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Coronary arterial system: pathophysiological hints from large clinical trials

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Chronic myocardial ischemia is a debilitating disease in terms of both morbidity and mortality. In the late 1960s myocardial revascularization with coronary artery bypass grafting (CABG) was first introduced. Only a few years later percutaneous coronary intervention (PCI) was announced as an alternative revascularization strategy. Although frequently investigated in comparative effectiveness studies, two major practical concerns have continuously accompanied clinical practice since then: is coronary revascularization better than medical therapy, and is CABG interchangeable with PCI in terms of efficacy?

Among the three treatment options (medical therapy, CABG and PCI), PCI represents the strategy more often being brought into question. The latest PCI versus medical therapy comparative effectiveness study was recently published in the *New England Journal of Medicine* [1].

On the other hand, the efficacy of PCI has been continuously juxtaposed to CABG. In this regard, most studies have suggested better outcomes with CABG for patients with three-vessel or diffuse disease and for those with left ventricular dysfunction [2, 3]. The superiority of CABG over PCI has been also suggested for patients with diabetes in the Bypass Angioplasty Revascularization Investigation (BARI) [4] and BARI-2D [5] trials. However, both revascularization techniques have evolved, with CABG performed off-pump and adopting arterial grafts and, on the other hand, PCI is performed with continuously advancing stenting technology and better availability.

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial [6] sought to compare the efficacy of CABG versus PCI with drug-eluting stents in 1900 patients with diabetes. At 5 years' follow-up, patients assigned to undergo CABG had significantly lower mortality (10.9% versus 16.3%) and fewer myocardial infarctions (6.0% versus 13.9%) than patients with diabetes undergoing PCI. However, CABG was associated with a higher rate of stroke (5.2% versus 2.4%), which occurred prevalently within 30 days after revascularization. Similar results were also obtained from the long-term follow-up of the SYNTAX trial [7] conducted in patients with three-vessel and/or left main disease but no diabetes mellitus.

Almost 40 years after the first trials of myocardial revascularization, new trials are asking the same questions. This attitude is principally based on the belief that evolving technology can significantly modify results. However, the data on patients with multivessel/left main disease speak for themselves: irrespective of newer technology with drug-eluting stents, cardiac surgery with graft implantation proves to have better outcomes than PCI.





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Clinical studies are designed on the basis of previously established concepts. However, the results of the above-mentioned trials suggest that we probably need to learn the lesson and ask the right question by going back to basic studies.

Similar to surgery, percutaneous revascularization virtually abolishes trans-stenotic pressure gradient. Nonetheless, patients treated with PCI have worse outcomes, and this does not appear to be related to the occurrence of repeat revascularization, a finding that is clearly more frequent in this patient population [8].

The coronary vascular tree is composed of a dynamic entity, including larger and smaller arteries, capillaries and smaller and larger veins. Each entity is subdivided into microdomains that bear different functions, aimed at satisfying changing circulatory needs. Alterations at varying levels of the regulatory mechanisms may compromise flow distribution and give rise to myocardial ischemia. The complex relationship between coronary macro and microcirculation is better evidenced following removal of a flow-limiting stenosis. Indeed, following a successful angioplasty, coronary flow reserve may return to normal, remain unchanged [9] or become impaired [10], and may show different behavior over time. What is more, activated platelets, produced at the level of epicardial segments, can affect microvascular resistance by microembolization and/or release of constrictive, pro-thrombotic, and pro-inflammatory factors. The negative interaction between platelet adhesion molecules and microvascular obstruction has been evaluated in experimental models of ischemia without coronary thrombosis [11], and this phenomenon has recently also been demonstrated in human studies [12]. In addition, an alternative interaction, with the epicardial segment (or implanted graft in the case of surgery) acting like the “hub” of parallel “microcirculatory spokes” can also be hypothesized. If

these are only some of the known and/or hypothesized interactions within the coronary tree, how can we be so sure and believe that abolishing epicardial gradient always corresponds to the remedy? •

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