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SCIENTIFIC INVESTIGATIONS

High frequency of coronary artery ectasia in obstructive sleep apnea

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Study Objectives: Patients with obstructive sleep apnea (OSA) have a greater risk of developing coronary artery disease. However, the frequency of specific coronary artery vascular phenotypes, such as coronary artery ectasia (CAE), which has a frequency of 5% in the general population, has not been studied in patients with OSA. This study aimed to estimate CAE frequency in patients with OSA who underwent coronary angiography.

Methods: A retrospective cross-sectional study was performed. The results of each polysomnography were reviewed, classifying OSA severity according to the apnea-hypopnea index. Each coronary angiography was reviewed. CAE was defined and classified according to the scales described in the literature. Two groups of patients were classified and compared (OSA/CAE group vs OSA/non-CAE group).

Results: We identified the frequency of CAE in 185 patients with OSA who underwent coronary angiography. The frequency of CAE was 18.4% in these patients. ST-elevation myocardial infarction as the indication for coronary angiography was significantly greater in the OSA/CAE group than the OSA/non-CAE group (26.5% vs 9.9%; $P = .02$); 62% of the patients having severe OSA (apnea-hypopnea index ≥ 30 events/h). These patients in the OSA/CAE group had a significantly higher median apnea-hypopnea index than in the OSA/non-CAE group (72.5 events/h vs 53.5 events/h, respectively; $P = .039$). The CAE severity was not directly related to the OSA severity.

Conclusions: The frequency of CAE in patients with OSA is higher than that reported for the general population. The severity of OSA is related to the presence of CAE but not to its severity.

Keywords: obstructive sleep apnea, coronary artery ectasia, acute coronary syndrome

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BRIEF SUMMARY

Current Knowledge/Study Rationale: The frequency of specific coronary artery vascular phenotypes, such as coronary artery ectasia, which is reported around 5% in the general population undergoing coronary angiography, has not been studied in patients with obstructive sleep apnea. This study aimed to estimate coronary artery ectasia frequency in patients with obstructive sleep apnea who underwent coronary angiography.

Study Impact: We found a frequency of coronary artery ectasia of 18.4%, which is higher than that reported for the general population.

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by a lack of inspiratory airflow despite respiratory effort due to an upper airway blockage, which causes repetitive apnea episodes. It has been associated with various cardiovascular diseases, including coronary artery disease,[1,2] which has been evaluated using invasive and noninvasive imaging, finding a greater volume and calcification of atherosclerotic plaque.[3] In addition, there is an increase in specific inflammatory molecules.[4]

Elevated levels of these molecules have also been described separately in the pathophysiology of other coronary artery vascular phenotypes, such as coronary artery ectasia (CAE),[5] which is related to slow flow, endothelial injury, and a proinflammatory state that sets up a predisposition to thrombosis and recurrent myocardial ischemic events. Its reported prevalence is less than 5% in general populations undergoing coronary angiography.[6,7] Considering the common inflammatory pathways in OSA and CAE, patients with OSA could have a greater CAE frequency; however, this is unknown. Therefore, we performed this study to estimate the CAE frequency diagnosed by coronary angiography in patients with diagnosed OSA.

METHODS

Study population and design

We identified patients over 18 years old with OSA diagnosed by polysomnography who had undergone coronary angiography from January 2017 to December 2018. Both procedures were performed at the institutions participating in the study (Fundación CardioInfantil Instituto de Cardiología and Fundación Neumológica Colombiana). Patients with a documented history of risk factors for CAE such as Kawasaki disease, Takayasu disease, systemic lupus erythematosus, and Marfan syndrome were excluded.[8] Patients with surgical myocardial revascularization and heart transplants were also excluded. A retrospective cross-sectional study was performed, and the data were recorded on a specific database. The institutional Ethics and Research Committee approved the study protocol.

Assessment of OSA

The results of each polysomnography were reviewed, and the diagnosis of OSA was defined as the presence of signs or symptoms of the disease, plus at least 5 apnea or hypopnea events per hour during the sleep study. The severity of OSA was classified according to the apnea-hypopnea index (AHI: number of apnea or hypopnea events per hour during the sleep study) as follows: mild AHI 5–14 events/h, moderate AHI 15–29 events/h, and severe AHI ≥ 30 events/h.[1,9] The 3% oxygen desaturation index (ODI3%), average oxygen saturation during the respiratory-events, and minimum desaturation recorded during the polysomnography were also reported. These polysomnographies were performed using Alice 6LDx and Alice LE (Philips Respironics, Murrysville, Pennsylvania, United States) or SOMNOscreen Plus (Somnomedics, Coral Gables, Florida, United States) equipment.

Assessment of CAE

Each coronary angiography was reviewed by a clinical cardiologist and an interventional cardiologist. CAE was defined as a dilation greater than 1.5 times the diameter of a normal adjacent vessel and was classified according to the scales described in the literature (**Table 1**).[8]

Objectives

This study aimed to estimate CAE frequency in patients with OSA who underwent coronary angiography in the Interventional Cardiology Department. Other objectives were to describe the clinical, polysomnographic, and angiographic characteristics. Furthermore, we evaluated the differences between patients with OSA and CAE (OSA/CAE group) and patients with OSA without CAE (OSA/non-CAE group). In patients with severe OSA, AHI was evaluated together with its relationship with the presence and severity of CAE. Additionally, an analysis of risks factors related to CAE in the OSA/CAE group was performed.

Statistical analysis

Continuous variables are presented as means and medians with their respective standard deviations, and the rest of the variables are presented as percentages. The comparative analysis of the characteristics of patients with and without CAE was done using Student's *t*-tests or Mann-Whitney *U* tests for continuous variables and ×2 for categorical variables. Dummy variables were created to compare variables with more than 2 categories and perform direct comparisons with Mann-Whitney *U*. A logistic regression model was performed to identify potential risks factors for CAE. A $P < .05$ was statistically significant. The statistical analysis was performed using SPSS software (SPSS Inc., IBM, Chicago, IL).

Table 1—Severity classification of coronary artery ectasia.

	Coronary Artery Ectasia Severity Types
Type I	Diffuse ectasia of 2 or 3 vessels
Type II	Diffuse ectasia of 1 vessel and localized in another vessel
Type III	Diffuse ectasia in 1 vessel
Type IV	Localized ectasia or segmental ectasia

RESULTS

Population characteristics

A total of 185 patients were included. The mean age was 64.6 ± 11.4 years, and most were male (60.5%, n = 112). The average body mass index was 28.7 ± 4.9 kg/m^2, and the most frequent comorbidities were arterial hypertension (62.2%, n = 115), dyslipidemia (56.2%, n = 104), and diabetes mellitus (24.3%, n = 45). According to AHI, 116 patients were classified as having severe OSA (62%). The mean of AHI and ODI3% was 45.4 ± 28 and 47.4 ± 30.1 events/h, respectively. The main indication for performing coronary angiography was the study of chest pain suggestive of coronary disease. Coronary artery disease with greater than 50% stenosis was present in 37.2% (69 out of 185) of the patients. Other characteristics are shown in **Table 2**.

Primary and secondary outcomes

A review of the coronary angiograms showed CAE in 34 patients, a frequency of 18.4%. A comparison of the OSA/CAE and OSA/non-CAE groups showed a significant difference in the rate of arterial hypertension (44% vs 67%, $P = .014$) and the indication for angiography due to ST-elevation myocardial infarction (26.5% vs 9.9%; $P = .02$). The polysomnogram characteristics of both groups were similar, including the severity of OSA (**Table 2** and **Figure 1**). However, an analysis of the AHI in patients with severe OSA (n = 116) revealed that the AHI was significantly higher in patients with CAE (median AHI of 72.5 events/h) than in those without (median AHI 53.5 events/h) ($P = .039$) (**Figure 2**). In the angiographic findings of patients with OSA/CAE, the most frequently affected artery was the right coronary in 29 cases (85.3%), and in terms of severity classification, the most frequent types were types I and II, in equal proportion (**Table 3**). No significant relationship was found between the AHI and the degree of severity of CAE ($P = .343$) (**Figure 3**), neither a significant relationship with any other desaturation index. In the regression models, we found that arterial hypertension (odds ratio:2.4; 95% confidence interval: 1.10–5.22, $P = .02$), AHI (odds ratio: 1.02; 95% confidence interval: 1.00–1.04, $P = .02$), and ODI (odds ratio: 0.98; 95% confidence interval: 0.95–1.01, $P = .06$) are potential risk factors for CAE in OSA/CAE group. However, only arterial hypertension and AHI were statistically significant, and the effect size was small (Nagelkerke R^2 value of .095).

DISCUSSION

The frequency of CAE in patients with OSA diagnosed by polysomnography was 18.4%. That is a higher percentage than the frequency of CAE reported in individuals undergoing coronary angiography, which is 1.2–4.9%.[10–12] This finding could be explained by increased proinflammatory activity in patients

Table 2—Clinical, polysomnographic, and angiographic characteristics.

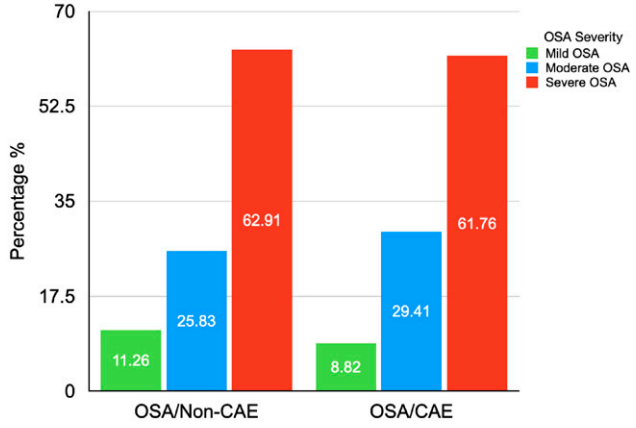
	Total (n = 185)	OSA/CAE (n = 34)	OSA/Non-CAE (n = 151)	*P*
Clinical characteristics				
Age (mean ± SD), y	64.65 ± 11.46	65.13 ± 11.12	62.50 ± 12.81	.227
Male, n (%)	112 (60.5)	22 (64,7)	90 (59.6)	.364
BMI (mean ± SD), kg/m^2	28.78 ± 4.9	29.20 ± 4.65	28.68 ± 4.97	.578
HTN,‡ n (%)	115 (62,2)	15 (44.1)	100 (66.7)	.014
Diabetes mellitus, n (%)	45 (24.3)	5 (14.7)	40 (26.7)	.143
Dyslipidemia, n (%)	104 (56.2)	18 (52.9)	86 (57.3)	.641
History of smoking, n (%)				.367
Active smoker	14 (7.6)	4 (11.8)	10 (6.7)	
Ex-smoker	53 (28.6)	8 (23.5)	45 (30)	
LVEF, % (mean ± SD)	49.25 ± 11.81	49.94 ± 10.01	49.09 ± 12.21	.707
Creatinine clearance (mean ± SD), mL/kg/1.73 m^2	89.31 ± 23.44	93.75 ± 16.24	88.27 ± 24.76	.144
Indication for coronary angiography, n (%)				
Chest pain	73 (39.5)	9 (26.5)	64 (42.4)	.128
NSTEMI	27 (14.6)	8 (23.5)	19 (12.6)	.103
STEMI†	24 (13)	9 (26.5)	15 (9.9)	.021
Other indication	61 (33)	8 (23.5)	53 (35.1)	.274
Polysomnographic characteristics				
AHI (mean ± SD), events/h	45.46 ± 28.48	50.78 ± 32.60	44.36 ± 27.45	.229
ODI (mean ± SD), events/h	47.49 ± 30.19	48.28 ± 35.23	47.33 ± 29.20	.878
ODI ≥ 30, n (%)	110 (59.5)	17 (58.6)	93 (65.5)	.526
Minimum O_2 desaturation (mean ± SD), %	71.66 ± 10.9	71.93 ± 11.75	71.61 ± 10.76	.885
Average O_2 desaturation (mean ± SD), %	81.86 ± 6.00	82.31 ± 5.75	81.77 ± 6.07	.660
Angiographic characteristics				
% Stenosis of the coronary artery disease, n (%)				
Without coronary stenosis	89 (48.1)	13 (38.2)	75 (49.7)	.202
Coronary stenosis < 50%	27 (14.6)	7 (20.6)	20 (13.2)	.273
50–70% stenosis	5 (2.7)	1 (2.9)	4 (2.6)	.642
71–99% stenosis	36 (19.5)	9 (26.5)	27 (17.9)	.253
Total occlusion	28 (15.1)	4 (11.8)	24 (15.9)	.544

‡Significantly lower rate of arterial hypertension in the OSA/CAE group than the OSA/non-CEA group (*P* = .014). †Indication of coronary angiography due to ST-elevation myocardial infarction is significantly more frequent in the OSA/CAE group than in the OSA/non-CAE group (*P* = .02). AHI = apnea-hypopnea index, BMI = body mass index, HTN = hypertension, LVEF = left ventricular ejection fraction, NSTEMI = non-ST elevation myocardial infarction, ODI = oxygen desaturation index, STEMI = ST-elevation myocardial infarction.

with OSA, who have elevated tumor necrosis factor-alpha, interleukin-6, and C-reactive protein;[13,14] inflammatory molecules also elevated in CAE.[15] Moreover, increased levels of adhesion molecules such as intercellular adhesion molecule-1, vascular cell adhesion molecule, and E-selectin have been found in patients with OSA and obstructive coronary artery disease, as well as in CAE. These adhesion molecules mediate cellular interactions and leukocyte transmigration across the endothelial wall, contributing to atherogenesis in the coronary vessels.[16,17] Our results could serve as hypotheses for future studies to examine this pathophysiological relationship. Additionally, the increased negative intrathoracic pressure in OSA has been associated as a pathological mechanism by which the aortic root is dilated during the increased systolic pressure in apneic episodes with a direct relationship between its diameter and the OSA severity.[18] Therefore, this mechanism could likewise be triggered in the coronary arteries, leading to CAE development (**Figure 2**).

In patients with severe OSA, a higher AHI was associated with a higher proportion of CAE, similar to the results described in another study in which patients with an AHI ≥ 30 events/h had a greater probability of developing coronary artery disease (68%). However, in this study, coronary artery disease was defined as a first myocardial infarction, death due to coronary disease, or revascularization,[19] but without a precise description of the coronary artery angiographic findings

Figure 1—Distribution of OSA severity in OSA/non-CAE and OSA/CAE groups.



CAE = coronary artery ectasia, OSA = obstructive sleep apnea.

which led to these outcomes, and without being able to determine if the CAE could be related to these results. Other studies have found a direct relationship between the ODI3% severity and the severity and progression of obstructive atherosclerotic coronary disease; however, the presence of CAE was not evaluated.[20,21] We do not find a significant difference between the severity of ODI3% and the presence or severity of CAE, probably by missing data in 14.7% of patients with CAE.

Although our study did not find OSA severity to be directly related to the severity of CAE, this would need to be confirmed in more extensive prospective studies in which the duration of OSA, as well as the beginning of and adherence to positive pressure treatment, be recorded, considering these factors could affect this relationship. Significant obstructive atherosclerotic coronary disease (> 50% stenosis) was found in 41.2% of the patients in the OSA/CAE group, contrary to previous studies in patients with CAE in which this percentage has been reported in up to 87%.[12] This result could be influenced by the number of patients in our study.

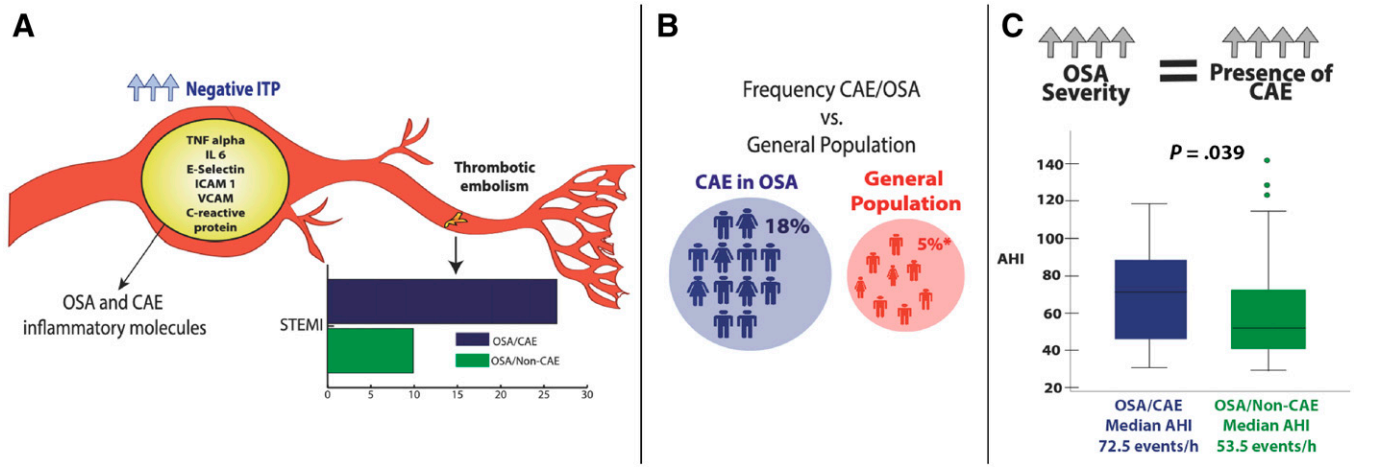
Two significant differences in the characteristics of the study population were found between the groups. First, arterial hypertension was less frequent in the OSA/CAE group (44.1%) than in the OSA/non-CAE group (66.7%), Nevertheless, the percentage of patients with arterial hypertension in the whole group of patients is similar to other studies of patients with OSA.[22,23] The second difference between the groups was the indication for coronary angiography, with ST-elevation myocardial infarction being significantly more frequent in patients with CAE. This result could be related to in situ thromboses and distal embolization, which can occur in patients with CAE.[6,7]

The coronary artery most frequently affected with ectasia was the right coronary artery, which agrees with other studies[7,12] but contrasts with recent reports in the literature in which the left anterior descending artery was the most common.[24]

Through an exploratory analysis using a logistic regression model, we found that hypertension and AHI are potential explanatory variables for CAE in OSA/CAE group. Hypertension could increase the risk of CAE twice in patients with OSA. Since this study was not designed for this aim, these results should be interpreted with caution. Further studies are warranted to assess the clinical impact of these factors in predicting CAE in patients with OSA.

Our study is the first to report the frequency of CAE in a population with OSA, with a rigorous evaluation including both polysomnography and coronary angiography, in addition to finding a

Figure 2—Common inflammatory molecules, frequency, and AHI in OSA and CAE.



(A) Common inflammatory molecules in OSA and CAE. Increased negative ITP is a possible mechanism related to CAE. In situ thrombosis or embolization in the OSA/CAE group; possible explanation of the greater percentage of STEMI. †P = .02. **(B)** Comparison of the reported frequency of CAE in our OSA population and the frequency in general populations (*percentage of CAE reported in unspecific populations undergoing coronary angiography). **(C)** AHI medians in patients with severe OSA (AHI > 30 events/h). The OSA/CAE group has a higher median AHI than the OSA/non-CAE group. AHI = apnea-hypopnea index, CAE = coronary artery ectasia, ICAM 1 = intercellular adhesion molecule-1, IL 6 = interleukin-6, ITP = intrathoracic pressure, OSA = obstructive sleep apnea, STEMI = ST-elevation myocardial infarction, TNF alpha = tumor necrosis factor-alpha, VCAM = vascular cell adhesion molecule.

Table 3—Angiographic characteristics of patients with CAE (n = 34).

	n (%)
CAE	
Left main	3 (8.8)
Left anterior descending	17 (50)
Circumflex	11 (32.4)
Right coronary	29 (85.3)
Severity classification of CAE	
Type I	10 (29.4)
Type II	10 (29.4)
Type III	9 (26.5)
Type IV	5 (14.7)

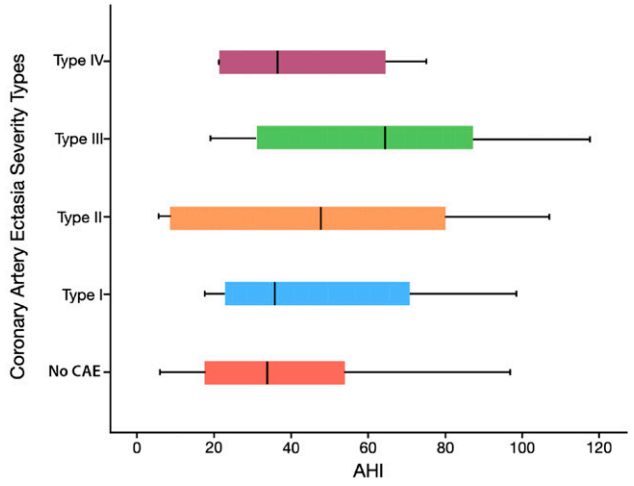
CAE = coronary artery ectasia.

greater frequency of CAE than that reported in the literature in individuals undergoing coronary angiography.[6,7,10–12] We understand the study's limitations, such as its retrospective design and not having a control group of patients with normal polysomnography undergoing coronary angiography. Moreover, a possible selection bias in having a majority of patients with severe OSA (62.7%), a limited number of patients with OSA and CAE, as well as the fact that it was carried out at a single institution, factors that avoid its results from being generalized; however, it does allow several hypotheses to be proposed for future studies.

CONCLUSIONS

The frequency of CAE in patients with OSA is greater than that reported in individuals undergoing coronary angiography. The indication for coronary angiography due to ST-elevation myocardial infarction was more frequent in patients with OSA and CAE than in patients without CAE. The severity of OSA is significantly related to the presence of CAE but is not directly related to its severity.

Figure 3—Distribution of AHI according to CAE severity.



P = .343. AHI = apnea-hypopnea index, CAE = coronary artery ectasia.

ABBREVIATIONS

AHI, apnea-hypopnea index
CAE, coronary artery ectasia
ODI, oxygen desaturation index
OSA, obstructive sleep apnea

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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Work for this study was performed at Fundación Cardioinfantil–Instituto de Cardiología and Fundación Neumológica Colombiana, Bogota, Colombia. The authors report no conflicts of interest.