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Interactions between Sleep Apnea and Coronary Artery Disease on the Incidence of Sudden Cardiac Arrest: A Multi-Center Case-Control Study

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Purpose: Sleep apnea (SA) is a risk factor for coronary artery disease (CAD), and SA and CAD increase the incidence of sudden cardiac arrest (SCA). This study aimed to investigate the effect of SA on the incidence of SCA and explore the effect of varying degrees of SA with or without CAD on the incidence of SCA.
Materials and Methods: This prospective multi-center, case-control study was performed using the phase II Cardiac Arrest Pursuit Trial with Unique Registry and Epidemiologic Surveillance (CAPTURES-II) database for SCA cases and community-based controls in Korea. The matching ratio of cases to controls was 1:1, and they were randomly matched within demographics, including age, sex, and residence. The primary variable was a history of SA, and the second variable was a history of CAD. We conducted a conditional logistic regression analysis to estimate the effect of SA and CAD on the SCA risk, and an interaction analysis between SA and CAD.
Results: SA was associated with an increased risk of SCA [adjusted odds ratio (AOR) (95% confidence interval, CI): 1.54 (1.16–2.03)], and CAD was associated with an increased risk of SCA [AOR (95% CI): 3.94 (2.50–6.18)]. SA was a risk factor for SCA in patients without CAD [AOR (95% CI): 1.62 (1.21–2.17)], but not in patients with CAD [AOR (95% CI): 0.56 (0.20–1.53)].
Conclusion: In the general population, SA is risk factor for SCA only in patients without CAD. Early medical intervention for SA, especially in populations without pre-existing CAD, may reduce the SCA risk.
ClinicalTrials.gov (NCT03700203)

Key Words: Sleep apnea; coronary artery disease; sudden cardiac arrest; risk factors

INTRODUCTION

Sudden cardiac arrest (SCA) is a major public health burden due to its high incidence and low survival rate. The global average incidence of SCA is 55 adult cases per 100000 person-years, and the survival to discharge rate is lower in Asia (4.5%) than those in Europe (11.7%) and North America (7.6%).[1,2]

Despite the importance and social burden of SCA, our understanding of the etiology is limited. Although the traditional risk factors for SCA, such as hypertension (HTN), diabetes mellitus (DM), and dyslipidemia, are well known, there are several unknown variables that directly or indirectly affect the occurrence of arrhythmias and cardiac function, which are related to the risk of SCA.[3,4]

Sleep apnea (SA) is a common disorder that has become an important public health problem, affecting about 9%–38% of the

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global adult population, and the public burden of SA is likely to increase.[5,6] SA is characterized by repetitive interruption of ventilation during sleep due to narrowing or total collapse of the pharyngeal airway despite breathing efforts, resulting in a decrease in oxygen saturation and arousal from sleep.[7] Repeated hypoxemia and arousal can cause coronary atherosclerosis,[8] increased platelet activity,[9] and myocardial ischemia.[10] SA has been reported to be associated with the development and progression of certain cardiovascular conditions, such as pulmonary and systemic HTN, coronary artery disease (CAD) and myocardial ischemia, congestive heart failure (CHF), cardiac arrhythmia, and stroke.[11]

There is growing evidence of the connection between SA and CAD.[12,13] Individuals with SA have a high burden of CAD, including CHF, a precursor of SCA. Thus, CAD likely mediates the association between SA and SCA.

SA is a risk factor for CAD, and previous studies have reported that SA and CAD increased the incidence of SCA. Therefore, we hypothesized that it is possible to elucidate the direct effect of SA on the occurrence of SCA by analyzing the relationships between SA and SCA depending on the presence or absence of CAD. This study aimed to investigate the effect of SA on the incidence of SCA, and observe the effect of SA depending on CAD status.

MATERIALS AND METHODS

Study design, setting, and data source

This prospective multi-center, case-control study was performed using the Phase II Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance (CAPTURES-II) database in Korea.

The CAPTURES project aimed to identify risk factors for SCA and evaluate the prognostic factors with short- and long-term follow-ups. CAPTURES-I was performed in 2014 with 27 participating hospitals. The CAPTURES-II project was conducted at 17 university hospitals from 2017 to 2020. The project contained SCA patients with presumed cardiac etiology identified by emergency physicians, who were transported by emergency medical service (EMS) to participating hospitals. The registration into the program included a face-to-face interview for demographics, comorbidities, and health behaviors and a medical record review, including laboratory tests, short- and long-term follow-ups (1 month, 6 months, and 12 months after hospital discharge), and blood test evaluating biomarkers. A community-based control group was also included; and during registration into the program, similar to the SCA group, a face-to-face interview and blood tests were done.

All of the collected data were transferred to the Quality Management Committee (QMC), and quality control and statistical analysis were performed. The QMC provided monthly feedback to each of participating hospital on the quality control of the data. When the study coordinators could not define a variable, the QMC was asked for clarification.

Study population

SCA cases were defined as adult SCA patients, aged 18 years or older, with a presumed cardiac etiology transported by EMS to one of the 17 participating hospitals from September 2017 to December 2020. SCA cases with unknown histories of SA or CAD were excluded.

Community-based controls were collected from two university hospitals (one metropolitan and one non-metropolitan). One center located in a metropolitan area (Seoul) collected metropolitan controls, and the other center located in a non-metropolitan area (Wonju) collected non-metropolitan controls. By collaborating with public health centers or various community centers, the CAPTURES-II project and control recruitment were promoted, and voluntary applicants were recruited as the control group. Age (10-year intervals), sex, and urbanization level of residence (metropolitan vs. non-metropolitan) matched controls were recruited in a 1:1 ratio per case, in order to minimize the influence of confounding variables.

Variables and measurements

The primary variable was a history of SA, measured via face-to-face interview with the patient or the patient's kin. SA history was defined as a positive case by an answer of "yes" to the question, "Have you ever suffered or been diagnosed with sleep apnea?" CAD was defined as a positive case by an answer of "yes" to the question, "Have you ever been diagnosed with angina pectoris or myocardial infarction?"

The CAPTURES-II project used the same questionnaire for SCA cases and controls. Information was collected about demographics, including age, sex, residence area, insurance, and education level; comorbidities, including HTN, DM, dyslipidemia, stroke, and metabolic disease; health behaviors, including smoking, alcohol use, physical activity, and obesity; and sleep disorders, including insomnia and snoring.

Statistical analysis

Continuous variables were compared using the paired t-test, and categorical variables were compared using the McNemar test. For the case-control dataset, a conditional logistic regression analysis was conducted to estimate the effect of SA on the risk of SCA, and to calculate the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) after adjusting for potential confounders identified in the directed acyclic graph models. To calculate AORs according to CAD, we used multivariable conditional logistic regression model with an interaction term (SA×CAD) as the final model for the outcomes. We dropped the interaction products according to the order of size of $p>0.01$ using the analysis of maximum likelihood estimates in the model. The interaction term with the biggest p value was removed from the model, and the remaining interaction terms

were also assessed. Additionally, we performed stratified analysis according to the age group [young age group (18–64) and old age group (65–100)]. All variables were assessed for multicollinearity, which was not detected in this analysis.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All *p*-values were two-tailed, and a *p* value of less than 0.05 was considered statistically significant.

Ethics statement

This study was approved by the Ethics Committees of all 17 participating university hospitals (IRB No: Chonnam National University Hospital, CNUH-2017-285; Chungbuk National University Hospital, CBNUH2017-09-009-001; Chungnam National University Hospital, CNUH2017-10-027; Dankook University Hospital, DKUH2018-12-019; Hallym University Kangnam Sacred Heart Hospital, HKS2018- 02-016; Hallym University Dongtan Sacred Heart Hospital, HDT2017-10-002; Korea University Anam Hospital, 2018AN0148; Korea University Ansan Hospital, AS17174; Kyungpook National University Hosptial, KNUH2017-10-035-006; Seoul National University Boramae Medical Center, 20171123/30-2017-66/123; Seoul National University Bundang Hospital, B-1711/430-304; Seoul National University Hospital, H-1709-053-883; Soonchunhyang University Bucheon Hospital, SCHBC2018-02-014-002; Sungkyunkwan University Samsung Medical Center, SMC2018-08-121; Ulsan University Asan Medical Center, S2018-1805-0001; Yonsei University Severance Hospital, 4-2017-1201; Yonsei University Wonju Severance Christian Hospital, CR317101). All participants, or their proxy, provided written informed consent before taking part in the study.

RESULTS

Demographic findings

A total of 948 SCA cases and 948 community-based control were enrolled in this analysis. The characteristics of the SCA cases and community-based controls are shown in Table 1. The percentage of SA history in the SCA cases and matched controls was 18.9% (179/948) and 15.1% (143/948), respectively. The percentage of CAD history in the SCA cases and matched controls was 11.7% (111/948) and 3.3% (31/948), respectively.

The characteristics of the study population according to the SA are shown in Table 2. The patients in the SA group were younger than those in the non-SA group, and more were males. The SA group also had a higher incidence of HTN. Additionally, the SA group had higher smoking, alcohol use, and obesity frequencies. The SA group also had more sleep disorders, such as insomnia and snoring. SCA incidence was significantly higher in the SA group (55.6%) compared to the control group (48.9%; $p<0.05$).

Table 1. Characteristics of the OHCA Case Group and Age-, Sex-, and Urbanization Level-Matched Control Group

Variables	All (n=1896)	OHCA case (n=948)	Community control (n=948)	*p* value
Age (yr)				>0.999
18–29	36 (1.9)	18 (1.9)	18 (1.9)	
30–39	98 (5.2)	49 (5.2)	49 (5.2)	
40–49	270 (14.2)	135 (14.2)	135 (14.2)	
50–59	494 (26.1)	247 (26.1)	247 (26.1)	
60–69	528 (27.8)	264 (27.8)	264 (27.8)	
70–100	470 (24.8)	235 (24.8)	235 (24.8)	
Sex, female	520 (27.4)	260 (27.4)	260 (27.4)	>0.999
Metropolis, yes	964 (72.6)	482 (72.6)	482 (72.6)	>0.999
Insurance, medical aid	200 (10.5)	99 (10.4)	101 (10.7)	0.884
Education, high	618 (32.6)	243 (25.6)	375 (39.6)	<0.001
Comorbidity				
HTN	772 (40.7)	423 (44.6)	349 (36.8)	<0.001
DM	385 (20.3)	252 (26.6)	133 (14.0)	<0.001
Dyslipidemia	352 (18.6)	127 (13.4)	225 (23.7)	<0.001
Stroke	106 (5.6)	78 (8.2)	28 (3.0)	<0.001
Metabolic disease	71 (3.7)	12 (1.3)	59 (6.2)	<0.001
CAD	142 (7.5)	111 (11.7)	31 (3.3)	<0.001
Smoking, yes	1077 (56.8)	564 (59.5)	513 (54.1)	0.024
Alcohol drinking, yes	1202 (63.4)	526 (55.5)	676 (71.3)	<0.001
Physical activity				<0.001
Vigorous	344 (18.1)	112 (11.8)	232 (24.5)	
Moderate	512 (27.0)	151 (15.9)	361 (38.1)	
Never	1040 (54.9)	685 (72.3)	355 (37.4)	
Obesity, yes	149 (7.9)	33 (3.5)	116 (12.2)	<0.001
Sleep disorder				
Insomnia	497 (26.2)	251 (26.5)	246 (25.9)	0.791
Insomnia, medication	88 (4.6)	57 (6.0)	31 (3.3)	<0.001
Snoring	1015 (53.5)	465 (49.1)	550 (58.0)	<0.001
SA	322 (17.0)	179 (18.9)	143 (15.1)	0.287

OHCA, out-of-hospital cardiac arrest; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; SA, sleep apnea.
Data are presented as n (%).

SA association with SCA risk

The results of the conditional logistic regression model, including AORs (95% CIs) for SCA incidence in SA and CAD cases, are shown in Table 3. SA was associated with increased SCA risk [AOR (95% CI): 1.54 (1.16–2.03)], and CAD was also associated with increased SCA risk [AOR (95% CI): 3.94 (2.50–6.18)].

Interaction analysis

We analyzed the interactions between SA or CAD and SCA incidence using the fully adjusted model. The AORs assessing the statistical interaction of SCA incidence with the conditional logistic regression analysis are presented in Table 4. SA was a risk factor for SCA, but only in patients without CAD [AOR (95% CI): 1.62 (1.21–2.17)] and not in patients with CAD

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Table 2. Characteristics of the Study Population according to SA

Variables	All (n=1896)	SA (+) (n=322)	SA (-) (n=1574)	*p* value
Case-control				0.037
OHCA case	948 (50.0)	179 (55.6)	769 (48.9)	
Community control	948 (50.0)	143 (44.4)	805 (51.1)	
Age (yr)				<0.001
18–64	1141 (60.2)	220 (68.3)	921 (58.5)	
65–100	755 (39.8)	102 (31.7)	653 (41.5)	
Sex, female	520 (27.4)	49 (15.2)	471 (29.9)	<0.001
Metropolis, yes	964 (72.6)	178 (84.8)	786 (70.1)	0.081
Insurance, medical aid	200 (10.5)	30 (9.3)	170 (10.8)	0.431
Education, high	618 (32.6)	122 (37.9)	496 (31.5)	0.034
Comorbidity				
HTN	772 (40.7)	165 (51.2)	607 (38.6)	<0.001
DM	385 (20.3)	70 (21.7)	315 (20.0)	0.481
Dyslipidemia	352 (18.6)	76 (23.6)	276 (17.5)	0.001
Stroke	106 (5.6)	15 (4.7)	91 (5.8)	0.425
Metabolic disease	71 (3.7)	24 (7.5)	47 (3.0)	<0.001
CAD	142 (7.5)	30 (9.3)	112 (7.1)	0.176
Smoking, yes	1077 (56.8)	222 (68.9)	855 (54.3)	<0.001
Alcohol drinking, yes	1202 (63.4)	224 (69.6)	978 (62.1)	0.011
Physical activity				0.993
Vigorous	344 (18.1)	58 (18.0)	286 (18.2)	
Moderate	512 (27.0)	86 (26.7)	426 (27.1)	
Never	1040 (54.9)	178 (55.3)	862 (54.8)	
Obesity, yes	149 (7.9)	47 (14.6)	102 (6.5)	<0.001
Sleep disorder				
Insomnia	497 (26.2)	108 (33.5)	389 (24.7)	<0.001
Insomnia, medication	88 (4.6)	21 (6.5)	67 (4.3)	0.082
Snoring	1015 (53.5)	310 (96.3)	705 (44.8)	<0.001

SA, sleep apnea; OHCA, out-of-hosptial cardiac arrest; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease.
Data are presented as n (%).

[AOR (95% CI): 0.56 (0.20–1.53)]. Similarly, SA was a risk factor for SCA in the young non-CAD group [AOR (95% CI): 1.76 (1.23–2.52)], and not in the young CAD group [AOR (95% CI): 0.77 (0.18–3.34)]. However, in the older age group, SA was not a risk factor for SCA in the non-CAD and CAD groups.

DISCUSSION

In this prospective multicenter case-control study, we demonstrated the association between SA and SCA according to the presence of CAD. SA was significantly associated with SCA incidence in non-CAD patients; however, SA was not associated with SCA incidence in CAD patients after adjusting for demographic characteristics, comorbidities, and health behaviors. This association was significant in the young but not in the older age group. To our knowledge, this is the first study to show that the impact of SA on SCA is only significant in non-CAD patients.

Table 3. Multivariable Conditional Logistic Regression Analysis of SA and CAD for OHCA

OHCA incidence	OHCA cases	Community controls	Model 1 AOR (95% CI)	Model 2 AOR (95% CI)	Model 3 AOR (95% CI)
SA (-)	769	805	ref.	ref.	ref.
SA (+)	179	143	1.49 (1.21–1.86)	1.54 (1.18–2.01)	1.54 (1.16–2.03)
CAD (-)	837	917	ref.	ref.	ref.
CAD (+)	111	31	3.98 (2.64–6.01)	4.08 (2.64–6.29)	3.94 (2.50–6.18)

SA, sleep apnea; CAD, coronary artery disease; OHCA, out-of-hosptial cardiac arrest; AOR, adjusted odds ratio; CI, confidence interval; ref, reference.
Model 1: adjusted for SA, coronary artery disease, age, sex, and metropolis; Model 2: adjusted for variables of Model 1+hypertension, diabetes mellitus dyslipidemia, stroke, and metabolic disease; Model 3: adjusted for variables of Model 2+education level, smoking, alcohol drinking, physical activity, and obesity.

Table 4. Interaction Analysis for SCA Incidence of SA according to CAD

OHCA incidence	SA (-) AOR	SA (+) AOR (95% CI)	*p* for interaction
Total population			<0.001
CAD (-)	ref.	1.62 (1.21–2.17)	
CAD (+)	ref.	0.56 (0.20–1.53)	
Young age group (18–64 years)			<0.001
CAD (-)	ref.	1.76 (1.23–2.52)	
CAD (+)	ref.	0.77 (0.18–3.34)	
Old age group (65–100 years)			0.118
CAD (-)	ref.	1.34 (0.79–2.30)	
CAD (+)	ref.	0.38 (0.09–1.63)	

SCA, sudden cardiac arrest; SA, sleep apnea; CAD, coronary artry disease; AOR, adjusted odds ratio; CI, confidence interval.

This study contributes to understanding the complex effects of SA and CAD on SCA risk, and will help develop strategies to reduce SCA in the general population.

In a previous multicenter study, patients with SA had a 1.7-fold increased risk of complex ventricular activity and a 3.4-fold increased risk of non-sustained ventricular tachycardia compared to patients without SA.[14] In addition, several other observational studies reported that SA is a risk factor for SCA incidence, similar to the results of this study.[15,16]

There are several possible pathophysiological mechanisms linking SA to SCA. First, the apneic event causes systemic hypoxemia, which is sometimes prolonged and severe. Repeated hypoxia in SA patients causes ventricular ectopy and hypercapnia. In addition, hypoxia activates chemo-reflex, causing increases in vascular sympathetic nerve activity and serum catecholamine levels.[17] Tachycardia and increased blood pressure occur at the end of apnea and increase the myocardial oxygen demand despite the hypoxic state, leading to myocardial ischemia and potential dysrhythmic processes. Second, platelet activation and aggregation and fibrinogen levels are increased

in SA patients, while fibrinolytic activity is decreased, resulting in a paradoxical increase in coagulability.[18] Lastly, although the exact association between autonomic function and SCA remains largely unknown, cardiac autonomic dysfunction may explain the increased risk of SCA in patients.[19-21]

In the interaction analysis of this study, SA did not increase the incidence of SCA in patients with CAD, but it was a significant risk factor for SCA in patients that did not have CAD. These results differ from the general hypothesis that patients with SA and CAD would have increased SCA. The possible mechanism of SA on the incidence of SCA is unknown; however, we hypothesized that SA has a lesser impact on SCA incidence in CAD patients than in non-CAD patients due to pre-existing dysfunctions in CAD patients. In addition, although not analyzed in our study, treatments for CAD may have been considered with concern to SA. Previous studies have reported that SA patients with behavioral therapies or mechanical therapies may decreased the severity of CAD and the incidence of SCA.[22,23] However, further studies on the relationship between SA treatment and incidence of SCA are needed.

The subgroup analysis indicated an association between SA and SCA incidence in the young CAD group; however, SA was not a risk factor for SCA in the groups of patients aged over 65 years, regardless of CAD. A previous study reported that the prevalence of SA increased with age. Additionally, it has been reported that SA has a higher severity with increasing age; and in one study, older patients aged over 70 years had a 22% higher probability of showing a pattern of high severity SA compared to younger patients. Moreover, numerous studies have reported that old age is associated with the occurrence of SCA, as well as poor prognosis.[24,25]

In this study, both SA and CAD increased the incidence of SCA; however, SA was significantly associated with the increased risk of SCA in non-CAD patients. These results suggest that SA patients without pre-existing CAD may be at higher risk for SCA than the average population. This study provides a theoretical basis for the need for early diagnosis and active treatment for SA patients without CAD to lower the risk of SCA.

Our study had several limitations. First, since SA and CAD were determined through a self-report or information obtained from the next of kin, the rates of SA and CAD may be under- or over-estimated. Second, we did not investigate whether the patients were being treated for SA in the registry questionnaire. There may be differences in the effect of SA on SCA risk depending on the type of SA and whether the disease is being treated, and these possible differences may have influenced the results of our study. Third, the causal relationship between SA and CAD is unknown and may have affected the results of this study. Fourth, in our study, for the sake of efficiency and management of control recruitment, only two hospitals (one metropolitan and one non-metropolitan) recruited the control group. Lastly, since this study was not designed as a randomized trial, there may have been a significant potential bias that was not controlled.

In conclusion, in the general population, SA has been shown to increase the incidence of SCA. However, this study only observed this relationship in patients with no history of CAD. Early medical intervention to treat SA, especially for subjects without underlying CAD, may reduce the risk of SCA.

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AUTHOR CONTRIBUTIONS

Conceptualization: Sung Oh Hwang. Data curation: Young Sun Ro and Hyun Ho Ryu. Formal analysis: Kyoung Chul Cha. Funding acquisition: Sung Oh Hwang. Investigation: Eujene Jung and Hyun Ho Ryu. Methodology: Sang Do Shin. Project administration: Hyun Ho Ryu and Sang Do Shin. Resources: Eujene Jung. Software: Eujene Jung and Young Sun Ro. Supervision: Hyun Ho Ryu and Young Sun Ro. Validation: Sung Oh Hwang. Visualization: Eujene Jung. Writing—original draft: Eujene Jung. Writing—review & editing: Hyun Ho Ryu. Approval of final manuscript: all authors.

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