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Angina after percutaneous coronary intervention: The need for precision medicine

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ABSTRACT

Persistence or recurrence of angina after successful percutaneous coronary intervention (PCI) represent an important clinical issue involving from one fifth to one third of patients undergoing myocardial revascularization at one-year follow-up. A systematic approach to this syndrome is strongly needed.
Precision medicine is particularly important in addressing angina after successful PCI because of the multiple underlying causes. Restenosis or coronary atherosclerosis progression explain symptom recurrence after successful PCI in some patients, while functional causes, including vasomotor abnormalities of epicardial coronary arteries and/or coronary microvascular dysfunction, explain symptoms in the remaining patients.
In this review, we summarize the mechanisms of persistent or recurrent angina after PCI, proposing a diagnostic algorithm and a systematic therapeutic approach.

1. Introduction

Recent trials [1–3] and meta-analyses [4,5] have shown conflicting results on the additive prognostic benefit of percutaneous coronary intervention (PCI) over optimal medical therapy (OMT) in patients with stable ischemic heart disease (CAD) [6–8].

In contrast, there is general agreement that PCI improves symptoms better than OMT [6–11]. Yet, in the COURAGE trial, 34% of patients randomized to PCI had persistent angina at 1-year follow-up, while differences in angina prevalence between patients randomized to PCI plus OMT vs those randomized to OMT decreased over time and became non significant at three year follow-up [1]. In the ARTS trial [12], angina was present in 21% of patients one year after PCI by bare-metal stent (BMS), and in a large retrospective study from the Mayo Clinic performed in the BMS era, 30% of patients treated by PCI reported recurrent angina [13]. Similar findings were observed in the drug-eluting stents (DES) era. Among 1874 patients undergoing PCI by DES enrolled in the NHLBI Dynamic Registry [14], persistent or recurrent angina were reported by 20% of patients; in the ABSORB III trial [15], angina rate at 1-year follow up was 18.4% in patients randomized to receive everolimus-DES and 18.3% in patients randomized to receive the bioresorbable vascular scaffold. Finally, in patients with multivessel or left main disease enrolled in the SYNTAX trial nearly 30% of patients randomized to receive DES had angina at 1-year follow up [16]. Of note, in the recently published NORSTENT trial [17], angina frequency was similar in patients treated by DES and BMS. Moreover, the FAME trial [18] reported recurrence of angina in 19% of patients randomized to fractional flow reserve (FFR)-guided PCI arm and 22% in those randomized to angiography-guided PCI arm (Table 1). Of importance, recurrent or persistent angina post-PCI is associated with a significant economic burden, with a total healthcare costs in the first year after the index PCI that were 1.8 times greater compared with patients without angina post-PCI [19].

Thus, angina post-PCI represents an important clinical syndrome approximately involving from one fifth to one third of patients undergoing myocardial revascularization at 1-year follow-up even when functional assessment is used to guide revascularization. In this review, we summarize the mechanisms of angina after PCI, suggesting a diagnostic algorithm and a systematic therapeutic approach.

2. Pathophysiological mechanisms of angina after PCI

The pathophysiology of angina persisting or recurring after successful PCI is complex and includes both structural and functional alterations (Fig. 1).

2.1. Structural causes of angina after PCI

Structural causes of post-PCI angina include in-stent restenosis (ISR), stent thrombosis, progression of atherosclerotic disease in other coronary segments, incomplete revascularization, and diffuse atherosclerosis without focal stenosis.

Stent thrombosis and ISR are the two major causes of stent failure, but are now rare cases of recurrent angina after PCI. The incidence of

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Table 1
Incidence of persistent or recurrent angina after PCI.

Study	Study design	Patients with angina post-PCI	Follow up time (months)
COURAGE [1]	RCT comparing PCI vs OMT	34%	12
ARTS [12]	RCT comparing PCI with BMS vs CABG	21%	12
ABSORB III [15]	RCT comparing PCI with EES vs PCI with BVS	18.4% in EES group, 18.3% in BVS group	12
SYNTAX [16]	RCT comparing PCI vs CABG	28.5%	12
FAME [18]	RCT comparing FFR-guided vs angio-guided PCI	19% in FFR group, 22% in angio group	12
NHLBI Dynamic Registry [14]	Registry	20%	12
Ben-Yehuda [19]	Registry	28%	12

Legend: BVS: bioresorbable vascular scaffold; CABG: coronary-artery bypass graft; EES: everolimus-eluting stent; FFR: fractional-flow reserve; OMT: optimal medical therapy; RCT: randomized controlled trial.

both, indeed, has considerably been reduced in recent years by the introduction of second and third-generation DES. Contemporary DES registries and randomized trials typically show rates of stent thrombosis <1% at 1-year and ~0.2–0.4% per year thereafter, and rates of clinically relevant ISR of 5% only at 1-year [20].

Recurrence of angina due to progression of coronary atherosclerosis in coronary segments different from those treated with PCI is also infrequent in the months after the procedure. Accordingly, <5% of major adverse events were related to non-culprit lesions in the PROSPECT study at 1 year follow up [21]. Recurrence of angina due to ISR or progression of atherosclerosis in untreated coronary segments appears to be higher in diabetic patients in whom it was found to be 12% at 1-year follow up in one study [22].

Angina persistence caused by incomplete coronary revascularization in patients with multivessel coronary disease is about 30% in the current PCI, although definitions of incomplete revascularization are heterogeneous [23].

Diffuse coronary atherosclerosis without focal stenosis in untreated segments and presence of myocardial bridges are other potential causes of persistent angina [24–26].

Taken together available data suggest that structural mechanisms explain not >50% of cases of persisting angina after successful PCI.

2.2. Functional causes of angina after PCI

Functional causes of angina after PCI include vasomotor abnormalities of epicardial coronary arteries and/or coronary microvascular dysfunction (CMD). In some patients persisting angina in the absence of myocardial ischemia can be caused by stent-related mechanical stretch of the arterial wall. Overall, they are the likely cause of persistent angina after successful stent implantation in about half of patients [27,28].

Significant vasoconstriction of epicardial coronary arteries at the level of or distal to the PCI site is a potential cause of recurrent angina. Of importance, Ong et al. [28] documented enhanced epicardial vasoconstriction (>75% narrowing), associated with reproduction of patient's symptoms, in response to intracoronary acetylcholine (ACh) administration (increasing intracoronary dose for the left coronary artery up to 200 μg and a fixed 80 μg dose for the right coronary artery) in 51 out of 104 patients (49%) undergoing coronary angiography for post-PCI recurrent angina and found to have no significant coronary stenosis, suggesting its likely role in angina recurrence. Of note, epicardial constriction was suggested to be also a predictor of poor vascular healing and subsequent stent thrombosis [29]. Activation of Rho-kinase pathway, the central molecular mechanism of spontaneous coronary spasm might be involved in the pathogenesis of DES-related enhanced epicardial vasoconstriction [30].

The role of CMD in post-PCI angina, type 3 according to the classification proposed by Camici and Crea [31], has been suggested by several studies. Li et al. [32], using the intracoronary thermodilution method, recently found a greater reduction of coronary blood flow (CBF) and a greater increase of the index of microvascular resistance (IMR) in response to intravenous adenosine (140 μg/Kg/min), in patients with post-PCI recurrent angina, compared to PCI patients without recurrent angina; of note, the hyperaemic CBF and IMR impairment was even more relevant in those with positive exercise stress test (EST) and abnormalities persisted at 6- and 12-month follow-up. These findings are in agreement with those by Milo et al. [33], who, using transthoracic Doppler echocardiography of the left anterior descending (LAD) coronary artery, found reduced CBF response to adenosine (140 μg/Kg/min) at 3- and 6-month follow-up in patients with successful PCI of single-vessel disease of the LAD artery with evidence of myocardial ischemia on treadmill EST, compared to those with negative EST. Importantly, a similar impairment of CBF response to cold pressor test also was found in this study, suggesting that endothelium-dependent vasodilator function of coronary microcirculation was impaired in these patients. Of note, a greater impairment of CMD predicted LAD restenosis at long-term follow-up in these patients [34]. Similar findings were demonstrated in other studies. Of note, Hokimoto et al. [35], in 105 patients who underwent PCI with second-generation DES, found an impairment of CBF response to both the endothelial-dependent stimulus ACh (<50% increase in CBF to the maximal dose of 100 μg) and the endothelial-independent stimulus adenosine (CBF response ratio <2.0). Overall, in this study, CMD was found in 59% of patients with previous PCI; among them, endothelium-dependent CMD alone, endothelium-independent CMD alone, and both being found in 40%, 23%, and 37%, respectively. Finally, Ong et al. found that coronary microvascular vasoconstriction might contribute to post-PCI recurrent angina. Indeed, in the previously quoted study [28], 18 patients (17%) showed evidence

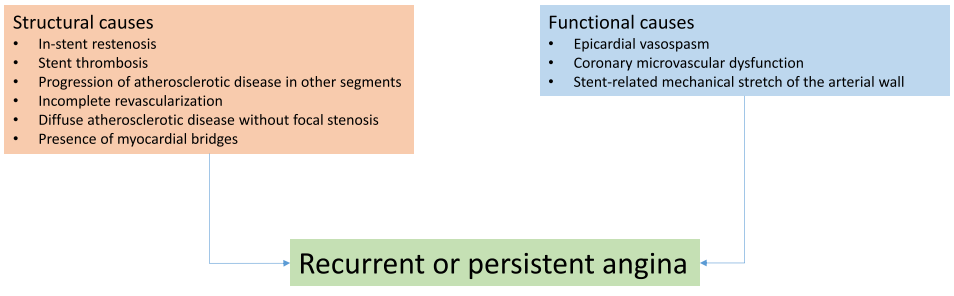

Fig. 1. Mechanisms of recurrent or persistent angina after percutaneous coronary intervention (PCI).

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