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Prevalence of Obstructive Coronary Artery Disease in Ambulatory Patients with Stable Angina Pectoris

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Abstract

Background: Myocardial ischemia with its clinical symptom angina pectoris is associated with increased morbidity and mortality. Obstructive coronary artery disease (CAD) is not the only cause for cardiac ischemia and the prevalence of obstructive CAD in patients with stable angina pectoris is still discussed. Therefore, we investigated the prevalence of CAD in patients with stable angina pectoris undergoing coronary angiography.

Methods: In a cross-sectional study, 2501 patients with stable angina pectoris scheduled for coronary angiography were observed in outpatient clinics in Germany. Baseline characteristics, results of ischemic stress testing, angina status as well as the result of the coronary angiography regarding the extent of coronary artery disease (CAD) were documented.

Results: In 1049 from the 2501 patients, obstructive to CAD was documented as a pre-existing disease in the patient's medical history, while the other 1452 patients had no previously documented CAD. In 85% of these patients with known CAD, the newly performed coronary angiography revealed progression of CAD as the most likely reason for angina pectoris symptoms. In contrast, only 16.5% had significant obstructive CAD documented by coronary angiography despite similar symptoms compared to patients with known CAD. Interestingly, only male sex, age over 65 years, dyslipidemia, as well as typical angina pectoris symptoms were predictive for obstructive CAD in a multivariate analysis performed in patients without known CAD. Other classic risk factors, including hypertension, smoking and the result of the ischemic stress test were not predictive for CAD in this group.

Conclusion: In patients with known CAD, progression of the disease was common as a cause for angina pectoris symptoms. Newly diagnosed CAD was far less prevalent in patients without pre-existing CAD. This is clinically relevant since symptoms were similar in patients with and without pre-existing CAD. Other causes for cardiac ischemia including endothelial dysfunction and microvascular abnormalities may be relevant for the clinical symptomatology of patients with stable angina pectoris.

Keywords: Angina pectoris; Myocardial ischemia; Syndrome X; Obstructive coronary artery disease; Microvessel

Introduction

Myocardial ischemia, with its clinical symptom stable angina pectoris (AP), is a relevant chronic disease associated with poor prognosis and high mortality rate as well as impaired quality of life. Moreover, increased incidence of AP is associated with higher hospitalization rates, thereby driving healthcare costs [1]. In clinical routine, AP is often thought to be the clinical equivalent of coronary artery disease (CAD) with obstructions limiting flow in epicardial coronary arteries resulting in myocardial ischemia. Therefore, in patients with clinically limiting stable AP, coronary angiography is often performed to diagnose and/or treat CAD.

Nevertheless, it is known that a fraction of patients presenting with AP and evidence of myocardial ischemia have normal or near normal coronary arteries in the coronary angiography. Therefore, in those patients flow-limiting epicardial coronary obstructions cannot be the single reason of myocardial ischemia [2-4]. These patients are often diagnosed with the so-called cardiac syndrome X [5]. Cardiac syndrome X is heterogeneous and may encompass various pathogenic entities explaining myocardial ischemia by microvascular abnormalities in the absence of obstructive CAD [6-8]. These abnormalities include endothelial dysfunction, [9] myocardial fibrosis, [10] microvascular dysfunction, [6] or coronary spasm, [11] It also includes relative ischemia due to arterial hypertension [12], cardiac hypertrophy associated with increased wall stress [13] and compression of the microvascular system due to diastolic dysfunction. [14,15]. All of these factors limit oxygen supply to myocytes, and therefore present a possible cause for AP symptoms. Despite the poor outcome of these patients, [16] the clinical relevance of this problem is often underestimated in daily clinical routine. Compared to noncardiac chest pain such as musculoskeletal pain and gastro-esophageal reflux disease, syndrome X is associated with poor prognosis and needs specialized care. A recent small study showed that patients with vasospastic angina who were resuscitated due to ventricular tachyarrhythmia in regard of myocardial ischemia have a high risk of cardiac death in the future [17]. Moreover, patients with AP and documented myocardial ischemia without obstructive CAD have a poor outcome in a large-scale clinical register [18].

In patients with AP the proportion of obstructive CAD compared to normal coronary arteries suggesting syndrome X is still unclear. There is conflicting evidence about the clinical significance of syndrome X with some studies suggesting a low incidence of 14% and others a high incidence of up to 61% [2,19-21].

We investigated the proportion of CAD in patients suffering from chronic stable AP scheduled for coronary angiography in an outpatient care setting.

Methods

Study design

The study was planned as a cross-sectional clinical epidemiological study including consecutive patients presenting with stable angina pectoris in 395 outpatient centers in Germany from November 2010 to March 2011. Centers were evaluated by distribution in Germany and the first respondents to the invitation from the sponsor were nominated as participating centers. All physicians practiced in the secondary care setting in Germany. The physicians received reimbursement for each patient included. The study was purely observational. Data were recorded on a paper case report form and entered into a database by a subcontracted CRO. This standardized assessment was completed for each patient by the treating physicians. There was no data source verification. There was no core lab or blinding in this cross-sectional observational study for the angiography. Treating physicians participating in this study used the cath-lab report of every patient to define the presence or progression of CAD. A new stenosis over 50% was defined as significant. All prevalence estimates reported in this paper were based exclusively on clinical diagnoses or specifications rated by the physician.

Patients

Clinical characteristics including sex, age, height, and waist circumference were documented, and body mass index was calculated accordingly. Secondary care physicans/cardiologists taking care of the patients assessed the clinical case history as well as current status. Moreover, concomitant diseases were documented with respect to history of stroke, hypertension, dyslipidemia, diabetes mellitus, chronic obstructive pulmonary disease, and renal impairment. Furthermore, the cardiovascular risk factor smoking was assessed. The severity and frequency of AP symptoms were evaluated (CCS class), as well as the weekly nitroglycerin intake. The prevalence of noninvasive diagnostic tests before coronary angiography was documented including results from ECG, bicycle ergometry, stress echocardiography or myocardial scintigraphy. The results were categorized as positive, negative, or equivocal. Finally, the result of coronary angiography was documented in view of the presence of CAD in all patients.

Statistics

Data are presented as mean ± standard deviation. Using descriptive statistics, we compared the distributions of variables amongst all categories. The Fisher's exact test was used for categorical variables and student's t-test for continuous variables. Multivariate logistic regression analysis was performed to identify independent predictors for obstructive CAD. Sensitivity, specificity, positive and negative predictive values for calculated for every stress test performed. A 2-tailed p-value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 20.0.

Demographics	no previous CAD	previous CAD	p
	n=1452	n=1049	
Age	66.7 ± 10.8	69.5 ± 10.5	<0.0001
Height	170.6 ± 9.6	171.3 ± 8.7	0.06
Body weight	81.9 ± 16.8	81.97 ± 14.99	0.86
Abdomen circumference	98.5 ± 13.5	99.6 ± 13.6	0.13
BMI	28.1 ± 4.9	27.9 ± 4.6	0.54
Male Sex	772 (53.8%)	767 (73.8%)	<0.0001
Risk factors/concomitant diseases			
Hypertension	1015 (69.9%)	817 (77.9%)	<0.0001
Dyslipidemia	627 (43.2%)	688 (65.6%)	<0.0001
Diabetes mellitus	284 (19.6%)	292 (27.8%)	<0.0001
COPD	116 (8.0%)	99 (9.4%)	0.219
Renal impairement	60 (4.1%)	80 (7.6%)	<0.0001
PAD	64 (4.4%)	100 (9.5%)	<0.0001
Previous myocardial infarction	0 (0%)	311 (29.6%)	<0.0001
Prior Stroke	42 (2.9%)	53 (5.1%)	0.006
Smoking	415 (28.6%)	303 (28.9%)	0.893
Pack years (smokers only)	29.2 ± 23.0	30.53 ± 32.1	0.6
Symptoms			
Classic AP	598 (41.2%)	541 (51.6%)	<0.0001
Atypical AP	470 (32.4%)	309 (29.5%)	0.126
Exertional dyspnea	632 (43.5%)	381 (36.3%)	<0.0001
Number of AP per week	3.1 ± 4	3.6 ± 4.2	0.003
Number of NTG-intake per week	0.64 ± 1.9	1.7 ± 3.4	<0.0001
Stress test (performed)			
Bicycle-Stress ECG	954 (65.7%)	646 (61.6%)	0.035
Stress echocardiography	123 (8.5%)	76 (7.2%)	0.295
Scintigraphy	115 (7.9%)	86 (8.2%)	0.823
cMR	20 (1.4%)	11 (1.0%)	0.584

Any positive stress test	567 (39.0%)	382 (36.4%)	0.182
Medical therapy			
Platelet inhibitors	664 (45.7%)	827 (78.8%)	<0.0001
Beta-blockers	731 (50.3%9	785 (74.8%)	<0.0001
ACE-inhibitors	535 (36.8%)	530 (50.5%)	<0.0001
AT1-receptor blockers	289 (19.9%)	243 (23.2%)	0.053
Calcium antagonists	260 (17.9%)	237 (22.6%)	0.004
Nitrates			
Long-acting	71 (4.9%)	198 (18.9%)	<0.0001
Short-acting	111 (7.6%)	194 (18.5%)	<0.0001
NTG spray or sublingual capsule	120 (8.2%)	210 (20%)	<0.0001
Statins	406 (28%)	762 (72.6%)	<0.0001
CAD (new or progression of known disease)	240 (16.5%)	892 (85%)	<0.0001

Table 1: Demographics of all patients included in this study. BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease.

Results

Patients

2501 patients were included in this study. 1049 patients had previously diagnosed CAD and 1452 patients had no documented history of CAD before inclusion.

Clinical characteristics

All patients included in this study: The clinical characteristics of all 2501 patients included in this study are presented in Table 1. Comparison of patients with a prior history of CAD (1049 patients) to those without prior CAD (1452 patients) revealed that patients with known CAD were older, more often male, had a higher prevalence of hypertension, dyslipidemia, renal impairment, diabetes mellitus, peripheral artery disease (PAD), and a history of stroke. According to the study design and group selection criteria, a history of myocardial infarction was only present in the group of patients with previously documented CAD. Importantly, typical AP was significantly increased in patients with known CAD. Exertional dyspnea was more prevalent in patients without previously diagnosed (unkown) CAD. The number of AP attacks per week was high in both groups, but significantly higher in patients with previously known CAD. This was associated with a higher use of nitroglycerine per week by. Stress testing was performed in a subset of both patients groups. Interestingly, the rate of positive stress tests was relatively low with 39% (no prior CAD) and 36.4% (known CAD) in both groups without a significant difference. More patients in the group with pre-diagnosed CAD were on beta-blockers, ACE inhibitors and statin therapy. In the whole group use of ranolazine was low with 1.72% (43 patients) before coronary angiography and 6.68% (167 patients) after it. Importantly, the result of coronary angiography differed significantly in patients with known CAD (85% had a progression of CAD) compared to patients without previously documented CAD (only 16.5% of those patients had significant obstructive CAD as final diagnosis after coronary angiography).

no previous CAD			
	CAD after angio (n=240, 16.5%)	**no CAD after angio (n=1212, 83.5%)**	**P value**
Age	68.3 ± 10.5	66.4 ± 10.8	0.01
Height	171.1 ± 8.6	170.5 ± 9.8	0.338
Body weight	82.2 ± 15.2	81.8 ± 17.1	0.748
Abdomen circumference	98.1 ± 13.7	98.6 ± 13.7	0.651
BMI	28.0 ± 4.5	28.1 ± 5.0	0.946
Sex (male)	143 (60.1%)	629 (52.5%)	0.033
Risk factors/concomitant diseases			
Hypertension	170 (70.8%)	845 (69.7%)	0.758
Dyslipidemia	127 (52.9%)	500 (41.3%)	0.001
DM	53 (22.1%)	231 (19.1%)	0.286
COPD	23 (9.6%)	93 (7.7%)	0.3
Renal failure	13 (5.4%)	47 (3.9%)	0.286
PAD	14 (5.8%)	50 (4.1%)	0.231
Stroke	12 (5.0%)	30 (2.5%)	0.054
Smoking	79 (32.9%)	336 (27.7%)	0.118
Symptoms			
Classic AP	124 (51.7%)	474 (39.1%)	<0.0001
Atypical AP	66 (27.5%)	404 (33.3%)	0.83
Exertional dyspnea	107 (44.6%)	525 (43.3%)	0.722
Number of AP per week	2.8 ± 3.2	3.1 ± 4.2	0.153
Number of NTG-intake per week	1.1 ± 2.8	0.5 ± 1.8	0.004
Stress test (performed)			
Bicycle-ECG	152 (63.3%)	802 (66.2%)	0.413
Stress echocardiography	22 (9.2%)	101 (8.3%)	0.703
Scintigraphy	18 (7.5%)	97 (8.0%)	0.896
cMR	6 (2.5%)	14 (1.2%)	0.123
Any positive stress test	98 (40.8%)	469 (38.7%)	0.563

Table 2: Demographics of patients without known CAD.

Patients without previously documented CAD: The clinical characteristics of the 1452 patients who had not been previously diagnosed with CAD are presented in Table 2. After coronary angiography, 240 patients (16.5%) were classified as having CAD (≥50% stenosis) while 1212 patients (83.5%) had no significant CAD. 1 vessel CAD was diagnosed in 41%, 2 vessel disease in 30.7% and 3-vessel disease in 28.3%. In the univariate analysis, patients with newly diagnosed CAD were significantly older, more often male and had a higher rate of dyslipidemia. The rate of patients presenting with typical AP was higher in the group with newly diagnosed CAD. The number of AP attacks per week was also similar. The rate and mode of stress tests as well as the rate of positive stress tests were similarly distributed between both groups. Importantly, other classic risk factors were equally distributed between patients with and without CAD, including abdominal circumference as a sign of abdominal obesity, hypertension, diabetes mellitus, history of stroke, renal impairment as well as smoking. Interestingly, a positive stress test in combination with typical symptoms (typical angina) was present in only 50 patients (20.8% of all patients) with newly diagnosed CAD after the angiography. Hence, 79.2% of the patients with newly diagnosed CAD had not both typical AP and a positive stress test.

Stress tests	sensitivity	specificity	Positive predictive value	negative predictive value
Bicycle-ECG	44.8%	56.8%	20.6%	80.5%
Stress echocardiography	70%	50.5%	29.6%	85%
Myocardial scintigraphy	82.6%	19.8%	20.7%	81.8%
cMR	83.3%	33.3%	38.5%	80%

Table 3: Predictive values of the stress tests and the occurrence of CAD.

Predictive factors for CAD in the group without pre-diagnosed CAD: Multivariate analysis (Figure 1) identified as predictors of CAD only sex, age, dyslipidemia as well as typical AP and the use of NTG. Other risk factors were not predictive. Importantly, the result of an ischemic stress test did not predict the diagnosis of CAD. Furthermore, the combined prognostic effect of a positive stress test and typical angina identified only 186 patients (20.9% of the patients with progression of CAD). 79.1% had not a positive stress test combined with typical AP.

No previous CAD			
	negative stress test (n=885, 61%)	**positive stress test (n=567, 39%)**	**P value**
Age	67 ± 10.8	66 ± 10.6	0.041
Height	170.2 ± 9.6	171.2 ± 9.6	0.045
Body weight	82.4 ± 16.8	81 ± 16.7	0.140
Abdomen circumference	99.1 ± 13.7	97.6 ± 13	0.128
BMI	28.4 ± 5	27.6 ± 4.85	0.002
Sex (male)	455 (52.1%)	317 (56.3%)	0.129
Risk factors/concomitant diseases			
Hypertension	618 (69.8%)	397 (70%)	0.953
Dyslipidemia	358 (40.5%)	269 (47.4%)	0.009
DM	176 (19.9%)	108 (19%)	0.735
COPD	82 (9.3%)	34 (6%)	0.029
Renal failure	44 (5%)	16 (2.8%)	0.058
PAD	35 (4%)	29 (5.1%)	0.297
Stroke	24 (2.7%)	18 (3.2%)	0.632
Smoking	235 (26.6%)	180 (31.7%)	0.037
Symptoms			
Classic AP	355 (40.1%)	243 (42.9%)	0.325
Atypical AP	285 (32.2%)	185 (32.6%)	0.863
Exertional dyspnea	406 (45.9%)	226 (39.9%)	0.026
Number of AP per week	3.1 ± 4.2	3.1 ± 3.8	0.811
Number of NTG-intake per week	0.65 ± 1.9	0.61 ± 2.1	0.723
Diagnosis of CAD after angiogram	142 (16%)	98 (17.3%)	0.563

Table 4: Demographics of patients without previously known CAD.

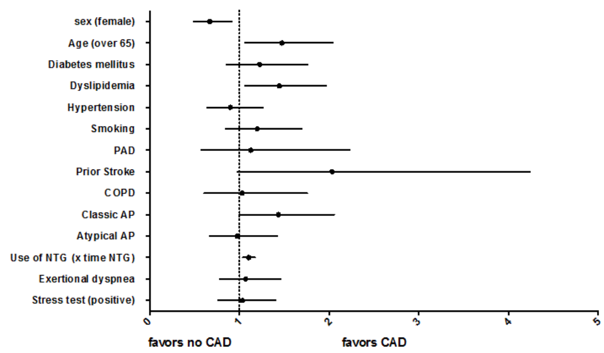

Figure 1: The odds ratio of different risk factors patients without prior diagnosed CAD to have CAD in the coronary angiography.

Discussion

The salient finding of this study is that in 83.5% of patients with unknown CAD no significant obstructive CAD (≥ 50% stenosis) was documented in the coronary angiography despite AP symptoms. This differed significantly in patients with a diagnosed history of CAD. In those patients progression of the disease could be documented in 85%. These results show that the underlying etiology for AP is not obstructive CAD only. This is clinically relevant and demonstrates that other etiologies for AP may be more frequent than previously thought in a large cohort of real-world patients in Germany (Table 3).

Characteristics of all patients included

Patients included in this study had an increased cardiovascular risk when typical risk factors with regard to e.g. the SCORE test from the European Society of Cardiology were taken into account. We observed a high incidence of diabetes mellitus, arterial hypertension, dyslipidemia and smoking in patients included in this study. An exercise or pharmacologic stress test was performed in a part of the patients, but not all of them resulted in a pathological positive result as shown previously [22]. Nevertheless, the number of AP attacks was higher in this study compared to other observational studies [23,24]. Importantly, it was shown by others that the number of weekly AP attacks correlates with quality of life. Moreover, the number of angina

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attacks is important, since a graded relationship was found between higher angina frequency and healthcare costs in patients with stable AP, at least after an acute coronary syndrome [1]. It is also known that high numbers of angina attacks as a parameter in the Seattle Angina Questionnaire score predict mortality in patients with AP and CAD [25,26]. Whether the number of AP attacks is important in patients without CAD is unclear. One trial suggests that the number of AP attacks translate into increased mortality in a patient cohort without CAD [17]. Moreover, a large register showed that the presence of AP in patients with normal coronary arteries increases mortality when compared to healthy volunteers without AP [18].

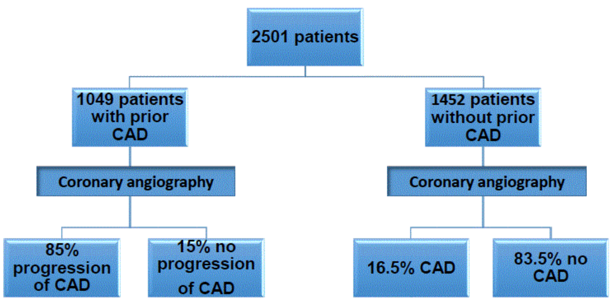

Figure 2: Study Flow with 2501 patients included. 1049 patients had a prior diagnosis of CAD. In these patients coronary angiography revealed progress of CAD in 85%. 1452 patients had no prior diagnosed CAD. In these patients only 16.5% had CAD in their angiography.

Differences between patients with known and unknown CAD

A large proportion of the patients (1452) included in this study had no history of CAD, hence coronary angiography was performed for the first time. Compared to those patients, the group with already known CAD (documented in a previous coronary angiography) was older, more often male, and had higher rates of dyslipidemia, hypertension and diabetes mellitus. This is consistent with the information found in a large U.S. register and also with other studies [2,21]. Nevertheless, we did not find differences in the most classic risk factor. For example smoking was similarly distributed between both groups, as was BMI.

Interestingly, symptoms differed in patients with known CAD compared to the unknown CAD group. In the unknown CAD patients, typical AP was significantly less prevalent while the numbers of weekly AP attacks were similar in both patient groups. AP equivalents (such as exertional dyspnea) were even increased in patients with unknown CAD compared to patients with known CAD. This is important, since current findings indicate that AP equivalents (such as dyspnea) are as predictive for morbidity and mortality as typical AP, at least in patients with diabetes [27]. These overlapping clinical characteristics make it difficult to discriminate patients that should undergo coronary angiography. Importantly, there were no differences in the percentage of positive stress tests in both patient groups.

When looking at the patients without previously known CAD who had a positive exercise test, they tended to be younger and have lower BMI, but higher incidence of dyslipidemia and smoking. Interestingly, there was no significant difference in the classical symptoms of angina between the two groups (Table 4). A positive stress test was again not predictive of diagnosis of CAD after the angiogram in this patient collective either.

Nevertheless, performing a stress test is of paramount importance for documenting cardiac ischemia and possibly guiding future treatment with regard to medical or interventional therapy. Cardiac ischemia seems to exist independently whether it is from macrovascular or microvascular origin. Coherently, in this study the stress test was not able to differentiate between CAD or no CAD and possible microvascular disease.

New onset or progression of CAD

In this observational study we found that in 16.5% of the patients without history of CAD obstructive stenosis could be documented in the angiography. This results in 83.5% without significant obstructive CAD as a possible reason for their AP symptoms. Other recent trials and registers showed high rates of angina patients without significant new onset CAD also, presenting numbers between 54% and 61% [2,21]. In our study, we extend these findings presenting the percentage of patients with progression of CAD in two different patient groups. While our patients without a history of CAD had a low incidence of CAD after coronary angiography, we show that in patients with a history of CAD, a progression of CAD was observed in 85%.

We further tried to elucidate the risk factors predicting new onset of CAD in patients with AP but no history of CAD. Interestingly, only male sex, age over 65 years as well as dyslipidemia was predictive for having CAD. Other risk factors, as hypertension, diabetes, smoking and prior stroke were not. Positive cardiac ischemic stress testing was also not predictive for CAD.

Possible explanations for AP in patients without new onset of CAD

As emphasized by others, [21,28] epicardial spasms as well as microvascular dysfunction are a common finding in patients presenting with stable AP and positive ischemic stress test when no obstructive CAD is present. In our study no distinct tests were performed to study the underlying etiology of AP in the absence of CAD, since this was an observational cross-sectional study only. This highlights the need for prospective controlled trials in patients with AP since many clinicians may attribute AP in these patients to non-cardiac reasons only after CAD is excluded invasively. The potential role of functional vasomotor testing is supported by a recent study describing a good safety profile of non-invasive tests for endothelial and microvascular dysfunction [29]. Ong and colleagues showed in an important study that epicardial spasms and microvascular dysfunction are associated with typical AP in patients without CAD, offering a possible explanation for our results [21,30]. This was further verified recently with similar results [31]. Although not tested directly, it appears likely that the causes for cardiac ischemia identify by those 2 works might also be relevant in the cohort presented here. These findings are important since cardiac ischemia is associated with an increased morbidity and mortality [18,32], importantly without evidence based treatment [33].

Limitation of the study

This study is an observational, cross-sectional study, therefore a bias of patient selection cannot be ruled out. Nevertheless, consecutive inclusion per design should limit this factor. All data reported here were calculated from questionnaires and not controlled by site selection visits or direct data monitoring. The relatively low rate of positive ischemic stress test is also a weakness of this study, since non-cardiac reasons for AP in patients without a positive test might influence the results. Both points are a major weakness of this study.

Nevertheless, the data may in fact mirror the patients treated in general practice and therefore might give an insight into clinical routine in Germany. Moreover, endothelial function was not assessed during coronary angiography routinely; therefore, we cannot present data for this. As well data for NYHA status and anemia was not recorded on the questionnaire as possible influential parameters.

Conclusion

Angina pectoris is a disabling burden for patients and increases morbidity and mortality. In symptomatic patients with known CAD, coronary angiography revealed a progression of CAD in 85% of the patients. In contrast, incident CAD was low with only 16.5% in patients without pre-diagnosed CAD (Figure 2). This knowledge is important for daily clinical practice since AP might be caused by other diseases and not only by obstructive CAD.

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Disclosures

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