Sleep Breath (2012) 16:695–701
DOI 10.1007/s11325-011-0559-0

ORIGINAL ARTICLE

Sleep apnea is a stronger predictor for coronary heart disease than traditional risk factors

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Received: 24 January 2011 / Revised: 26 April 2011 / Accepted: 6 July 2011 / Published online: 28 July 2011

Abstract
Background Sleep apnea (SA) may be linked to coronary artery disease (CAD). Both conditions have similar risk factors, confounding the analyses. Investigation of the lipid profile is routine in the adult population, even without symptoms or suspected cardiac ailment. SA, however, remains underdiagnosed even in the presence of unambiguous clinical manifestations.
Purpose The aim of this study was to verify the association between SA and CAD, adjusting for usual CAD risk factors.
Methods Patients who underwent diagnostic or therapeutic coronariography and portable type III polysomnography were studied. The severity of SA was determined by the apnea–hypopnea index (AHI). We measured classic CAD risk factors: fasting glucose; total, HDL, and LDL cholesterols; triglycerides; uric acid, and high-sensitivity C-reactive protein. We excluded patients older than 65 years, with body mass index higher than 40 kg/m^2, with diabetes, and with history of smoking in the last year.
Results Of 55 included patients, 28 had AHI>14, showing an odds ratio of 8.7 for CAD. Patients without (n=29) and with CAD (n=26), showed AHI of, respectively, 11±11 and 23±14 per hour (P=0.001). In a binary logistic regression to predict CAD, controlling for all the above risk factors, the only variables entered in the stepwise model were AHI (either as continuous or categorical variable) and uric acid.
Conclusion In a sample without smokers, morbidly obese, or diabetic patients, AHI is the main predictor of CAD. SA should integrate the set of risk factors routinely assessed in clinical investigation for coronary disease risk stratification.

Keywords Sleep apnea · Coronary artery disease · Cardiovascular disease · Coronary angiography · Angina · Polysomnography

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Introduction

Sleep apnea (SA), a relevant public health problem, is characterized by recurrent complete or partial upper airway obstruction during sleep. Each apneic episode leads to oxygen desaturation and arousal. Common consequences are daytime sleepiness and cardiovascular diseases [1, 2].

SA is associated with hypertension, coronary artery disease (CAD), heart failure, cardiac arrhythmias, reduced heart rate variability, atrial fibrillation, stroke, and sudden death [3–10]. The pathophysiological basis for the relationship between SA and CAD may be similar to that described for the SA–hypertension relationship [11].

While the possibility of SA as a causal mechanism in chronic cardiovascular disease is attractive, this relationship remains unclear. Gottlieb et al. failed to demonstrate a clear association between SA and incident CAD in 4,422 subjects of the Sleep Heart Health Study cohort [12]. Peker et al., in 62 patients, after controlling for age, gender, and body mass index (BMI), and adjusting for traditional risk factors, concluded that SA, current smoking, and diabetes mellitus were independently associated with CAD, while hypertension and hypercholesterolemia were not [13]. Considering that smoking and diabetes are powerful coronary aggressors, we hypothesized that excluding these factors would make the effect of hypertension and dyslipidemia more evident. The present study aims to verify the relationship between SA and CAD, controlling for the usual biochemical risk factors, but excluding cases with major well-established risk factors.

Methods

Patients

This is a secondary analysis of a sample screened to study oxidative stress in SA and CAD [14]. The study was performed at the catheterization laboratory, Division of Cardiology of our Institution, conducted between March 2007 and February 2008. Flow diagram of subject recruitment is displayed in Fig. 1. Consecutive patients complaining angina, between 35 and 65 years of age, were referred by their physicians for diagnostic coronary angiography. The exclusion criteria were smoking in the last year, clinical diagnosis of diabetes mellitus, BMI>40 kg/m^2; any physical, psychological, or social issue encumbering the attainment of the home polysomnographic test, and previous coronary intervention (myocardial revascularization or angioplasty). A full medical history was taken from all study participants. Dyslipidemia was diagnosed when cholesterol levels were greater than 200 mg/dL or the patient was under statin therapy. Hypertension was defined based on patients' reports. BMI was calculated as weight divided by height squared (kilograms per square meter). Subjects signed written informed consent forms, and the protocol was approved by the Institutional Ethics Committee.

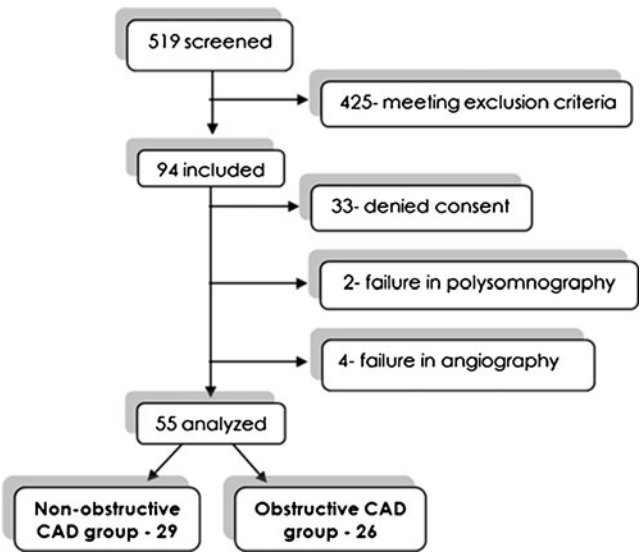

Fig. 1 Flow diagram of subject recruitment

Laboratory measurements

Blood collection

In the morning, 18-mL arterial blood samples were collected from each patient, fasted for at least 8 h, at the site of femoral artery puncture for catheterization. Blood was collected in three vials, containing coagulation activator, EDTA, or citrate. Immediately after the collection, the samples were refrigerated, centrifuged at 0°C for 10 min, aliquoted, and stored at −80°C. Hemolysates were prepared by lysing red blood cell with ethanol 2% (ratio 1:10) followed by centrifugation to obtain crude extracts. Total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, dyslipidemia, uric acid, high-sensitivity C-reactive protein (hs-CRP), and fasting glucose were measured in the routine clinical analysis laboratory.

Sleep study

The volunteers underwent portable polysomnography using a level III monitor (SomnoCheck, Weinmann, Germany), a procedure previously validated by our group [15]. In brief, air flow and snoring were detected through a nasal cannula connected to a pressure transducer; additionally, ventilatory effort, pulse oximetry, heart rate, and sleep position were evaluated. The recordings were made at the patient's home, usually between 11 PM and 7 AM. The respiratory analyses of the polysomnography records were made by one board-certified sleep specialist in a different location, blind to the catheterization results.

Apneas were defined as airflow reduction to 10% or less of the baseline value for 10 s or more; hypopneas as airflow reduction of 50% or more, associated with at least 3% oxygen desaturation and/or autonomic arousal evidenced by an increase in heart rate greater than five beats per minute [16]. The severity of SA was assessed by the AHI, calculated by dividing the number of apneas and hypopneas by the number of hours of artifact-free recording.

Coronary angiography study

All patients were assessed by quantitative angiography, using the same equipment (SIEMENS D40) and projections, with the table and image intensifier kept at constant height. Image quantification was carried out in all cases by the same investigator, who was blinded to laboratory and polysomnography results. A magnification of 7 in. was used for all images. The cases were defined as with CAD when vessel lumen narrowing >50% of at least one coronary segment (CAD group). Patients with no lesion or with lesions ≤50% of luminal narrowing were considered as controls (non-obstructive CAD group).

Statistical analysis

Data were analyzed using SPSS v.16 (SPSS Inc., Chicago, IL, USA) to obtain descriptive statistics of frequency, mean value and standard deviation, or median and interquartile range. Comparisons of baseline characteristics between the groups were made by Student's *t* test or Mann–Whitney *U* test for nonparametric variables. Logistic regression models were employed to predict CAD, including stepwise forward model by likelihood ratio. The following regressors were used: gender, age, BMI, fasting glucose, hs-CRP, lowest O_2, uric acid, high blood pressure, dyslipidemia, and AHI. AHI, indicating OSA severity, was analyzed as follows: (1) continuous variable; (2) two groups divided at the median value of 14 events per hour (AHI>14); (3) four groups divided according the recommended OSA severity criteria (<5, 5–15, 15–30, and >30 events per hour; AHI-4). A *P* value<0.05 was considered statistically significant. Odds ratios are presented with their 95% confidence intervals.

Results

Table 1 shows the characteristics of the total sample and of the groups formed by the angiographic result of catheterization. Male gender and age differ between cases and controls, but not BMI or ethnic background. Cases with 50% or greater coronary occlusion were using more medication, but, of 13 pharmaceutical classes analyzed,

Table 1 Anthropometric, biochemical and polysomnographic characteristics of the population divided by the result of catheterization

	Total *N*=55	Controls (non-obstructive CAD) *n*=29	Cases (CAD) *n*=26	*P*
	Anthropometry			
Age (years)	54±6.8	52±6.9	57±5.7	0.005
Male gender (*n*)	55% (30)	41% (12)	69% (18)	0.039
Body mass index (kg/m^2)	28±3.8	27±4.0	28±3.7	0.6
Caucasian (*n*)	84% (46)	79% (23)	89% (23)	0.5
	Medication			
Alpha-adrenergic inhibitor	57% (31)	45% (13)	72% (18)	0.04
Statin	46% (25)	31% (9)	68% (16)	0.007
	Biochemistry			
Total cholesterol (mg/dL)	171±43.9	186±45	156±38	0.013
High-density lipoprotein (mg/dL)	46±13.3	51±13	41±12	0.003
Low-density lipoprotein (mg/dL)	100±36.4	109±35	89±36	0.043
Triglycerides (mg/dL)	114 (74/150)	93 (68/135)	129.5 (82/158)	0.077[a]
Dyslipidemia (*n*)	67% (37)	55% (16)	80% (21)	0.042
High blood pressure (*n*)	78% (43)	72% (21)	88% (22)	0.153
Uric acid (mg/dL)	5.6±1.5	5.2±1.4	6.2±1.4	0.012
hs C-reactive protein (mg/L)	1.86 (0.81/5.91)	1.59 (0.64/7.37)	2.13 (1.02/4.79)	0.592[a]
Fasting glucose (mg/dL)	106±11	105±13	107±9.6	0.495
	Type III PSG monitoring			
AHI (events/h)	15 (7/23)	7 (3/17)	17 (14.5/27.5)	0.001[a]
AHI>14 (*n*)	51% (28)	28% (8)	77% (20)	0.001
Lowest SaO_2% (*n*)	96% (53)	86% (28)	85% (25)	0.155

Values are mean±SD or median (P25; P75) or % (*n*); *P* for independent sample *t* test

AHI apnea–hypopnea index, *CAD* coronary artery disease, *hs* high-sensitivity

[a] Mann–Whitney or chi-square tests

the difference was significant only for statins and alpha-adrenergic inhibitor. Controls with <50% coronary lesions exhibited significantly lower AHI.

Table 2 shows the sample characteristics of patient groups divided at median AHI, AHI ≤14 and >14. No significant difference was seen in BMI and biochemical markers for CAD risk. Basically, the same results were obtained utilizing the continuous variable AHI or categorizing AHI in four severity groups.

Figure 2 shows prediction of CAD by four binary logistic regression models. In model 1, classical cardiovascular risk factors were individually analyzed in the binary logistic regression, including one variable at a time. Gender, age, uric acid, and dyslipidemia were significant predictors, besides AHI. In model 2, two variables were included at a time, being one of them AHI. Using AHI>14, uric acid persisted significant (P=0.44), but neither using continuous AHI nor AHI-4. Therefore, including AHI>14 caused variables that were significant in the univariate model, such as male gender, age, dyslipidemia, and BMI to become non-significant as risk factors for CAD.

In Fig. 2, model 3, including all regressors simultaneously in the binary logistic regression to predict CAD risk, only AHI>14 and dyslipidemia showed statistical significance. All the three forms of including AHI in the model, AHI>14 (P=0.012), AHI-4 (P=0.009), and continuous AHI (P=0.034) were significant. The increment of one event per hour in the continuous AHI increases 11% the probability of CAD.

In Fig. 2, model 4, AHI>14 and uric acid were the only factors entered in the stepwise forward model. Using AHI-4 instead of AHI>14 in the model increases 3.2 times the probability of CAD for each increase in severity category (e.g., from mild to moderate); raising 1 mg/dL of uric acid concentration, increases 70% (with AHI>14) and 66% (with AHI-4) the risk for CAD. Utilizing the continuous variable AHI, dyslipidemia enters the model with an odds ratio (OR) of 4.8 (1.06–22; P=0.042).

Discussion

Our study suggests that AHI, measured by validated portable home monitoring, is the most important risk factor for coronary lesion in a sample of angina patients when individuals with diabetes, morbid obesity, smoking history, and age >65 years are excluded. The results are particularly interesting because even with a reduced sample size, the statistical significance of AHI to predict CAD resisted multivariate analysis, controlling for most risk factors used in checkups for CAD prevention. One implication of this finding is that, if SA really explains the risk imposed by hypertension, cholesterol, C-reactive protein, future studies on risk factors for cardiovascular disease will be incomplete if lacking information on SA. At the present time, few studies include SA in the listing of cardiovascular risk factors.

The fact that we screened 519 patients arriving at the catheterization laboratory to obtain a sample of only 55 cases shows the importance of smoking and age >65 years in causing CAD (Fig. 1). In spite of the predominance of middle-aged men in our sample, after controlling the CAD risk for age and gender in the regression model, AHI persisted significant, suggesting that SA is directly involved in the genesis of CAD, in spite of gender and age.

There is evidence that SA may contribute to obesity and, in particular, to deposition of visceral fat [17]. There is also evidence of correlation between BMI and hs-CRP levels in SA patients [18, 19]. The relationship between hs-CRP and sleep-disordered breathing is still controversial [20, 21], due mainly to the fact that hs-CRP levels are directly

Table 2 Anthropometric characteristics and results of biochemistry tests of the patients grouped by apnea–hypopnea index

	AHI≤14 n=27	AHI>14 n=28	P
	Anthropometry		
Age (years)	51±7	57±5	0.001
Male gender (%)	41% (21)	68% (19)	0.044
Body mass index (kg/m^2)	27.6±4.2	27.5±3.45	0.9
Hypertension (n)	67% (18)	93% (25)	0.019
	Biochemistry		
Total cholesterol (mg/dL)	168±43	174±45	0.6
High-density lipoprotein (mg/dL)	49±12	43±14	0.14
Low-density lipoprotein (mg/dL)	95±33	104±39	0.4
Triglycerides (mg/dL)	123±115	135±64	0.6
Dyslipidemia (n)	59% (26)	75% (21)	0.2
Uric acid (mg/dL)	5.4±1.71	5.9±1.21	0.17
C-reactive protein (mg/L)	4±5	5±6	0.8
Fasting glucose (mg/dL)	104±12	107±10	0.3

Values are mean±SD or % (n). P for independent sample t test or chi-square test

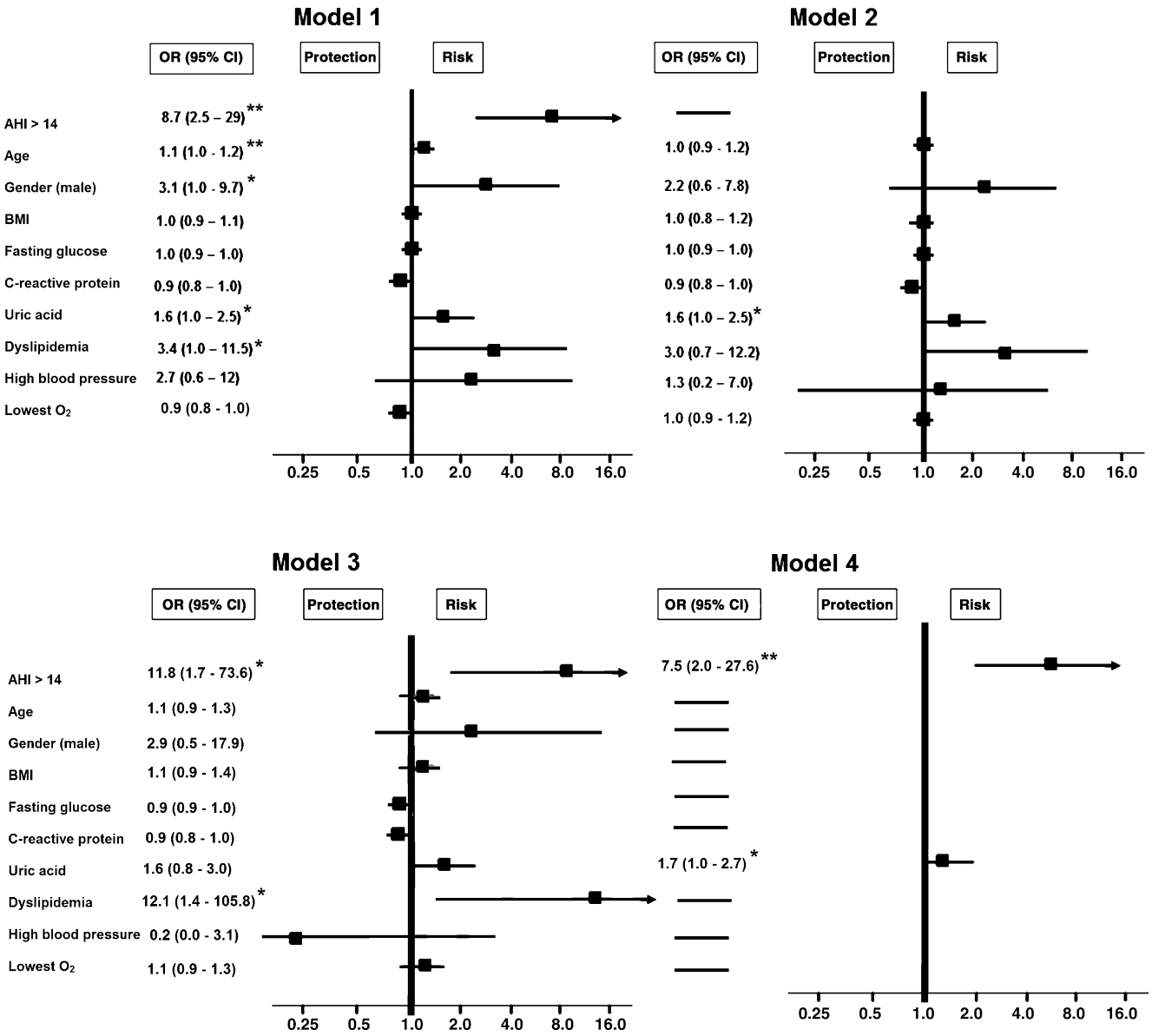

Fig. 2 *Model 1* univariate analysis, *model 2* bivariate analysis using AHI >14 with each regressor, *model 3* full model multivariate binary logistic analysis, *model 4* stepwise binary logistic analysis, *CI* confidence interval, *OR* odds ratio, *AHI* apnea–hypopnea index; **P*=<0.05; ***P*=<0.01

correlated with obesity [22]. The hs-CRP levels were similar between groups either divided by percentage of coronary occlusion or by median AHI.

It is difficult to assess the importance of inflammation and dyslipidemia as risk factor in this sample due to the higher proportion of individuals under statins among cases (68%) than among controls (31%). Besides lowering lipids, statins may have lowered the hs-CRP. There is increasing evidence that SA is independently associated with dyslipidemia. Other cross-sectional studies suggested that SA is independently associated with increased levels of total cholesterol, low-density lipoprotein, and triglycerides [23–25].

In our analysis, the frequency of cases with hypertension was significantly higher in the group with AHI>14 per hour. The measured blood pressure was not different between groups, because virtually, all hypertensive cases were receiving antihypertensive medication. Our results are in agreement with the literature showing association of SA with hypertension, especially in the resistant form [26, 27].

In our study, uric acid was the second predictor for CAD in the regression model. A recent systematic review showed that hyperuricemia may marginally increase the risk of cardiovascular outcomes, independently of other traditional cardiovascular risk factors [28]. This OR is significant only when the remaining variables do not enter the model. The increased formation of free radicals in SA happens via the conversion of xanthine dehydrogenase into its oxidase form during hypoxia, followed by the activation of the oxidase

form during reoxygenation by the hypoxanthine formed during hypoxia. This xanthine oxidase activity generates superoxide radical, superoxide radical, and uric acid [29]. Uric acid may be involved in platelet aggregation and adhesiveness, in inflammatory processes, as well as in the genesis of hypertension [30, 31]. The actual effect of this antioxidant and its relationship with atherosclerosis and SA remains uncertain.

The high covariance among the risk factors in such a small and selected sample may be interfering in the significance of the various tested models. Uric acid remaining in our model does not favor uric acid being a better predictor of CAD than, for instance, hs-CRP. AHI, however, enters and resists combinations with all risk factors. Sleep apnea is, therefore, a risk factor to be taken seriously.

The small sample size is a clear limitation. We attempted to circumvent this lack of power by excluding powerful risk factors, such as old age and smoking, and by doing multivariate analysis with a limited number of variables or in a stepwise fashion. The design of this study prevents us from identifying causal relationship. We report an association between CAD and SA, but not proof that SA leads to CAD. Not every known CAD risk factor was included in the analysis, limiting the adjustments to the aspects analyzed.

The main finding in the present study is that AHI, a marker of SA severity, proved to be a strong risk factor for CAD, independent of age, gender, BMI, and other traditional risk factors. Being our results limited by a small sample does not disqualify the importance of identifying sleep-disordered breathing in patients at risk for cardiovascular disease. Effective treatment of the SA may decelerate the atherogenesis process, as evidenced by intima-media thickness decrease after 4 months of CPAP treatment [32].

Another well-known confounder in the SA–CAD relationship is obesity. Cases and controls had non-significant difference in BMI. The mean BMI around 27 kg/m^2 indicates that the sample was mostly overweight, with just one third of the sample, 17 patients, exhibiting BMI between 30 and 36 kg/m^2. The OR of BMI did not reach significance in any attempt to control for this important variable. Morbid obesity is a known inflammatory state [33], and its exclusion may have helped to show the effect of SA on CAD risk in the present study.

The relationship between OSA and CAD is complex [34]. The association has been researched in large samples [12] and even using the Berlin Questionnaire [35]. Inflammation happens in the core of the atherogenic process, and patients with OSA have higher levels of inflammatory markers that are reversed by CPAP therapy [32]. Endothelial damage in OSA can be caused by mechanisms as shear stress, due to blood pressure oscillations, and oxidative stress, due to hypoxia/reoxygenation [36, 37]. Platelets also play a central role in CAD. Patients with OSA have increased platelet activation and it is reduced after CPAP therapy [38]. Cardiac dysfunction, however, has to be considered as cause of obstructive and central sleep apnea [39]. CAD may impair hemodynamics causing fluid retention. Rostral fluid displacement from the lower limbs increases peripharyngeal and pulmonary liquid content. This increases upper-airway collapsibility and ventilation, facilitating the occurrence of obstructive and of central apneas [39].

This small study provides evidence that SA is a better predictor of coronary lesions than recognized risk factors when aging, smoking, morbid obesity, and diabetes are excluded. Future studies should be performed to confirm the data in unselected populations. The present findings, although preliminary, are potentially useful if used by clinicians for risk stratification and risk factor modification in clinical practice.

Acknowledgments Drs. Jorge Pinto Ribeiro and Marco Vugman Wainstein are thanked for their valuable contribution in providing data from the cineangiocoronariography.

Financial support Students received grants from the Brazilian government through CAPES and CNPq. The main support was offered by the Research Incentive Fund (FIPE) of the Hospital de Clínicas de Porto Alegre (Porto Alegre, Rio Grande do Sul, Brazil).

Conflict of interest The authors declare that they have no conflict of interest regarding the present study.

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