Ischemia-Guided Myocardial Revascularization: the Oculo-ischemic Reflex

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In stable coronary artery disease, the indication for revascularization procedures based on the anatomical detection of stenotic coronary lesions, regardless of clinical findings, has been called 'oculostenotic reflex'. That expression was ironically created by Topol E. and Nissen S., and aimed at warning about the fact that not every obstruction has to be approached invasively[1]. At least from the academic viewpoint, that reflex seems to have been overcome, being currently considered an overtreatment[2]. However, the belief that the demonstration of myocardial ischemia by use of complementary methods indicates the need for revascularization still persists, and has been called 'oculo-ischemic reflex'.

Let us consider an asymptomatic individual, undergoing routine myocardial scintigraphy, which detects ischemia in two coronary artery territories. Based on that result, the patient is submitted to coronary angiography, which identifies 75% stenoses in the middle third of the anterior descending coronary artery and in the proximal third of the right coronary artery. Although the patient is asymptomatic and has good ventricular function, the physician indicates pharmacological stent implantation in both lesions, based on the presence of myocardial ischemia identified in both vascular territories.

The hypothesis that revascularization is beneficial in cases like that is grounded in the association between myocardial ischemia presence/extent and worse prognosis, which characterizes ischemia as a risk marker[3,4]. However, the idea that interfering with a risk marker necessarily ensures clinical benefit is an example of normalization heuristic[5]. That cognitive error occurs when a physician believes that the mere correction of parameters (ischemia) will necessarily imply a benefit to a patient. In that scenario, the indication of a coronary intervention requires the demonstration of its clinical benefit via studies evidencing interaction between the presence of ischemia and the efficacy of myocardial revascularization. The present study review the scientific evidence that tests the 'oculo-ischemic reflex' by use of interaction analysis in randomized clinical trials.

Keywords

Myocardial Revascularization; Myocardial Ischemia; Coronary Artery Disease.

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Randomized clinical trials

In stable coronary artery disease, randomized clinical trials have shown that myocardial revascularization does not usually prevent major cardiovascular events, such as death and myocardial infarction[6-8]. What those clinical trials have reported on patients with myocardial ischemia should be assessed. That is, would myocardial revascularization provide an additional benefit regarding the prevention of major cardiovascular events to patients with ischemia?

The COURAGE trial

The most cited clinical trial in that scenario is the COURAGE (*Clinical* Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial[7], which has compared randomly and by intention to treat the initial management of stent coronary intervention *versus* control, and both groups underwent optimized clinical treatment. That study was negative for its primary objective, evidencing identical incidence of death or myocardial infarction in both groups. Thus, the only reason to perform percutaneous coronary intervention in stable disease is to control clinically relevant symptoms.

Regarding the paradigm that revascularization should be performed in case of myocardial ischemia, it is important to assess if the conclusion of the COURAGE trial is valid for ischemia identified on complementary tests. Of the patients undergoing myocardial scintigraphy in the COURAGE trial (61% of that trial sample), 89% had ischemia, and 67% showed ischemia in multiple coronary territories. Because the election of patients to undergo scintigraphy has not been based on disease severity, their data allowed us to infer that the inclusion criteria of the COURAGE trial were sufficient to select patients with a significant ischemic load.

Complementing that analysis, a recent sub-study of the COURAGE trial has tested the statistical interaction between moderate-severe ischemia and the effect of the coronary intervention[9]. Moderate-severe ischemia has been defined as the one present in at least three of the six ventricular walls (anterior, lateral, inferior, posterior, septal and apical). According to that classification, 30% of the patients in that trial had moderate-severe ischemia. In addition, the interventional treatment has benefited neither the group without moderate-severe ischemia (19% *versus* 19% of death/infarction, respectively), nor that with moderate-severe ischemia (24% *versus* 21%, respectively). From the statistical viewpoint, there was no interaction ($p = 0.65$) between the presence of ischemia and the effect of percutaneous myocardial revascularization.

It is worth noting that, in 2008, that same sub-study was published in *Circulation*[10], and the authors showed an association of the presence of residual ischemia with worse

prognosis (risk marker). Based on that, revascularization has been suggested for those patients, representing another example of the normalization heuristic. In addition, the association between ischemia and outcome lost statistical significance on multivariate analysis, which was not valued in that article's conclusion. Thus, the current publication of the nuclear sub-study of the COURAGE trial[9], cited in the previous paragraph, represents a correction of that mistaken publication[10].

BARI-2D trial

The BARI-2D (Bypass Angioplasty Revascularization Investigation) trial has randomly compared the revascularization strategy *versus* the non-revascularization strategy in patients with type 2 diabetes on optimized clinical treatment[6]. The revascularization could be either percutaneous or surgical, depending on medical decision. Similarly to the COURAGE trial, the BARI-2D trial has shown no reduction in major outcomes (death, infarction and cerebrovascular accident) with the revascularization strategy.

A sub-study of the BARI-2D trial, testing the interaction between ischemia and the benefit of revascularization, has been recently published[11]. In that sub-study, 1,505 patients (64% of the sample) have undergone myocardial scintigraphy. The percentage of ischemic myocardium has been calculated according to the analysis of 17 segments. No interaction between the percentage of ischemic myocardium and the treatment effect on cardiovascular events has been identified ($p = 0.44$). That is, independently of the ischemic burden, no reduction in major outcomes has been observed with revascularization.

STICH trial

The STICH (Surgical Treatment for Ischemic Heart Failure) trial has randomized 1,202 patients with ischemic cardiomyopathy and left ventricular ejection fraction ≤ 35% for either surgical revascularization or clinical treatment[12]. The STICH trial, thus, has tested the same hypothesis of the COURAGE and BARI-2D trials, but in a different population, characterized by severe left ventricular systolic dysfunction. In addition, differently from the other studies, the revascularization treatment was necessarily surgical. The STICH trial has shown no reduction in mortality with surgical treatment, expanding the external validity of the learning originating from the COURAGE and BARI-2D trials.

Regarding the interaction with myocardial ischemia, a sub-study with 399 patients from the STICH trial who had undergone stress test imaging (radionuclide stress test or dobutamine stress echocardiography) was published in 2013. That study showed no benefit of revascularization, independently of the presence of ischemia (P of interaction = 0.64)[13].

FAME-II trial

The FAME-II (Fractional Flow Reserve Versus Angiography in Multivessel Evaluation) trial has included patients with coronary artery lesions associated with fractional flow reserve (FFR) < 0.80, that is, functionally significant. Those patients have been randomized to coronary intervention *versus* control, and both groups have received optimized clinical treatment[8]. The incidence of death or infarction was identical in both groups, a result similar to that obtained in the COURAGE trial[5] and BARI-2D trial[4]. Unlike previous clinical trials, the FAME-II trial has included the need for revascularization as part of the primary composite outcome, which alone accounted for the benefit obtained in that outcome. Thus, that is one more evidence that the presence of ischemia on a complementary test (FFR) does not ensure the reduction in major clinical outcomes.

ISCHEMIA trial (future perspective)

Within a few years, the result of the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial (http://clinicaltrials.gov/show/NCT01471522) will be known. That is a clinical trial similar to the COURAGE trial, and with the following differences: (1) only patients with moderate or severe ischemia have been included; (2) revascularization can be either surgical or percutaneous, according to clinical criteria. Considering the large expectations regarding that study, one can try to predict its results as a scientific exercise. Following Bayesian reasoning, considering the consistent lack of interaction between ischemic burden and revascularization treatment benefit, the presumptive likelihood that that study will show benefit regarding the primary outcome of death or infarction is small. In other words, if moderate-severe ischemia has not proven to be the determinant of benefit according to all evidence, the selection of patients with that degree of ischemia would not result beneficial for the intervention.

On the other hand, a positive result will be more likely if the inclusion criterion of the ISCHEMIA trial originates from a sample with extremely severe disease (three-vessel disease), in addition to the predominance of the surgical revascularization approach. In that case, we will have another scenario: three-vessel patients receiving surgical treatment. Considering the recent results of the FREEDOM[14] and SYNTAX[15] trials, surgery is more effective than percutaneous treatment in predominantly three-vessel patients, regarding major clinical outcomes. This supports the possibility that the predominance of surgical treatment might result positive.

However, a positive result of the ISCHEMIA trial should not be interpreted as evidence that validates the 'oculo-ischemic reflex'. The ISCHEMIA trial could only test that hypothesis if it comprised patients with and without significant ischemia, which would enable the interaction analysis.

Myocardial ischemia imaging: marker or risk factor?

The expression 'risk factor' denotes a variable that increases the patient's risk. Differently, a 'risk marker' is positively associated with risk, but does not contain the origin of the risk. Myocardial ischemia is undoubtedly part of the pathophysiology of coronary artery disease and serves as a causal mediator of clinical outcomes, such as ventricular arrhythmia and dysfunction. However, what we should discuss is whether the detection of ischemia on complementary tests should be related mainly to the concept of risk factor or risk marker.

The idea that chronic myocardial ischemia should be treated invasively results from the cognitive error of concluding causality from a mere association. The presence of causality depends on several scientific criteria that have been organized by Bredford Hill[16]. We will analyze the following three major criteria to assess whether ischemia is a cardiovascular risk factor: plausibility, independent association, and reversibility.

Acute coronary events are caused by instability of the atherosclerotic plaque. Myocardial ischemia is known to be determined by the extent of coronary artery obstruction rather than by the plaque's vulnerability to instability. Angiographic studies have shown that a large amount of infarctions result from non-obstructive plaques, which would cause no ischemia[17]. Thus, there is a pathophysiological dissociation between the presence of ischemia and the risk of plaque destabilization, making the direct association between ischemia and incidence of major coronary events less likely. Let us consider a patient with multiple non-obstructive plaques (stenosis < 50%) on the coronary bed, in addition to one single obstructive plaque (stenosis > 70%) that causes ischemia. The implantation of one stent in that obstructive plaque will reduce ischemia, but the patient will remain vulnerable to infarction because of the other plaques that cause no ischemia.

An older COURAGE sub-study has shown the association between the presence of residual ischemia on scintigraphy and the risk of cardiovascular events. However, when adjusting to confounding variables, that association lost statistical significance ($p = 0.26$)[10]. The lack of independent association between residual ischemia and cardiovascular risk suggests that such relationship is mediated by other risk variables that are simultaneously associated with the predictor and outcome, called confounding variables. This is one more suggestion that ischemia is not the major risk factor determining the prognosis.

Finally, reversibility is the most important criterion of causality, occurring when the treatment of the condition causes a reduction in the patient's risk. For example, treating high LDL-cholesterol levels promotes a reduction in infarction rate, and reducing arterial blood pressure promotes a reduction in cerebrovascular accident. Thus, elevated cholesterol and arterial blood pressure levels are risk factors for cardiovascular events. On the other hand, treating ischemia with invasive procedures reduces the risk of neither infarction nor cardiovascular death.

So far, evidence has shown that, in predicting a coronary atherothrombotic event, stable myocardial ischemia should be interpreted as a risk marker and not as a risk factor to be approached with revascularization procedures.

Change to the clinical paradigm

The true guide for revascularization need should be clinical findings. More than the tests that confirm ischemia, the clinical findings represent the patient's actual functional assessment. If ischemia is interfering negatively with the patient's daily routine, because of the presence of symptoms, revascularization might be beneficial. That benefit has been confirmed by the COURAGE trial, which has shown better symptom control when patients undergo revascularization[7].

North-American statistics have shown that only half of elective percutaneous coronary interventions are classified as appropriate[18], and most of the inappropriate ones result from performing procedures in asymptomatic patients. This seems to be measured by the phenomenon that we call 'oculo-ischemic reflex'. Such reflex should be corrected via a patient-centered and evidence-based medical practice.

In addition, because resource wasting with futile procedures should be avoided, the best evidence available supports the idea that for patients with asymptomatic ischemia, less might be more.

Author contributions

Writing of the manuscript: Correia LCL; Critical revision of the manuscript for intellectual content: Correia LCL, Noya-Rabelo M, Barreto-Filho JA.

Potential Conflict of Interest

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