Short Communication

Interventional Cardiology

Revascularization of chronic total occluded coronary arteries: probable benefits and possible harms

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Introduction

Chronically total occluded (CTO) coronary artery that is occluded for more than 3 months are commonly identified at angiography [1]. These can be found in 20 to 40% of patients with coronary artery disease [1]. They are a common cause of angina, left ventricular dysfunction and a predictor of cardiovascular mortality. Mortality in patients with total occlusion of the left anterior descending (LAD) coronary artery or of an artery other than the LAD are around 10% and 4% annually [2-3].

Such high mortality rates might seem counterintuitive in the setting of a chronic, stable coronary condition [1-3]. However, adverse events in this patient population occur not exactly from progression of the chronic occlusion, but usually from new obstructions elsewhere in the coronary arteries [2-3]. Patients with total occlusion of one vessel have a limited ability to withstand new events [1-3]. This happens mainly because of pre-existing LV dysfunction and also due to the fact that the occlusion of a second coronary vessel would probably compromise not only its related myocardial territory, but also the viable myocardium related to the first occlusion, secondary to the sudden impairment of collateral flow [1-3].

The role of myocardial revascularization is clear in those patients presenting with an acute coronary syndrome or limiting angina, according to several international guidelines [4-6], the role in those patients presenting either incidentally diagnose of coronary artery disease, with predominant heart failure symptoms, or in those presenting mild angina is less well defined and lacks randomized outcome data to support its adoption [5-6]. Thus, there is still a frequent and controversial debate in-between cardiologist, interventional cardiologists and cardiac surgeons about the necessity to promote revascularization of the myocardial related to an occluded vessel in several patients presenting CTO [4-6].

There are several commonly cited justifications for attempting an angioplasty or cardiac surgery to promote revascularization in CTO patients: for treatment of angina or other symptoms of coronary insufficiency; in response to important abnormal findings on stress testing; to decrease left ventricle (LV) remodelling; to improve LV function; and, mainly, to improve survival [4-6]. Thus, there is a common sense that, if there is evidence of a good extension of viable "hibernating" or "stunned" myocardium, especially if associated with symptoms related to myocardial ischemia, some type of cardiac revascularization should be performed. The majority of international guidelines support this conduct [4-6]. The "stunned" myocardium may arise from different conditions that may lead to this altered myocardial function, such as: episodic and / or chronically reduced blood flow, tissue ischemia and resulting remodeling without necrosis, and altered metabolic processes in the myocardial cell in relation to contractile function, residual contractile reserve in response to inotropic stimulation and recovery of contractile function after successful revascularization [7-10].

However, it is not that simple to indicate revascularization of the myocardium related to CTO arteries, especially in asymptomatic or even in mild symptomatic patients [4-6]. Another big challenge in daily clinical practice is to decide whether or not to indicate revascularization, in those patients with heart failure symptoms, but without clear evidence about the presence of large

viable myocardial [4-6]. All the possible complications and mortality associated with percutaneous or surgical revascularization are always big concerns and should always be taken into account [4-6].

At the beginning of this century, and before the development of drug eluting stents, attempting angioplasty in the setting of total coronary occlusion (TCO) was, usually, not reasonable. At that time, we had few tools, techniques and experts to deal with this situation [11]. Success rates in opening occluded vessels were then, around 70%. The restenosis rates with conventional stents were also very high (around 50%), with a 10% chance of total re-occlusion in the following months after recanalization [11].

However, during the past decade, we witnessed an incredible development in tools, techniques and technical capacity of interventional cardiologists to deal with this difficult situation [12]. The rates of success at reopening CTO depends on the availability of tools to deal with this angiographic challenge, on the availability of drug eluting stents and on the experience of the interventional team [12]. Teewen et al. for instance, recently described excellent results with the recanalization of CTO, obtaining good results after 9 months in the PRISION IV trial (target vessel failure rates of 6.6%) [12].

Besides all the good results obtained in recent years with coronary interventions, we have to remember all the possible complications related with the attempts to open the CTO vessels. When trying to open occluded vessels, a more aggressive technique may be necessary to cross a total occlusion; therefore, an increased risk of dissection or perforation and consequently cardiac tamponed or death should always be a concern [6,10-12].

Historically, surgical cardiac revascularization was always considered the gold pattern to conduct patients with CTOs and extensive areas of ischemic myocardial. With the improvement of surgical myocardial revascularization techniques and results in recent years, surgery indication will always have to be considered for all patients, especially, if LAD is also totally or partially compromised. But, surgical rate mortality varies a lot in different hospitals and regions from around 3 to 10% [6-10]. Thus, local rates of success and complications after cardiac surgery should also be considered [6-10].

But, despite the instinctive and natural feeling that we should always open or implant a graft in an important occluded coronary vessel, we still do not have good scientific proof that revascularization should always be performed in patients with CTO. Two trials frequently cited by scientists while debating the management of patients with CTO are the OAT TRIAL [8] and the STICH TRIAL [13].

There is not enough data to compare prognosis of patients presenting CTO vessels while submitted to different approaches (medical treatment, PCI or surgical revascularization-CABG) [13]. Although including patients with sub-acute coronary occluded arteries (not properly CTO), the OAT Trial showed no reduction in death, myocardial infarction (MI), or class IV heart failure when stable patients with persistent infarct artery occlusion underwent routine coronary recanalization using percutaneous coronary intervention (PCI) with stent implantation compared with optimal medical therapy alone [13]. Patients were followed over a 2.9 years mean follow-up period [13]. Actually, there was an adverse trend in the PCI group in the secondary endpoint of nonfatal re-infarctions (p=0.08) [14]. The viability study confirmed that most OAT patients (70%) had at least moderately retained viability in the infarct zone and that PCI did not affect EF or volume changes compared to medications, even among patients with viability [15]. Besides these disappointing results, angina was reduced in the PCI group through 3 years in the main trial [8].

Although having included patients with all types of ischemic cardiomyopathy (ICM), and not only patients presenting CTOs, the STICH trial [9] assessed the impact of surgical revascularization on clinical outcomes in ICM. In this study, 1212 patients with an ejection fraction of less than 35% and coronary artery disease were randomized to undergo CABG alongside optimal medical therapy (OMT) or OMT alone [16]. The 5 year follow up of this study, published in 2011, involving patients with ICM, did not demonstrate an overall mortality benefit with revascularization in comparison to medical treatment alone for ischemic patients [16]. However, surprisingly, the ten year follow up of this largest completed trial to date, involving patients with ICM, published in 2016, showed a mortality rate of 58.9% (359 patients) in the CABG group and of 66.1% (398 patients) in the medical-therapy group (hazard ratio with CABG vs. medical therapy, 0.84; P=0.02 by log-rank test) [17]. Rates of death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes were significantly lower over 10 years among patients who underwent CABG in addition to receiving medical therapy than among those who received medical therapy alone [17]. These benefits with CABG seem to be especially greater in younger patients [17].

PCI intervention may regulate processes involved in the episodic and/or chronically reduced blood flow, tissue ischemia and cardiac remodeling, and altered metabolic processes in the myocardial cells. PCI may recover residual contractile reserve and contractile function by a successful revascularization. In fact, PCI may induce an up-regulation in endothelial progenitor cells that may induce and regulate all these supposed mechanisms [18].

Similarly, these patients may present an altered inflammatory tone and oxidative stress regulation in atherosclerotic plaque, and are involved in these adaptive processes that may be improved after percutaneous revascularization of the CTO [19].

Smoke has a profound effect on vessel homeostasis through the activity of single smoking compounds and it can affect each stage of the atherosclerotic process, from development until degeneration and rupture of the atherosclerotic plaque with consequent thrombotic events [20]. Many intrinsic factors can affect plaque instability; among these, the most relevant are the degradation of extracellular matrix proteins and their reduced synthesis, the increased infiltration of inflammatory cells, and intra-plaque haemorrhage. All of these phenomena are affected by smoke and atherosclerotic plaques of smokers are characterized by a predominance of lipid core, and the fibrotic cap is thinner than in non-smokers [21,22]. Smoking cessation should be emphasized in patients with CTO.

Conclusion

In conclusion, the management of patients presenting a CTO coronary vessel should always be individualized. There is still no unique, standard and perfect strategy for all patients. The decision about how to manage this frequent situation in our daily clinical practice should be based, not only in the presence of limiting symptoms, but also in a careful analysis of the presence and extent of viable and ischemic myocardial. Several clinical conditions such as age, life expectancy, presence of comorbidities (diabetes, renal insufficiency, pulmonary chronic disease, liver disease, fragility, higher bleeding or thrombotic risk) and angiographic characteristics (LV function, number of compromised vessels, left main or proximal LAD obstruction, presence of associated arrhythmias, LV thrombus, valve dysfunctions or aorta disease) will always have to be carefully analyzed for each individual patient decision. At the same time, the availability of adequate tools, the knowledge of all the interventional techniques to access CTO vessels, the technical capacity of the interventional team and the local mortality related to cardiac surgical procedures should also be considered and used to orientate the best clinical decision about which treatment should be indicated: medical management, stent implantation, surgery or hybrid approach.

References

1. Ge JB. Current status of percutaneous coronary intervention of chronic total occlusion. *J. Zhejiang. Univ. Sci. B.* 13(8): 589-602 (2012).
2. Borowski A, Godehardt E, Dalyanoglu H. Surgical decision making for revascularization of chronically occluded right coronary artery. *Gen. Thorac. Cardiovasc. Surg.* 65(1): 17-24 (2017).
3. Schob A, Auerbach E. Chronic Total Occlusions. In: Interventional Cardiology Secrets. *Hanley. & Belfus.* pp: 189 (2003).
4. Windecker S, Kolh P, Alfonso F, *et al.* 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart. J.* 278: 52 (2014).
5. Yancy CW, Jessup M, Bozkurt B, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 128(16): e240–e327 (2013).
6. Montalescot G, Sechtem U, Achenbach S, *et al.* 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the Management of Stable Coronary Artery Disease of the European Society of Cardiology. *Eur. Heart. J.* 34(38): 2949–3003 (2013).
7. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium". *J. Am. Coll. Cardiol.* 8: 1467(1986)
8. Rahimtoola SH. The hibernating myocardium. *Am. Heart. J.* 117: 211 (1989).
9. Ling LF, Marwick TH, Flores DR, Jaber WA, Brunken RC, Cerqueira MD. Identification of therapeutic benefit from revascularization in patients with left ventricular systolic dysfunction: inducible ischemia versus hibernating myocardium. *Circ. Cardiovasc. Imaging.* 6(3): 363-372 (2013).
10. Milei J, Fraga CG, Grana DR, Ferreira R, Ambrosio G. Ultrastructural evidence of increased tolerance of hibernating myocardium to cardioplegic ischemia-reperfusion injury. *J. Am. Coll. Cardiol.* 43(12): 2329-2236 (2004).
11. McMurray JJV, Adamopoulos S, Anker SD, *et al.* ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. *Eur. J. Heart. Fail.* 14(8): 803–869 (2012).
12. Sallam M, Spanow V, Briguori C, *et al.* Predictors of re-occlusion after succesful recanalization of chronic total occlusion. *J. Invas. Cardiol.* 13: 511-515 (2001).
13. Teeuwen K, van der Schaaf R , Adriaenssens T, *et al.* Randomized Multicenter Trial Investigating Angiographic Outcomes of Hybrid Sirolimus-Eluting Stents With Biodegradable Polymer Compared With Everolimus-Eluting Stents With Durable Polymer in Chronic Total Occlusions: The PRISON IV Trial. *JACC. Cardiovac. Interv.* 10(2): 133-143 (2017).
14. Hochman JS, Lamas GA, Buller CE, *et al.* Coronary intervention for persistent occlusion after myocardial infarction. *N. Engl. J. Med.* 355: 2395–2407 (2006).
15. Velazquez EJ, Lee KL, Deja M, *et al.* Coronary-artery bypass surgery in patients with left ventricular dysfunction. *N. Engl. J. Med.* 364(17): 1607–1616 (2011).
16. Udelson JE, Pearte CA, Kimmelstiel CD, *et al.* The occluded artery trial (OAT) viability ancillary study (OAT-NUC): influence of infarct zone viability on left ventricular remodeling after percutaneous coronary intervention versus optimal medical therapy alone. *Am. Heart. J.* 161:611–621 (2011).
17. Bonow RO, Maurer G, Lee KL, *et al.* Myocardial viability and survival in ischemic left ventricular dysfunction. *N. Engl. J. Med.* 364(17): 1617–1625 (2011).
18. Velazquez EJ, Lee KL, Jones RH, *et al.* Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. *N. Engl. J. Med.* 374(16): 1511-1520 (2016).
19. Petrie MC, Jhund PS, She L, *et al.* Stich Trial Investigators. Ten-Year Outcomes After Coronary Bypass Grafting According to Age in Patients With Heart Failure and Left

Ventricular Systolic Dysfunction: An Analysis of the Extended Follow-Up of the STICH Trial (Surgical Treatment for Ischemic Heart Failure). *Circulation.* 134(18): 1314-1324 (2016).

20. Balestrieri ML, Rizzo MR, Barbieri M, *et al.* Sirtuin 6 expression and inflammatory activity in diabetic atherosclerotic plaques: effects of incretin treatment. *Diabetes.* 64(4): 1395-1406 (2015).
21. Gambardella J, Sardu C, Sacra C, Del Giudice C, Santulli G. Quit smoking to outsmart atherogenesis: Molecular mechanisms underlying clinical evidence. *Atherosclerosis.* 16: S0021-9150 (2016).
22. A. Csordas, D. Bernhard, The biology behind the atherothrombotic effects of 244 Editorial / Atherosclerosis cigarette smoke. *Nat. Rev. Cardiol.* 10: 219-230 (2013).