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The coexistence of obstructive sleep apnea in patients with slow coronary flow: a cross-sectional study

Koroner yavaş akım hastalarında obstrüktif uyku apnesi birlikteliği: kesitsel bir çalışma

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ABSTRACT

Aim: Interestingly, obstructive sleep apnea and coronary slow-flow have similar pathogenic mechanisms, including increased sympathetic activity and endothelial dysfunction. However, the association between obstructive sleep apnea and coronary slow-flow is not known well. If undiagnosed, obstructive sleep apnea is a cause of increased cardiovascular morbidity and mortality. In this study, we investigated the presence of obstructive sleep apnea in the patients diagnosed coronary slow-flow after coronary angiography.

Material and Method: The prospective cross-sectional study included 4515 patients admitted angiography laboratory from February 2018 to December 2019. After coronary angiography of 4515 patients, 336 patients were diagnosed as slow coronary flow. These patients were examined by pulmonology and sleep specialist. Of the 336 patients, 276 patients were found high risk in terms of obstructive sleep apnea by using Berlin questionnaire. Only 75 of 276 patients underwent polysomnography testing. Control group patients (n=40) had normal coronary artery and no obstructive sleep apnea.

Results: Of 4515 patients, 336 (7.4%) met the criteria for coronary slow-flow. After Berlin questionnaire, 276 of 336 patients had high-score Berlin questionnaire (82.1%). The study group consisted of 276 patients (188 males, 88 females). The mean ages of the study group were 48.48±7.61 years. Body mass index according to WHO criteria was 33.02±2.18 kg/m^2. When 75 patients underwent polysomnography were divided on two groups as mild obstructive sleep apnea and moderate/severe obstructive sleep apnea according to respiratory disturbance index. We found a significant positive correlation between mean corrected TIMI frame countand respiratory disturbance index. While corrected TIMI frame count-Lad in mild obstructive sleep apnea group was 32.73, corrected TIMI frame count-Lad in moderate/severe obstructive sleep apnea group was 35.04 (p=0.022). While corrected TIMI frame count-Cxin mild obstructive sleep apnea group was 31.67, corrected TIMI frame count-Cx in moderate/severe obstructive sleep apnea group was 35.26 (p=0.001). While corrected TIMI frame count-Rca in mild obstructive sleep apnea group was 32.57, corrected TIMI frame count-Rca in moderate/severe obstructive sleep apnea group was 36.33 (p<0.001).

Conclusion: This study revealed the coexistence between coronary slow-flow and obstructive sleep apnea. Moreover, we demonstrated a significant relationship between mean corrected TIMI frame count and respiratory disturbance index. Determining the clinical association of obstructive sleep apnea and coronary slow-flow may be help to understand pathophysiology of coronary slow-flow.

Keywords: Coronary slow-flow; Obstructive sleep apnea; polysomnography

ÖZ

Amaç: Obstrüktif uyku apnesi ve koroner yavaş akımilginç olarak artmış sempatik aktivite ve endotelyaldisfonksiyon gibi benzer patolojik mekanizmalara sahiptir. Fakatobstrüktif uyku apnesive koroner yavaş akım arasındaki birliktelik çok iyi bilinmemektedir. Eğer tanı konmazsa, obstrüktif uyku apnesi artmış kardiyovasküle rmortalite ve morbidite nedenlerinden biridir. Biz bu çalışmada koroner anjiyografi sonrası koroner yavaş akım tanısı almış hastalarda obstrüktif uyku apnesi varlığını araştırdık.

Gereç ve Yöntem: Bu prospektif kesitsel çalışma Şubat 2018-Aralık 2019 yılları arası anjiyografiye alınan 4515 hastayı kapsamaktadır. Koroner anjiyografi sonrası 4515 hastanın 336'sına koroner yavaş akım tanısı konmuştur. Bu 336 hastanın 276'sı Berlin anket bulgularına göre yüksek riskli olarak bulunmuştur. Çalışma grubu 276 hastadan oluşmaktaydı. Bu hastalardan 75 ine polisomnografi testi yapılmıştır. Kontrol grubu (40 hasta) normal koroner arterli ve obstrüktif uyku apnesiolmayan hastalardı.

Bulgular: 4515 hastanın 336'sı koroner yavaş akım tanısı almıştı (%7,4). Berlin anket çalışması sonrası 336 hastanın 276'sı yüksek risk grubu idi (%82,1). Çalışma grubu 188 erkek, 88 kadından oluşmaktaydı (toplam 276 hasta). Ortalama yaş 48,48±7,61 yıl idi. Vücut kitle indeksi 33,02±2,18 kg/m^2 idi. Polisomnografi yapılan 75 hasta solunum bozukluk indeksine göre hafif ve orta/ağır derece olarak iki gruba ayrılmıştır. Biz solunum bozukluk indeksi ve düzeltilmiş TIMI sayımı arasında pozitif ilişki saptadık. Hafif grupta düzeltilmiş TIMI sayımı-Laddeğeri 32,73, orta/ağır grupta düzeltilmiş TIMI sayımı-Lad değeri 35,04 (p=0,022). Hafif grupta düzeltilmiş TIMI sayımı-Cx değeri 31,67, orta/ağır grupta düzeltilmiş TIMI sayımı-Cx değeri 35,26 (p=0,001). Hafif grupta düzeltilmiş TIMI sayımı-Rca değeri 32,57, orta/ağır düzeltilmiş TIMI sayımı-Rca değeri 36,33 (p<0,001).

Sonuç: Bu çalışma obstrüktif uyku apnesi ve koroner yavaş akım arasında birliktelik olduğunu ortaya koymuştur. İlave olarak biz solunum bozukluk indeksi ile ortalama düzeltilmiş TIMI sayımı arasında anlamlı ilişkiyi gösterdik. Obstrüktif uyku apnesive koroner yavaş akım birlikteliğinin saptanması koroner yavaş akımın patofizyolojisini anlamada yardımcı olabilir.

Anahtar Kelimeler: Koroner yavaş akım, obstrüktif uyku apnesi, polisomnografi

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INTRODUCTION

Coronary slow-flow phenomenon (CSF) was defined as delayed distal opacification of the coronary artery without significant coronary artery disease (1,2).The clinical presentation of CSF has a varied presentation from mild chest discomfort to ST-segment elevation myocardial infarction (3). On the other hand, obstructive sleep apnea (OSA) has defined as decreased airflow due to repetitive complete or partial obstruction of the upper airway associated with progressive respiratory effort to overcome the obstruction (4). If untreated, OSA cause increased cardiovascular morbidity and mortality. Unfortunately, population-based studies estimate that 90% of cases OSA in the communities of advanced economies remain undiagnosed and untreated (5,6).

Both OSA and CSF have similar pathogenic mechanisms, such as chronic sympathetic activation, upregulation of inflammatory pathways, oxidative stress, and endothelial dysfunction (7, 8). However, importance true coincidence and of CSF and OSA is not known very well. In this study, we examined the presence of OSA by using the Berlin questionnaire (BQ) (9) and polysomnography (PSG) testing in the patients diagnosed CSF after coronary angiography.

MATERIAL AND METHOD

This prospective cross-sectional study included 4515 patients admittedangiography laboratory because of possible coronary artery disease in between February 2018 to December 2019. The indication for coronary angiography was the presence of angina or dyspnea with a high-risk non-invasive test. All patients were informed and a written informed consent was obtained from each patient. The study was approved by Medicana International Ankara Hospital Human Research Ethic Committee (2018/1). The study was conducted in accordance with the principles of Declaration of Helsinki.

Of the patients, 336 patients were diagnosed CSF in coronary angiography. The patients withCSF were examined by pulmonology and sleep specialist. After then, 276 of the 336 patients were foundhigh risk according to BQ. The study group consisted of 276 patients. Only 75of 276 patients underwent polysomnography (PSG) testing because of technical and cost problems.

The demographic data, clinical histories, atherosclerosis risk factors, and laboratory and angiographic findings of all CSF were collected. CSF was diagnosed based on the TFC (2).

The exclusion criteria were valvular heart disease (more than mild), ventricular dysfunction pulmonary arterial hypertension (pulmonary artery systolic pressure above 25 mm Hg in transthoracic echocardiography),coronary slow flow secondary to coronary ectasia or spasm, connective tissue disorders, presence of congenital heart anomalies, heart rhythm disorders other than sinus tachycardia, and acute coronary syndrome.

Control group patients (n=40) had normal coronary artery, which was no slow coronary flow, no OSA. Of the patients, five patients underwent PSG.

Coronary Angiography, CTFC Slow Coronary Flow

Standard left and right coronary angiography was performed in all case and control patients via the femoral approach, using Judkins catheters. The angiograms were assessed, and coronary flow quantification was performed using the corrected TFC method (CTFC) described by Gibson et al. (2). The assessment was performed by an expert interventional cardiologist who was blinded to the clinical details of the study population. The first frame was defined as the first frame in which dye completely filled the entrance of the artery with antegrade flow, and the last frame was defined as the frame in which dye entered the distal landmark branch. After then, the values CTFC method described by Gibson et al. (2) were obtained. The frame counts in the LAD were divided by 1.7 to correct for the increased length. The diagnosis of SCF was defined as CTFC >27 frames (images acquired @30 frames/s) and the delayed distal vessel opacification is in at least one epicardial vessel (2).

Berlin Questionnaire And Polysomnography

The Berlin questionnaire (BQ) includes questions about snoring, daytime somnolence, body mass index (BMI), and hypertension, is a brief and validated screening tool that identifies persons in the community who are at high risk for OSA. According to BQ, the patients were recorded as being at high-risk for OSA if they had a positive score on two or more categories(9).

According to International Classification of Sleep Disorders (ICSD)-3 (10), the diagnosis of OSA needs PSG-determined obstructive respiratory disturbance index (RDI) ≥5 events/h associated with the typical symptoms of OSA (unrefreshing sleep, daytime sleepiness, fatigue or insomnia, awakening with a gasping or choking sensation, loud snoring, or witnessed apneas), or an obstructive RDI ≥15 events/h (even in the absence of symptoms).

According to American Academy of Sleep Medicine (AASM) guidelines, the "Practice Parameters for the Indications for Polysomnography and Related Procedures: An Update for 2005, the apnea-hypopnea index (AHI) cutoff was accepted as ≥5 events/h of OSA diagnosis. OSA was defined as mild 5≤ AHI <15 events/h; moderate 15≤ AHI <30 events/h; severe ≥30 events/h (11).

We classified OSA definition as mild 5≤ RDI <15 events/h; moderate 15≤ RDI<30 events/h; severe ≥30 RDI events/h.

Statistical Analysis

The quantitative distribution of returned questionnaires, individual patient variables, and results of polysomnography testing were expressed by descriptive statistics (frequencies, means and standard deviations, and range). The comparison of CTFC features, body mass indexes, and age of study group with control group were evaluated using the chi-square test.Chi-square test was used to assess the between relationship RDI and CTFC. A p value <0.05 was used to determine statistical significance.

RESULTS

Of 4515 patients, 336 (7.4%) met the criteria for CSF (**Figure 1**). After BQ, 276 patients had high-score BQ (82.1%). These 276 patients were evaluated.Of 276 patients had 188 males (68%). The meanages were 48.48±7.61 years.Body mass index (BMI, (kg/m2) according to WHO criteria (14) was 33.02±2.18 kg/m2.CTFC in CSF group were LAD 33.85±3.66, LCX 33.71±4.56, and RCA34.31±4.04. CTFC values were compared with control group (no slow coronary flow patients, n=40). In control group, CTFC values were LAD 23.83±1.80, LCX 20.83±2.51, RCA 21.75±2.86 (p<0.05). Demographic data in 276 CSF subjects were presented in **Table 1**.

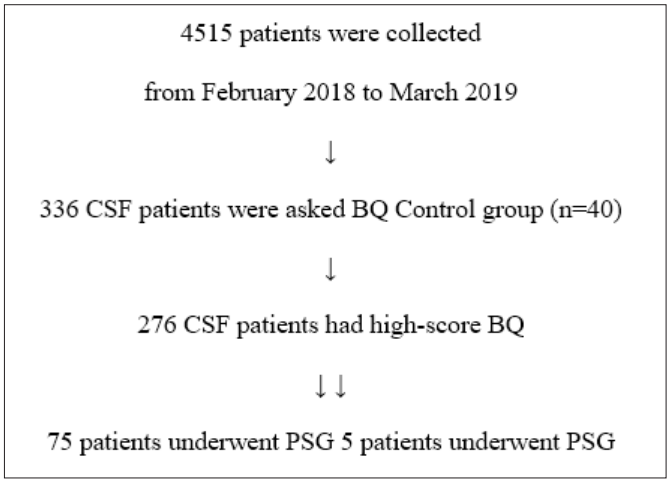

Figure 1. Flow chart of OSA patients and control patients screening in the study
CSF: Coronary slow flow patients group, OSA positive, Control group: Normal coronary artery group, OSA negative

Table 1. Baseline characteristics of 276 patients with slow coronary flow (CSF)

	X±SD	%
Age (years)	48.42±7.65	
Men (gender)	188	68
Women (gender)	88	32
Hypertension	118	42.7
Diabetes Mellitus	27	7.5
BMI (kg/m^2)	33.02±2.18	

In **Table 2** the relationship between angiographic CTFC features, body mass index, and age of study group (SCF (+), OSA (+)) with control group (SCF (-), OSA (-) were compared.

Table 2. The comparison of Angiographic Corrected TIMI frame count features, BMI and age of study group (SCF (+), OSA (+)) with control group (SCF (-), OSA (-))

	Study group (n=276)	Control group (n=40)	p
LAD ctfc	33.85±3.66	23.83±1.80	<0.001
LCX ctfc	33.71±4.56	20.83±2.51	<0.001
RCA ctfc	34.31±4.04	21.75±2.86	<0.001
BMI	33.02±2.18	27.12±2.16	<0.001
Age	48.42±7.65	48.05±7.07	>0.05
BQ scores	276/336	5/40	<0.001

SCF: Slow Coronary Flow, OSA: Obstructive Sleep Apnea, LAD: Left Anterior Descending Artery, LCX: Left Circumflex Artery, RCA: Right Coronary Artery, CTFC: Corrected TIMI Frame Count, TIMI: Thrombolysis in Myocardial Infarction, BMI: Body Mass Index, BQ score: Berlin questionnaire scores

Berlin Questionnaire Scores

The BQ includes questions about snoring (category 1), daytime somnolence (category 2), and hypertension or BMI>30 kg/m2 (category 3). Patients were scored as being at high-risk for OSA if they had a positive score on two or more categories. Of 276 high-risk patients, 155 (56.1%) had a positive score in category 1 of the BQ, 165 (59.7%) had a positive score in category 2, and 195 (70.6%) had a positive score in category 3.

Polysomnography Results

Of 276 patients, 75 patients underwent PSG testing. In PSG testing RDI results, while 48 patients (mild OSA) had 11.85±4.29 events/h, 27 patients (moderate and severe OSA) had 26.88±3.99 (Minimum17 events/h–maximum 84.3 events/h). Minimum oxygen saturation (min SaO_2) was 83.78±4.02 (**Table 3**).

Table 3. The findings of polysomnography and CTFC of 75 patients with CSF patients

	RDI index (/h)
Mild (48 patients)	11.85±4.29
Moderate and severe (27 patients)	26.88±3.99
CTFC lad	32.25±5.04
CTFC Cx	31.65±6.40
CTFC rca	32.30±6.04
SaO_2 minimum	83.78±4.02

SaO_2= Oxygen saturation CTFC: Corrected TIMI Frame Count, RDI index=Respiratory disturbance index

In 75 patients underwent PSG testing, CTFC-Lad was 32.25±5.04, CTFC-Cx was 31.65±6.40, and CTFC-Rca was 32.30±6.04. When these 75 patients were divided on two groups as mild OSA and moderate/severe OSA, there was a statistically significant difference in CTFC between the groups (**Table 4**). We found a significant positive correlation between mean CTFC and RD index.

While CTFC-Ladin mild OSA group was 32.73, CTFC-Lad in moderate/severe OSA group was 35.04 (p=0.022). While CTFC-Cxin mild OSA group was 31.67, CTFC-Cx in moderate/severe OSA group was 35.26 (p=0.001). While CTFC-Rca in mild OSA group was 32.57, CTFC-Rca in moderate/severe OSA group was 36.33 (p<0.001).

Table 4. CTFC comparison in mild OSA (<15 events/h) and moderate-severe (≥15 events /h) (mild 48, moderate and severe 27 patients) according to Respiratory disturbance index

	RDI	N	Mean	t	P
CTFC lad	mild	48	32.73	-2.36	0.022
	moderate and severe	27	35.04		
CTFC Cx	mild	48	31.67	-3.47	0.001
	moderate and severe	27	35.26		
CTFC rca	mild	48	32.57	-4.07	<0.0001
	moderate and severe	27	36.33		

RDI = Respiratory disturbance index, CTFC: Corrected TIMI Frame Count

DISCUSSION

Although no pathologic mechanism of CSF under¬stand completely, CSF is associated with causes such as inflammation, small vessel disease, endothelial dysfunction, and impaired glucose tolerance (12). Moreover, the patients with SCF concomitant a high incidence of metabolic syndrome which leads to development of coronary microvascular dysfunction (13). Endothelin-1 (ET-1) levels were found high in patients with SCF (14). In addition, the level of C-reactive protein is significantly higher in SCF patients (15). Moreover, hypoxemia stimulates chemoreflex stimulation, which causesympathetic activation and vasoconstriction(16). The chemoreflex responses to hypoxemia are heightened in patients with OSA.There are very high levels of sympathetic activation in the patients with OSA during normoxic daytime wakefulness(17).

The pathogenic mechanisms, such as chronic sympathetic activation, upregulation of inflammatory pathways, oxidative stress, and endothelial dysfunction have seen both OSA and CSF. Therefore, to expect the association between OSA and CSF could not amazing.

Polysomnography is the gold standard test for diagnosing OSA, but given the expense, time-consumption (18). Berlin questionnaires was found to have a high sensitivity for OSA (proportion of patients with OSA who screen positive) (19). The high-risk group have a sensitivity of 0.86, a specificity of 0.77, a positive predictive value of 0.89 for predicted OSA (9). Therefore, BQ is a bedside and validated screening tool that identifies persons in the community who are at high risk for OSA.

Yumino et al. (20) showed that the prevalence of OSA was 57% in acute coronary syndromes. Lee et al. (24) reported that 65.7% of patients presenting with ST-segment elevation myocardial infarction had undiagnosed OSA. Moreover, the present study had no patients with acute coronary syndromes. According to our results, 276 out of 336 (82.1%) CSF patients were high risk of OSA due to BQ.Moreover, it has been known that there are ethnic differences in the prevalence and severity of OSA (21).

Body mass index and gender are important factor to interpreting the OSA study. It has been confirmed increase in the prevalence of OSA with any increase in measures of BMI (21). Hence, there may need to adjust the BMI factor to exclude the possible confounder in OSA studies. However, in our study, BMI was 33.02±2.18 kg/m2. Besides, the prevalence of OSA is only 1.5–3 times higher in men than women (20).The present study patients had 188 males (68%).These results were well-matched with other studies.

Present study established that OSA couldassociated with CSF pattern.When the patients were divided on two groups as mild OSA and moderate/severe OSA, there was a statistically significant difference in CTFC between the groups according to OSA events/h. We found a significant positive correlation between mean CTFC and RD index. Therefore, the patients with CSF should be questioned about OSA.

To know association of OSA and CSF may be contribute to understand pathophysiology of CSF. OSA may perhaps trigger the pathways leading to CSF or CSF can contribute to OSA morbidity-mortality). Hence, the presence of OSA might take into consideration in the therapeutic approach to CSF.

Limitations: Only 75 of 276 patients underwent PSG testing due to technical and cost problems.

CONCLUSION

We demonstrated associated with coronary CSF and OSA via the usage of BQ and polysomnography. Moreover, we found a significant relationship between mean CTFC and RDI.Determining the clinical association of OSA and CSF may be contribute to understand pathophysiology of CSF and common pathway OSA together CSF. However, more large prospective controlled studies using PSG and CSF are required to further evaluate the relationship between OSA and CS.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Medicana International Ankara Hospital Human Research Ethic Committee (2018/1).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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