

The stent, the Procrustes for chronic total coronary occlusions?

See page 1175 for the article to which this Editorial refers

Procrustes, annoyed with the variable height of visitors, stretched the short ones and chopped off the feet of the tall ones to make them all equal. According to the paper of Schofer *et al.*^[1] the stent does the same with chronic total occlusions during coronary angioplasty.

Chronic total occlusions defy coronary angioplasty predominantly at the front end of the procedure (failure to pass). But they are also a problem at the back end (higher rate of recurrence and reocclusion) albeit in a less conspicuous manner. Because of these two blemishes, chronic total occlusions are a primary reason for referring a patient to coronary bypass surgery rather than to angioplasty^[2,3].

Intrigued by earlier reports comparing the results of coronary angioplasty in chronic total occlusions with those in stenoses, such as in the MARCATOR trial^[4], Schofer *et al.* dug into their own data bank. Among 1276 patients with coronary stent placement and angiographic follow-up, they matched 144 patients with a chronic total occlusion at the outset with 144 patients with a non-total lesion. The set of matching criteria were demanding and included variables such as sex, diabetes, de novo or restenotic lesions, vessel diameter, type of stent used, and stented segment length. The authors were curious as to whether the difference in reocclusions, which amounted to 19% for previous occlusions and 7% for previous stenoses in the MARCATOR trial, and the difference in restenoses documented in numerous other studies were still present after stenting of such lesions. While based on absolute figures, they did find a disadvantage as regards prior occlusion (restenosis 33% for occlusions and 27% for stenoses, reocclusions 5% and 3%, respectively), this difference was small and far from reaching statistical significance in their patient cohort. Although a type-II error cannot be excluded, it is safe to assume that such a small difference would hardly be clinically relevant even if proved real by a randomized study with sufficient power. The paper indicates that it is not the totality of the initial lesion that determines the long-term outcome but the length of the stented segment.

These results are important to aggregate to the decision making process but they come as no surprise. The difference in restenosis rates was of similar

smallness in the MARCATOR trial (49% in occlusions compared with 42% in stenoses) where stents were not yet an important factor^[4]. A similar study published recently has shown that the difference in restenosis rates between occlusions and stenoses treated with stenting was negligibly small (restenosis and reocclusion rates 27% vs 22% and 6% vs 3%, respectively)^[5]. While in this paper the assimilation of the results was credited, at least in part, to guidance with intravascular ultrasound, Schofer *et al.*^[1] achieved the same without ultrasound.

The high restenosis and reocclusion rates after angioplasty of chronic total coronary occlusions have been attributed to longer lesions, an aggressive approach with increased damage to the artery leading to enhanced proliferative stimuli and thrombosis, and reduced flow secondary to the (partially) infarcted myocardium distal to the occlusion and elevated coronary wedge pressure^[6,7]. The concept of the influence of length on angiographic recurrence was corroborated both by Schofer *et al.*^[1] and Moussa *et al.*^[5]. But the increased vessel trauma seems to be compensated for by stenting. After all, the stent carries the colloquial middle name 'equaliser'. The influence of collateral pressure, finally, does not seem to matter as much as previously thought. However, the papers pointing to the influence of collaterals as a harbinger of restenoses in non-stented lesions have targeted this question specifically and deserve more credibility than the retrospective analysis in the two stent papers. In these papers the presence or absence of collaterals was derived from a data bank. In the paper of Schofer *et al.*^[1], the data bank documented no collaterals in 28% of patients in whom a chronic total occlusion was tackled. It is hard to believe that in one out of four chronic total occlusions the peripheral vascular bed was not visible. This is generally considered a contraindication to attempt chronic total occlusions. It is more likely that the data bank was incomplete in this respect and that therefore conclusions on the role of collaterals from these data are highly speculative.

Nevertheless, the fact remains that the difference in angiographic recurrence after stenting occlusions or stenoses is remarkably small. The initial fear that restenoses will always be frequent in the subset of chronic occlusions, because collateral pressure remains high even after successful recanalization has been subdued by these new data. To a certain extent,

stents may occlude important collateral contributors placed immediately adjacent to the occlusion and therefore lower the coronary wedge pressure immediately. If this is an important mechanism of action, the other side of the medal will be that the risk of infarction is raised in the case of a reocclusion either soon or late after recanalization.

What else have we learned from stenting of chronic total occlusions? The long-term result after stenting is still dependent on the classic variables such as lesion length, post-intervention result, balloon-to-vessel ratio, and amount of dissection after first balloon inflation^[8], but less so than the result after conventional angioplasty. Stenting significantly reduced the need for reintervention for up to 3 years after chronic total occlusion angioplasty in randomized studies^[9-11].

All this is interesting to note and affects the way we deal with chronic occlusions. Let us not forget that recanalization of chronic total occlusions is the only indication for coronary angioplasty, short of primary angioplasty in acute myocardial infarction that has been shown to prolong life^[12,13]. This was achieved without a significant contribution by stenting. If stenting significantly improves the results of these interventions, this further fuels the enthusiasm to tackle chronic occlusions. This mandates endeavours on the 'front side' of the procedure where there is still a lot to do in spite of progress made by hydrophilic and other dedicated recanalization guide wires.

Assuming that restenosis rates can indeed be reduced by about 20% with stenting is no reason to ask for stenting in 100% of patients. First, restenosis in a recanalized chronic total occlusion is frequently clinically silent or trivial. Even if implanting stents in 100 patients obviates the need for repeat angioplasty in 10, we are overpaying for what we are getting. Repeat angioplasty in a formerly occluded artery is a simple and low risk procedure with an excellent chance of success. Admittedly, as reocclusion after recanalization is more difficult to tackle, the fact that about 5 per 10 reocclusions can be prevented by implanting 100 stents has to be looked at separately. But again, I do not think that it is cost-effective in this light either. Moreover, restenosis and reocclusion occur after stenting as well, and in-stent recurrences are more intricate to treat, particularly if long stents have been used. All authors concur that the need for long stents is a typical feature of chronic occlusion angioplasty.

A reasonable compromise is to carry the stent gun ready to draw but to leave it in the holster in 30%–50% of cases. These are the cases where balloon angioplasty results in a pleasing angiographic result with excellent flow in a large vessel, the cases where the clinical

importance of the recanalized vessel is small and bypass surgery is not considered because of the possibility of permanent reocclusion, the cases where it has been difficult to advance even a balloon catheter and stent placement is likely to fail or produce complications, and the cases where a long stent would be needed to achieve an angiographically ideal result but good flow has already been achieved without stenting. Finally, the presence of a single large collateral that would be covered and possibly occluded by the stent to be implanted should be an argument in favour of plain balloon angioplasty. Should the collateral be shut down by the stent, it would be regretted not only in the (admittedly rare) case of stent occlusion, but also in case of disease progression in the former collateral donor, which would then be dependent on reversed collaterals.

Procrustes has a long-standing bad reputation. This argues against adopting his methods in any field of medicine, or life for that matter. Evidence-based medicine works at its best when the evidence focuses on an extremely well-defined subgroup of patients. Patients with chronic total coronary occlusions are still too large and too inhomogeneous a group.

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Metabolic treatment of myocardial ischaemia

See *European Heart Journal Supplements Suppl. O* which accompanies this issue

The metabolic treatment of myocardial ischaemia is the topic of the Supplement which accompanies this issue.

Alterations of metabolic pathways are recognised as *primum movens* of myocardial ischaemia. Although there are several possible definitions for myocardial ischaemia, it is common knowledge that myocardial ischaemia is a condition that occurs when blood flow cannot supply the required amount of oxygen needed for mitochondrial oxidation. Once mitochondrial impairment is established, a series of typical metabolic alterations, such as intracellular acidosis, anaerobic metabolism and reduced production of high energy phosphates, occur. These all result in haemodynamic impairment, such as contractile down-regulation and reduction of ventricular compliance.

Even though the above-reported metabolic alterations seem to be intrinsic to the concept of myocardial ischaemia, and, thus, closely linked to the myocardial ischaemia itself, it is also a fact that the maintenance of the metabolic capacities of the cell should be the primary objective of the treatment of myocardial ischaemic. In fact, maintenance of the metabolic capacities of the cell is synonymous with the maintenance of its vitality, as is largely demonstrated by the recent discovery of the hibernating myocardium.

Although all the above seem very easy to bring into practice, no consensus has been reached on the metabolic treatment of myocardial ischaemia, despite the uncontroversial theoretical principles lying behind it. We actually 'prefer' to cure myocardial ischaemia with drugs as they have definite haemodynamic

effects, which, in turn, result in definite metabolic effects. Thus, the real challenge — the topic of this Supplement — is the possible clinical use of drugs which might bypass the 'relatively-easy-to-achieve' haemodynamic effects, exerting 'primary' metabolic activity.

The research in this field is still ongoing, but promising substances are already giving results. One of these substances trimetazidine, is one of the so-called 'metabolic' agents for the treatment of ischaemia^[1]. Trimetazidine inhibits fatty acid oxidation and increases the oxidation of glucose^[2]. In addition, it is believed that trimetazidine acts at a cellular level, maintaining a high energy and store and reducing cell acidosis. Experimental studies also show that trimetazidine may reduce oxygen free-radical production and exert a cytoprotective effect on ischaemic myocytes.

Cytoprotection is the capacity of the molecule to exert its action on the cell without affecting the haemodynamic condition of the cell itself^[1]. This can occur by maintaining ionic homeostasis, enhancing mitochondrial respiration, or ameliorating membrane function.

These characteristics of trimetazidine render its approach, in conventional combination therapy, unique. The clinical efficacy of trimetazidine in stable angina has been demonstrated when administered as a single agent (vs propranolol), or in combination with diltiazem, beta-blockers or isosorbide dinitrate^[3–5].

Given its differing mechanism of action, the beneficial effects of trimetazidine may be additive to haemodynamic treatment, and possibly effective in patients resistant to such agents. All this — and much more — is the topic of the enclosed supplement.

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