RESEARCH LETTER

Invasive assessment of the microvascular coronary circulation in patients with coronary artery aneurysmal disease

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Introduction Coronary artery aneurysmal disease (CAAD) is a rare condition of the epicardial arteries. It has a complex etiology, including congenital defects of the tunica media as well as atherogenesis, inflammation, and iatrogenic mechanisms.[1-3] The most common clinical presentation of CAAD is stable angina pectoris; manifestations occurring significantly less frequently are myocardial infarction or aneurysm complications, that is, thrombus formation and distal embolization, development of a fistula, and aneurysm rupture.[4,5]

Although atherosclerosis is considered the most common cause of CAAD in adults, approximately 50% of patients with aneurysms and angina pectoris do not develop obstructive coronary artery disease (CAD). At the same time, noninvasive examinations, such as perfusion scintigraphy and stress test, might reliably confirm myocardial ischemia in this subgroup of patients.[6,7] The most probable cause of myocardial malperfusion with no evidence of CAD is coronary microcirculation disease (CMD). The pathophysiology of CMD encompasses a wide variety of potential mechanisms. The main classification includes functional (systolic and diastolic) and structural (vascular remodeling) dysfunctions. Given that both endothelial dysfunction and extensive vascular remodeling are observed in CAAD, the probability of CMD is high in this group.

This study aimed to assess the coronary microcirculation dysfunction in patients with CAAD in comparison with individuals with ischemia and no obstructive coronary arteries (INOCA) without CAAD.

Patients and methods **Study design and patient selection** The present study is a retrospective analysis of patients with typical symptoms of angina pectoris in whom coronary angiography revealed no significant coronary artery stenosis (stenosis <40% of the vessel diameter or 40%–60% of the vessel diameter assessed as insignificant in functional testing, such as fractional flow reserve [FFR >0.8]), and who met none of the study exclusion criteria. The patients were referred for coronary angiography following the European Society of Cardiology recommendations for chronic coronary syndromes[8] after assessment of the clinical probability of ischemic heart disease. Magnetic resonance myocardial perfusion imaging revealed ischemia in 2 patients in the CAAD group and 12 patients in the INOCA group. In addition, 3 patients in the INOCA group were referred for invasive evaluation due to positive results of an exercise stress test. The remaining patients were referred for coronary angiography without noninvasive diagnostics due to severe angina (Canadian Cardiovascular Society class III) and ischemic changes on resting 12-lead electrocardiography. All the patients were evaluated for the presence of CMD, including coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) assessment, as part of the diagnosis of INOCA. CMD was diagnosed when IMR was equal to or greater than 25 and/or CFR was below 2.0. Overall, 5 consecutive patients with CAAD confirmed on coronary angiography (CAAD group) and 25 consecutive patients without CAAD (non-CAAD group) were included in the analysis. CAAD was defined as segmental, single, or, less commonly, multiple dilations of the vessel lumen with a diameter 1.5 times the diameter of the patient's widest coronary artery.

The study exclusion criteria were as follows: presence of an acute inflammatory condition (high-sensitivity C-reactive protein level >10 mg/l), active neoplastic disease, systemic connective tissue diseases, treatment with

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TABLE 1 Baseline clinical characteristics of the study patients

Baseline data	CAAD group (n = 5)	non-CAAD group (n = 25)	*P* value
Female sex	2 (40)	20 (80)	0.1
Age, y	60 (60–67)	59 (50–67)	0.23
BMI, kg/m^2	28.9 (27.7–30.8)	28.7 (26.7–31)	0.91
Previous MI	1 (20)	5 (20)	0.25
Previous PCI	1 (20)	2 (8)	0.16
Hypertension	5 (100)	18 (72)	0.30
Heart failure	0	6 (24)	0.55
LVEF, %	60 (55–60)	60 (55–60)	0.82
Diabetes mellitus	1 (20)	7 (28)	0.59
Hyperlipidemia	4 (80)	18 (72)	0.59
Cigarette smoking	1 (20)	6 (24)	0.67
Family history of CVD	1 (20)	8 (32)	0.52

Continuous variables are presented as median (interquartile range), and categorical variables as number (percentage).

Differences were considered significant at $P < 0.05$.

Abbreviations: BMI, body mass index; CAAD, coronary artery aneurysmal disease; CVD, cardiovascular disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention

interferon, bleeding diathesis due to platelet or plasma disorders, acute renal failure or chronic kidney disease with estimated glomerular filtration rate below 30 ml/min/1.73 m^2, allergy to iodinated contrast media, regadenoson, or adenosine, uncontrolled asthma, second- or third--degree atrioventricular block, and the lack of informed consent.

Method description Coroventis CoroFlow Cardiovascular System (Abbott Vascular, Santa Clara, California, United States), which enables a functional assessment of both large epicardial arteries (FFR, CFR) and the coronary microcirculation (IMR), was used for the microcirculation assessment. The target vessel for invasive coronary microcirculation assessment was the left anterior descending artery (LAD). The choice of a guiding catheter was at the discretion of the operator. Before the start of the procedure, unfractionated heparin (100 U/kg) was administered intravenously to obtain therapeutic anticoagulation (activated clotting time approximately 250 s), and nitroglycerin (0.2 mg) was administered intracoronary to avoid epicardial artery spasm.

Statistical analysis Continuous variables were presented as median (interquartile range) as all of them followed a non-normal distribution. Due to the small size of the study group, nonparametric tests were used to compare the groups. Categorical variables were presented as numbers and percentages. The Mann–Whitney test was used to compare the continuous variables with a distribution deviating from the normal. The categorical variables ware compared using the Fisher exact test. *P* values below 0.05 were considered significant. We used PQStat Software (PQStat v.1.8.0.476, Poznań, Poland) for the statistical analysis.

Results Baseline characteristics of the CAAD and non-CAAD groups are presented in TABLE 1. The groups were similar with respect to demographic data and cardiovascular risk factors or comorbidities ($P > 0.05$). The coronary microvascular assessment revealed significant differences in the IMR value between the groups (Supplementary material, *Figure S1*). IMR was significantly higher in the CAAD group than in the non-CAD group (42 [41–57] vs 32 [24–41]; $P = 0.03$). There was no significant difference in the CFR values between the groups (CAAD group vs non-CAD group, 1.9 [1.7–2.4] vs 2.4 [1.7–3.4], respectively; $P = 0.56$).

Discussion The present study evaluated CMD in patients with CAAD and no significant stenosis. We demonstrated that coronary microcirculation resistance, as represented by the IMR value, is significantly higher in the CAAD group than in the non-CAAD patients with INOCA (Supplementary material, *Figures S2* and *S3*). There was no significant difference in the CFR values between the 2 groups.

Previously, the crucial method of a functional assessment of coronary microcirculation was CFR evaluation, assessed in LAD using a Doppler wire. However, the measurement of CFR has limitations.[9,10] It evaluates the entire coronary circulation and is not capable of distinguishing abnormal epicardial physiology from microvascular physiology. Furthermore, CFR measurement is characterized by poor reproducibility and is affected by resting hemodynamics. IMR is a new quantitative measure of the coronary microvasculature function.[11] It has already been tested in many groups of patients, including individuals with stable angina, acute ST-segment elevation myocardial infarction (STEMI), or those after a heart transplantation. The advantage of IMR over CFR is that the measurement of IMR is straightforward, specific for the microvasculature, quantitative, reproducible, and independent of hemodynamic changes. Assessment of the microcirculation using the invasive method with IMR measurement has thus become the gold standard in CMD diagnosis. Nevertheless, in the current study, CFR in the CAAD group was lower than in the non-CAAD group; however the difference did not reach statistical significance.

CMD-related ischemia increases the risk of major adverse cardiovascular events. In a certain group of patients, for example, those after a heart transplantation, with hypertrophic cardiomyopathy or STEMI, the severity of CMD constitutes a potent independent risk factor for clinical deterioration and death.[12]

Remodeling of the coronary microcvessels leads to decreased density of arterioles and arteriole wall hypertrophy, which further result in increased flow resistance and, consequently, reduced perfusion. It has been shown that

the density of capillaries inversely correlates with clinical symptoms.[11]

Adverse vascular remodeling is considered a possible mechanism of CAAD development.[13-15] Therefore, assuming that the processes mentioned above involve the entire vascular bed, coronary microcirculation remodeling is thought to be a possible cause of CMD in patients with CAAD. Moreover, a turbulent blood flow in aneurysms fosters the development of thrombi, which may result in distal embolization and thus impair the coronary microcirculation.[15]

A limitation of the present study is undoubtedly a small group of patients with CAAD. However, it should be emphasized that CAAD is a rare coronary disease, and the concomitant absence of significant stenosis, which constitutes an indication for the assessment of CMD presence, is even less frequent.

To our best knowledge, CMD has not been assessed in CAAD patients so far. Our study is the first preliminary report indicating a significant dysfunction of the coronary microcirculation in individuals with CAAD as compared with other INOCA patients, despite such a small study group. The results highlight the need for further research, including an evaluation of the impact of CMD on the prognosis of patients with CAAD.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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