component summary score included age, Japanese version of Epworth Sleepiness Scale score, hemoglobin level, and RLS (Table 4).

Table 1
Baseline characteristics

Variable	Restless legs syndrome		p
	No (n = 300)	Yes (n = 26)	
Age (years)	66.1 ± 11.5	68.1 ± 12.0	0.399
Women	42 (14.0%)	4 (15.4%)	0.847
Body mass index (kg/m^2)	25.2 ± 3.7	25.3 ± 4.3	0.872
Atrial fibrillation	13 (4.4%)	3 (11.5%)	0.160
Current smoker	69 (23.3%)	6 (25.0%)	0.912
Hypertension	216 (72.7%)	20 (76.9%)	0.639
Dyslipidemia	230 (77.4%)	20 (76.9%)	0.952
Diabetes mellitus	129 (43.4%)	12 (46.2%)	0.789
Acute coronary syndrome	106 (36.9%)	8 (32.0%)	0.620
Systolic blood pressure (mmHg)	125.2 ± 19.9	127.8 ± 16.9	0.519
Diastolic blood pressure (mmHg)	69.0 ± 14.3	68.6 ± 10.5	0.885
Heart rate (beats/min)	69.6 ± 12.8	70.2 ± 12.3	0.836
Left ventricular ejection fraction (%)	61.0 ± 11.7	63.1 ± 9.9	0.479
Hemoglobin (g/dL)	13.5 ± 1.8	13.3 ± 2.5	0.567
Iron (μg/dL)	89.0 ± 38.7	98.4 ± 44.2	0.272
Total iron binding capacity (μg/dL)	281.1 ± 52.7	279.4 ± 57.6	0.889
Ferritin (ng/ml)	267.6 ± 287.2	250.3 ± 270.8	0.782
Estimated glomerular filtration rate (ml/min/1.73m^2)	77.6 ± 23.0	80.4 ± 24.2	0.564
Sodium (mmol/L)	140.7 ± 2.8	140.5 ± 2.7	0.628
Potassium (mmol/L)	4.2 ± 0.4	4.1 ± 0.3	0.473
C-reactive protein (mg/dl)	0.44 [1.2]	0.29 [0.5]	0.548
Brain natriuretic peptide (pg/ml)	46.7 [100.0]	62.0 [111.7]	0.758
Triglycerides (mg/dl)	135.9 ± 74.2	132.3 ± 58.7	0.807
High density lipoprotein cholesterol (mg/dl)	44.4 ± 0.7	42.5 ± 2.3	0.433
Low density lipoprotein cholesterol (mg/dl)	95.7 ± 36.2	91.7 ± 21.5	0.580
Beta blockers	26 (8.7%)	2 (11.5%)	0.642
Vasodilator	50 (16.8%)	6 (23.1%)	0.436
Angiotensin-converting enzyme inhibitor/ angiotensin receptor blockers	177 (59.6%)	17 (65.4%)	0.560
Aldosterone blockers	12 (6.7%)	0 (0%)	0.224
Diuretics	34 (11.5%)	3 (11.5%)	0.989
3% Oxygen desaturation index (/hour)	14.0 ± 12.5	12.6 ± 10.3	0.631

Hypertension = systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg, or the use of antihypertensive medications; Dyslipidemia = low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol ≤40 mg/dl, triglyceride ≥150 mg/dl, or current treatment with statins and/or lipid-lowering agents; Diabetes mellitus = either hemoglobin A1c ≥ 6.5% or insulin or oral hypoglycemic drug use.

DISCUSSION

Our findings provide novel insights into the clinical importance of RLS in patients with coronary artery disease. First, we observed RLS in 8.0% of coronary artery disease patients. Second, there was no significant difference in the baseline characteristics of coronary artery disease patients between those with and without RLS. Third, despite the lack of relation between subjective sleepiness and RLS, RLS significantly disrupted their sleep quality and health-related quality of life. Finally, the relation between RLS and disrupted sleep quality and between RLS and impaired health-related quality of life remained significant even in multivariable analysis. These findings suggest that RLS is not a rare comorbidity in patients with coronary artery disease and that coexisting RLS may be clinically important by disrupting patient sleep and impairing health-related quality of life. Thus, RLS should be identified and treated, when possible, in coronary artery disease patients.

Several studies reported the relation between RLS and cardiovascular diseases such as coronary artery disease. A cross-sectional study of 3,433 patients enrolled in the Sleep Heart Health Study identified RLS in 3.3% of men and 6.8% of women and identified the relation between RLS and coronary artery disease even in a multivariable logistic regression analysis in which patients with RLS had a 2.2-fold greater odds for coronary artery disease.[13] In addition, Li et al reported that a prospective cohort of women with RLS for at least 3 years had a 46% higher risk of developing coronary artery disease than those without RLS.[14] Molnar et al reported that incident RLS was associated with higher risks of mortality, incident coronary artery disease,

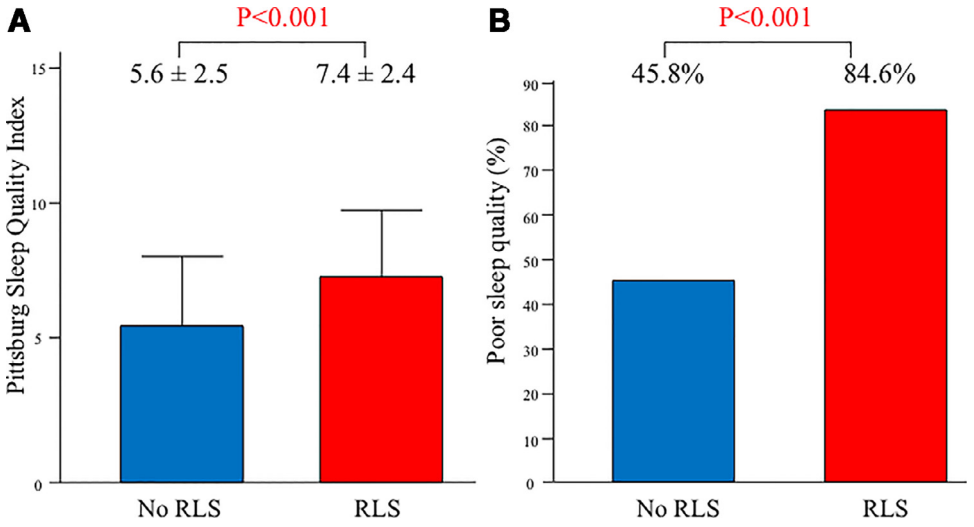

Figure 1. *(A)* Comparisons of Pittsburg Sleep Quality Index scores and proportions of subjective sleep quality between patients with and without RLS. Pittsburg Sleep Quality Index scores were significantly higher in patients with RLS than in those without RLS (p <0.001). Values are mean and ±SD. *(B)* Comparisons of proportions of subjects with poor sleep quality between patients with and without RLS (i.e., Pittsburg Sleep Quality Index >5, p <0.001). RLS = restless legs syndrome.

Table 2
Simple and stepwise multiple linear regression analyses for Pittsburg Sleep Quality Index scores

	Simple		Multiple	
Variable	β	p	B	p
Japanese version of Epworth Sleepiness Scale scores	0.212	<0.001	0.203	<0.001
Diastolic blood pressure	0.093	0.099	–	–
Potassium	−0.167	0.003	−0.157	0.004
Beta blockers	0.097	0.085	–	–
Diuretics	0.125	0.026	–	–
Restless legs syndrome	0.189	<0.001	0.174	0.001

stroke, and chronic kidney disease in the large-scale, long-term follow-up cohort.[15] However, analysis of a retrospective cohort suggested that primary RLS was not associated with cardiovascular disease or coronary artery disease but was associated with a slightly increased risk of hypertension.[16] In another prospective population study with a 10-year follow-up of almost 2,000 men, RLS was associated with a significant increase in stroke but not coronary artery disease compared to those in subjects without RLS.[17] However, to our knowledge, the prevalence of RLS in patients with coronary artery disease has never been investigated. Thus, the present study is the first to report the prevalence of RLS in the coronary artery disease population; this prevalence (8.0%) was relatively higher than that reported in the general population of Japan (2% to 5%).[2]

RLS has been associated with iron deficiency and renal function.[18] However, no significant differences in these factors between groups were observed in the present study. Genetic factors also play a role in RLS pathogenesis[18]; however, these were not assessed in the present study. Other possible mechanisms for the relatively high prevalence of RLS in coronary artery disease patients may include central dopaminergic activity affected by increased sympathetic nerve activity due to coronary artery disease[19,20] and its associated downregulation of the dopamine receptors.[18] However, the pathogenetic mechanisms of RLS are not fully understood and the reason for the increased prevalence of RLS in coronary artery disease patients is uncertain. The mechanisms by which RLS is relatively prevalent in coronary artery disease patients remain to be elucidated and further studies are needed.

RLS can impair sleep quality and health-related quality of life. Previous studies suggested the relation between poor sleep quality and RLS. Liu et al reported a significant independent relation between poor sleep quality and RLS based on the Pittsburgh Sleep Quality Index.[21] Similarly, in the present study of patients with coronary artery disease, we showed that coexisting RLS was independently associated with a greater Pittsburgh Sleep Quality Index score; that is, poor sleep quality. In general, poor sleep quality has been suggested as a risk factor for coronary artery disease.[22] Thus, poor sleep quality in association with RLS may not only be a comorbid condition of but also a cause of coronary artery disease, which may contribute to the relatively high prevalence of RLS in these patients.

The significant relation between the presence of RLS and quality of life has also been reported in noncoronary artery disease populations and RLS treatment has been suggested to improve the quality of life.[23] Kushida et al reported that RLS deteriorated physical-related quality of life more than mental-related quality of life.[24] Rothdach et al reported that RLS in the elderly was associated with poorer mental-related quality of life.[25] In the present study, patients with RLS and coronary artery disease had significantly decreased both physical and mental-related quality of life. Although varying results may be explained by differences in study populations, coexisting coronary artery disease and RLS can decrease both physical and mental-related quality of life.

This study has several limitations. First, the sample size was relatively small. Second, we could not assess vitamin

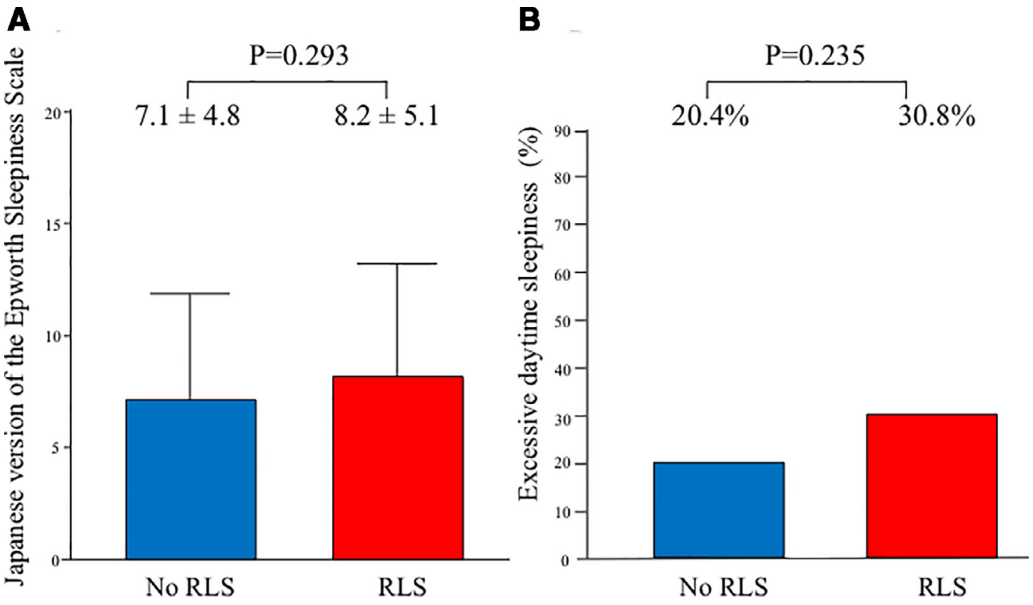

Figure 2. *(A)* Comparisons of Japanese version of the Epworth Sleepiness Scale scores and proportions of excessive daytime sleepiness between patients with and without RLS. Japanese version of the Epworth Sleepiness Scale scores were not significantly different between patients with RLS and those without RLS (p = 0.293). Values are mean and ±SD. *(B)* Comparisons of proportion of excessive daytime sleepiness between patients with and without RLS (i.e., Japanese version of the Epworth Sleepiness Scale scores >10, p = 0.235). RLS = restless legs syndrome.

B12 and folic acid, which might be related to RLS. Third, although we performed nocturnal pulse oximetry to assess sleep-disordered breathing, we could not perform full polysomnography, which was a gold standard for sleep-disordered breathing and periodic limb movement diagnosis. Fourth, although we found that RLS was independently

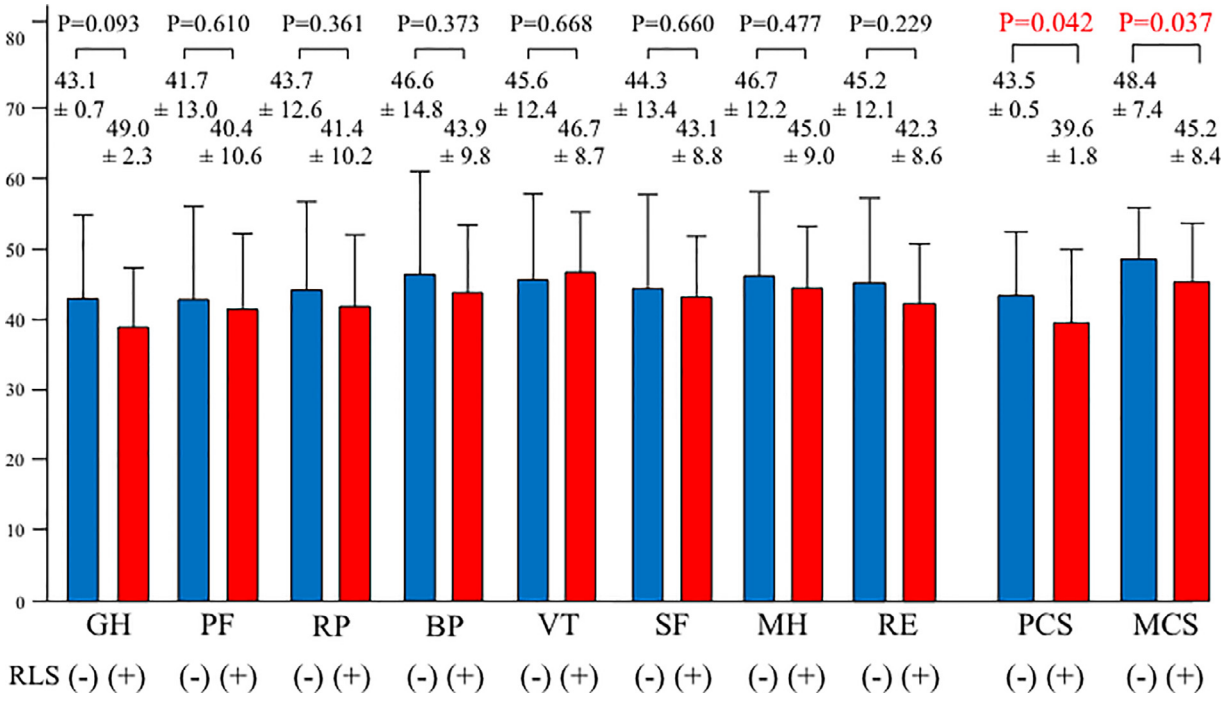

Figure 3. Comparisons of Short Form-8 subscales and component summary scores between patients with and without RLS. PCS and MCS scores were significantly lower in patients with RLS than in those without RLS (p = 0.042 and p = 0.037, respectively). Values are mean and ±SD. RLS = restless legs syndrome; PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health perception, VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health; PCS = physical component summary; MCS = mental component summary.

Table 3
Simple and stepwise multiple linear regression analyses for physical component summary scores

	Simple		Multiple	
Variable	β	p	B	p
Age	−0.139	0.014	–	–
Men	0.107	0.058	–	–
Body mass index	−0.122	0.031	−0.173	0.004
Hypertension	−0.095	0.093	–	–
Heart rate	−0.126	0.027	–	–
Hemoglobin	0.145	0.010	–	–
Ferritin	0.165	0.008	0.146	0.013
Vasodilators	−0.192	<0.001	0.144	0.016
Diuretics	−0.134	0.019	–	–
Log brain natriuretic peptide	−0.222	<0.001	−0.271	<0.001
Log C-reactive protein	−0.106	0.069		
Restless legs syndrome	−0.114	0.042	−0.127	0.029

Table 4
Simple and stepwise multiple linear regression analyses of mental component summary scores

	Simple		Multiple	
Variable	β	p	B	p
Age	0.106	0.060	0.176	0.006
Japanese version of Epworth Sleepiness Scale scores	−0.193	<0.001	−0.161	0.005
Atrial fibrillation	0.096	0.092	–	–
Hemoglobin	0.113	0.047	0.203	0.001
Total iron binding capacity	0.119	0.055	–	–
Vasodilator	−0.112	0.048	–	–
Restless legs syndrome	−0.118	0.037	−0.113	0.042

associated with poor sleep quality and impaired health-related quality of life, it remains unknown whether RLS is associated with poor clinical outcome and whether treatment of RLS improves sleep quality and quality of life in patients with coronary artery disease.

The prevalence of RLS was relatively high in the coronary artery disease patient population. RLS can be an important factor associated with deteriorated sleep quality and health-related quality of life in patients with coronary artery disease. Therefore, further larger-scale and longitudinal studies are required.

Disclosures

Drs. Takatoshi Kasai, Shoko Suda, Hiroki Matsumoto, and Sayaki Ishiwata are affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi. K. Miyauchi received manuscript fees, research funds, and scholarship funds from Amgen, Astellas Pharma Inc, MSD, Bayer Health Care, Sanofi, Takeda Pharmaceutical Co. Ltd., Dai-ichi Sankyo Company, Boehringer-ingelheim, and Bristol-Myers Squibb. H. Daida received manuscript fees, research funds, and scholarship funds from Kirin Co. Ltd., Kaken Pharmaceutical Co., Ltd., Abbott Japan Co., Ltd., Astellas Pharma Inc, Astrazeneca K.K., Bayer Yakuhin, Ltd, Boston Scientific Japan K.K., Bristol-Myers Squibb, Daiichi Sankyo Company, MSD K.K., Pfizer Inc., Philips Respironics, Sanofi K.K., and Takeda Pharmaceutical Co. Ltd. The other authors report no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.017.

1. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: rest general population study. *Arch Intern Med* 2005;165:1286–1292.
2. Tsuboi Y, Imamura A, Sugimura M, Nakano S, Shirakawa S, Yamada T. Prevalence of restless legs syndrome in a Japanese elderly population. *Parkinsonism Relat Disord* 2009;15:598–601.
3. Walters AS, Rye DB. Review of the relationship of restless legs syndrome and periodic limb movements in sleep to hypertension, heart disease, and stroke. *Sleep* 2009;32:589–597.
4. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, Zucconi M, Ferri R, Trenkwalder C, Lee HB. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria−history, rationale, description, and significance. *Sleep Med* 2014;15:860–873.
5. Buysse DJ, Reynolds CF, 3rd Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
6. Koikawa N, Shimada S, Suda S, Murata A, Kasai T. Sex differences in subjective sleep quality, sleepiness, and health-related quality of life among collegiate soccer players. *Sleep Biol Rhythms* 2016;14:377–386.
7. Doi Y, Minowa M, Uchiyama M, Okawa M, Kim K, Shibui K, Kamei Y. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Res* 2000;97:165–172.
8. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–545.
9. Takegami M, Suzukamo Y, Wakita T, Noguchi H, Chin K, Kadotani H, Inoue Y, Oka Y, Nakamura T, Green J, Johns MW, Fukuhara S. Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. *Sleep Med* 2009;10:556–565.
10. Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 1998;51:1037–1044.
11. Tokuda Y, Okubo T, Ohde S, Jacobs J, Takahashi O, Omata F, Yanai H, Hinohara S, Fukui T. Assessing items on the SF-8 Japanese version for health-related quality of life: a psychometric analysis based on the nominal categories model of item response theory. *Value Health* 2009;12:568–573.
12. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–992.
13. Winkelman JW, Shahar E, Sharief I, Gottlieb DJ. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. *Neurology* 2008;70:35–42.
14. Li Y, Walters AS, Chiuve SE, Rimm EB, Winkelman JW, Gao X. Prospective study of restless legs syndrome and coronary heart disease among women. *Circulation* 2012;126:1689–1694.
15. Molnar MZ, Lu JL, Kalantar-Zadeh K, Kovesdy CP. Association of incident restless legs syndrome with outcomes in a large cohort of US veterans. *J Sleep Res* 2016;25:47–56.
16. Van Den Eeden SK, Albers KB, Davidson JE, Kushida CA, Leimpeter AD, Nelson LM, Popat R, Tanner CM, Bibeau K, Quesenberry CP. Risk of cardiovascular disease associated with a restless legs syndrome diagnosis in a retrospective cohort study from Kaiser Permanente Northern California. *Sleep* 2015;38:1009–1015.

17. Elwood P, Hack M, Pickering J, Hughes J, Gallacher J. Sleep disturbance, stroke, and heart disease events: evidence from the Caerphilly cohort. *J Epidemiol Community Health* 2006;60:69–73.
18. Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. *J Neurol* 2017;264:1634–1641.
19. Kawahara Y, Kawahara H, Westerink BH. Comparison of effects of hypotension and handling stress on the release of noradrenaline and dopamine in the locus coeruleus and medial prefrontal cortex of the rat. *Naunyn Schmiedebergs Arch Pharmacol* 1999;360:42–49.
20. Buharin VE, Butler AJ, Rajendra JK, Shinohara M. Enhanced corticospinal excitability with physiologically heightened sympathetic nerve activity. J Appl Physiol *(*1985) 2013;114:429–435.
21. Liu Y, Liu G, Li L, Yang J, Ma S. Evaluation of cardiovascular risk factors and restless legs syndrome in women and men: a preliminary population-based study in China. *J Clin Sleep Med* 2018;14:445–450.
22. Twig G, Shina A, Afek A, Derazne E, Tzur D, Cukierman-Yaffe T, Shechter-Amir D, Gerstein HC, Tirosh A. Sleep quality and risk of diabetes and coronary artery disease among young men. *Acta Diabetol* 2016;53:261–270.
23. Cho YW, Hong SB, Kim DH, Lee HW, Joo EY, Kim JH, Shin WC, Park KH, Han SJ, Lee HW. The effect of ropinirole on the quality of life in patients with restless legs syndrome in Korea: an 8-week, multicenter, prospective study. *J Clin Neurol* 2013;9:51–56.
24. Kushida C, Martin M, Nikam P, Blaisdell B, Wallenstein G, Ferini-Strambi L, Ware JE Jr. Burden of restless legs syndrome on health-related quality of life. *Qual Life Res* 2007;16:617–624.
25. Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and morbidity in Augsburg elderly. *Neurology* 2000;54:1064–1068.