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Chronic Total Coronary Occlusions: A Review of their Special Features and the Existing Techniques of Percutaneous Treatment

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Chronic total occlusion (CTO) of a coronary artery is the complete obstruction of the vessel aged at least one month according to most researchers or three months according to others. The term is also used to describe total occlusions with TIMI grade 1 flow, the so-called "functional occlusions", which are defined as the presence of only faint, late anterograde flow in the absence of a discernible lumen.

These occlusions represent 5% to 15% of the total number of angioplasty procedures of a cath lab activity and this percentage depends on the selection of the cases and the experience of the staff. Successful recanalization of a chronic total coronary occlusion remains even today, 20 years after the first angioplasty procedure was performed, a challenge for interventional cardiologists. The most significant limitation to successful recanalization is the failure of the guide wire to cross the lesion.

Pathologic features

The occluded segment of the vessel lumen includes two types of tissue: atheromatous plaque and old thrombus. The relative density of each element primarily depends on the total occlusion mechanism. Two causal pathogenetic phenomena are implicated: (a) the late organization and development of an acute occlusion (involving a large area of an old thrombus), generated by atheromatous plaque rupture, which is usually located at the distal end of the minimum lumen diameter and (b) the progressive occlusion of a long-term high-degree stenosis (involving a large area of atherosclerotic plaque and quite often additional layers of plaque surface thrombus). The occlusive mass is mainly composed of fibrous and mixed components including a small quantity of cholesterol, which progressively decreases with time and is replaced by dense collagen and calcium deposits. Usually the plaque fibrous cap (which is the hardest part of the plaque) is located at both ends of the occlusion. The intraluminal process is often accompanied by a negative remodeling (vessel shrinkage) of the artery, which is mainly observed in chronic occlusions older than 3 months. The negative remodeling process is connected to the replacement of soft plaque tissue with fibrous tissue, mainly in the middle section of the occlusion. The importance of the replacement of these elements is greater in total occlusions of small length. In larger occlusions, the thrombus organization is responsible for the presence of a soft inner core in the center of the occlusion which is also the targeted most vulnerable point during the attempted transluminal perforation procedure. The angiographic morphology of the occlusive lesion can close abruptly with almost a complete absence of vessel stump, can display a stump with progressive narrowing of the lumen or can include formation of neovessels with an average diameter of 200μ. The frequency of neovessel formation progressively increases in proportion to the duration of the occlusion (reaching 85% in occlusions older than a year). Neovessel formation is not affected by the length of the occlusion while there are conflicting views with respect to the existence of links between these vessels. Some publications report a connection between neovessels and the formation of neovascular channels, whose presence contributes in a positive way in cases of attempted transluminal recanalization, while others report the existence of links between neovessels and the vasa vasorum of the adventitia, which negatively affect the advancement of the guide wire through the obstruction and predispose to the development of complications. It is more than likely that both types of links coexist in the majority of cases.

Clinical presentation of patients with chronic total coronary artery occlusion

The patients' clinical symptoms can include all types of angina, while special types of angina that are often observed in total occlusion patients are the following: (a) angina occurring during the first effort of the day, while other activities are carried out in the absence of pain, (b) angina observed at the onset of physical exertion which improves despite the continuation of physical activity and (c) diminishing exercise tolerance which is associated with silent ischemia (especially in young physically active individuals).

Transluminal recanalization of chronic total occlusions

Coronary angioplasty of CTOs is associated with specific limitations. As expected, the primary success rate is lower, while expenses (quantity of used materials and contrast) and radiation exposure to both patients and physicians associated with angioplasty of occluded coronary arteries are increased, compared to angioplasty of subtotal occlusions[1-4]. Failure in most cases is due to unsuccessful crossing of the guide wire and less often to a failure of balloon insertion through the obstruction. Even in cases of initial vessel recanalization, the presence of local thrombus may lead to peripheral embolization of thrombotic material or even plaque debris resulting in slow or lack of angiographic flow through the vessel (no reflow phenomenon). The existence of collateral circulation, before recanalization, can cause a slow angiographic flow due to the antagonism of collaterals against the peripheral segment[5]. In addition, CTOs that are successfully opened show a higher rate of angiographic restenosis despite technological advances and increased operator experience[3,6,7]. Therefore, the nature of the lesion and the "more traumatic" materials used, as well as the coronary substrate in which they are used, are associated with a lower initial success rate than angioplasty of arteries that are stenotic but not occluded. Thus the careful selection of patients and angioplasty materials becomes a major determinant for the successful and safe completion of the procedure.

Clinical indications for CTO angioplasty

It is generally accepted that to adequately justify an attempt of coronary artery CTO recanalization the following conditions should apply: (a) presence of serious angina despite appropriate medical treatment, a fact which is linked to the existence of a large area of viable and active myocardium, (b) anticipation that the reperfusion of the hibernating myocardium will improve the partial and total left ventricular contractility, at the same time limiting its remodeling, which is an important factor of unfavorable long term clinical outcome ("open artery hypothesis") and (c) hope that the restoration of the obstructed vessel patency can aid in the development and provision of collateral circulation towards the contralateral artery in case the latter becomes occluded at a later stage.

In patients with single-vessel disease, the indication for recanalization is a combination of its functional importance in causing severe ischemia and limiting the physical activity of the patient who is receiving full medication on the one hand and, on the other hand, of the presence of favorable angiographic characteristics. The absence of the latter is not a strictly forbidding criterion in cases where the patient's functional capacity is severely limited despite an optimum medical treatment. In patients with multivessel disease, CTO recanalization rarely constitutes the target-lesion, but it is included in the intervention sites for full revascularization. In these cases, the inability to reopen the occluded segment or the existence of particularly unfavorable angiographic characteristics are the main reasons for selecting surgical intervention as the treatment of choice. Clearly this strategy can be modified if a total reperfusion of the patient is not considered to be mandatory.

Clinical success factors

The only well-documented clinical factor is the age of the occlusion which correlates negatively with a successful intervention[8,12,29]. Most often the age of the occlusion is empirically determined in patients with single-vessel disease, depending on when angina or prolonged thoracic pain first developed. The same rationale cannot be applied though in patients with multi-vessel disease and a long history of angina. The most accurate way to determine the age of the occlusion is the presence of a previous angiography; as a result, at least in 25% of the cases it is not possible to accurately determine this. The possibility of an unsuccessful CTO recanalization increases (>50%) when the occlusion duration is greater than 3 months. This fact is associated with the changes in histological composition that take place such as: accumulation of fibrous tissue, calcium deposits and substitution of the "soft" components of the lesion with other stiffer components, neovessel formation and negative remodeling of the vessel. However, it seems that a very old total occlusion (aged several years) does not differ, with respect to its behavior and the recanalization feasibility, from an occlusion 3-12 months old.

Angiographic success factors

In cases of CTO angioplasty all the known limitations for the success of this method apply: location in the circumflex artery or in the distal segments of the coronary vessels, presence of marked tortuosity and bends in the target-artery as well as calcifications proximal to or at the lesion site. There are however additional specific factors that determine the chance of successful recanalization[3,8-11]:

- The origin of a lateral branch at the site of occlusion is an important adverse factor (success rate 32% versus 83% in the absence of such). A minimum distance of 2mm is necessary between the origin of the lateral branch and the site of occlusion.
- The presence of bridging collaterals towards the distal segment characterizes occlusions with a duration of at least 2 months (late angiogenesis) and constitutes an adverse factor for the success of the intervention, as well as a risk factor for possible vessel perforation. The development of neovessels in the form of a "medusa's head" is almost always a site of non-dilatable total occlusion.
- The angiographic image of the stump carries a predictive value. A progressively narrowing diameter represents a particularly favorable morphology while, on the other hand, a rounded-ends diameter has unfavorable prognosis. A central course of the stump lumen is also a favorable factor.
- The length of the occlusion is a major determinant of success and many researchers consider a length of 15mm to be a critical success limit, especially if a curve is involved.
- The occlusion type (total or functional) is a controversial factor. Functional occlusions can be caused by the existence of a very small diameter in the absence of an angiographically discernible lumen, usually display a higher success rate or may be associated with the development of neovessels, indicative of an old and well-organized CTO.

Patient preparation

This is similar to the preparation for standard angioplasty. It is necessary to pre-administer ticlopidine or clopidogrel combined with aspirin due to increased need for stent implantation. A second arterial pathway is used when double coronary infusion is needed to control the contralateral artery which provides the collateral circulation, in order to facilitate the attempted recanalization and to maintain the guide wire within the true lumen and steer it in the right direction. Heparin administration should not usually exceed a dose of 3,000 IU before the wire crosses the occlusion, in order to prevent serious events (in case the procedure needs to be stopped). The administration of platelet inhibitors Gp IIb/IIIa should be avoided before the start of the operation and these factors should be administered after the successful crossing of the guide wire through the occluded segment and after its intraluminal course is verified or even after the intervention is successfully completed in certain dubious cases.

Interventional strategy and maneuvers

CTO angioplasty consists of the following individual objectives: (1) perforation of the total occlusion with the use of a guide wire and advancement of the guide wire to the distal segment of the vessel, (2) dilatation of the underlying lesion or removal of occlusive material in order to restore the patency of the lumen and (3) preservation of the patency of the recanalized vessel by the administration of medication and the implantation of intracoronary stents.

1) Occlusion perforation. Selection of material-devices

This step is the most crucial one in CTO angioplasty, since the inability to cross these lesions with a guide wire is the principal cause of failure (>50%) of the intervention[3,13,14]. In cases of suboccluded lesions angioplasty, the advancement of a soft wire through the lesion is usually easy and fast. During an attempted recanalization of a CTO, the guide wire should pass through the initial usually hard and fibrous segment of the lesion, advance to the central core of the occlusion which is composed of elements of varying degree of hardness, being careful not to steer it in a subendothelial course, and finally perforate the distal segment of the occlusion, which usually consists of hard fibrous material. Thus, the special characteristics which determine the choice of a guide wire are: its hardness, the ability to direct it within the occlusion, the ability to safely perforate without taking a subendothelial course and the characteristics of reduced friction at its distal end. Today several types of guide wires are available for CTO angioplasty: of varying diameter, length and distal end morphology, with special polymer coating that increases its sliding ability and the ability to direct it within the occlusion. The use of "over-the-wire" angioplasty catheter systems or special thin catheters (Multifunctional probing®, Tracker®) is recommended to adequately support the wire during the attempt to perforate the total occlusion and to maintain its central position within the occluded segment and away from the vascular wall. The use of these systems also helps in the distal imaging of the vessel through the catheter lumen, especially in cases of unclear positioning of the wire in the distal segment of the occlusion as well as in the angiographic determination of the true vascular lumen. However, the fact remains that due to the different characteristics of the lesions, which are not obvious beforehand, it is often necessary to use multiple wire types in order to successfully complete the procedure.

The age and the length of the occlusion are the main determinants of success[12,30]. In the first historic CTO angioplasty series which included a mixed population with occlusions of a mean duration 1-4 months, a successful recanalization is reported at a rate of 42% to 63%[15-20]. This rate decreases as the duration of occlusion increases and a rate of 11%[18] to 55%[19] is reported in the angioplasty of CTOs aged >6 months. More recent publications also report, despite the technological improvement of the materials used, a persistent low initial success rate of the method in CTO cases, especially when those cases have adverse features (39% to 56%)[21-26].

Serious research attempts at designing new wires or techniques have not led to a significant improvement of the results, while they have increased the cost and the percentage of perioperative complications[23,24,27], and as a result their use and especially that of laser wires, has almost been abandoned in clinical practice. The effectiveness of the usage of laser wires, even the latest generation, in the recanalization of chronic total occlusions did not seem to be superior to the usage of conventional wire, according to the results of the TOTAL study[24,25]. A particularly attractive new CTO angioplasty technique with an increased success rate was developed by L.K. Michalis et al[26,28-30] called angioplasty using "vibrating wires". According to this new technique, the proximal end of a common guide wire within an "over the wire" catheter is connected to a portable electrically-driven device which is powered by battery. The activation of this device causes a slight vibration along the longitudinal and transverse axis of the wire at a frequency of 16-100 Hz. The wire movement is transmitted through the catheter and causes a complex movement of the distal end of the wire in the same axes. The degree and range of the distal end movement depends on the response frequency and the length of the wire that protrudes from the end of the angioplasty catheter. With this technique it is possible to advance the wire within the occlusion through the most pliable regions, while securing its intraluminal course. The investigators report successful recanalization and finally successful CTO angioplasty at a rate of 85.9% and 75.6% respectively in a patient population with particularly adverse characteristics, such as chronic lesions (aged >6 months in >80% of the patients), presence of bridge collaterals in 42% and occlusion length >15 mm in 69.2%, with a small percentage of serious perioperative adverse events[26,30]. It seems that the vibrating wires CTO angioplasty technique is an innovative, easy and inexpensive method of safely reopening and dilating these lesions that can be applied by the majority of experienced interventional cardiologists.

2) Dilatation of the underlying lesion

This part of the operation usually poses small difficulty, particularly if adequate support is provided by the guiding catheter and wire. It is recommended to use "over the wire" balloons at least for the initial opening. Small diameter and low profile balloons are used for the initial opening of the lumen and larger ones are used when it's patency is restored. It is possible to use also long balloons when there is a larger length occlusion. The intracoronary infusion of relatively large quantities of nitrates is necessary for the functional restoration of the recanalized distal segment of the vessel. A no reflow syndrome is treated with intracoronary infusion of vasodilators, adenosine, small and repeated doses of adrenalin and/or platelet Gp IIb/IIIa inhibitors. In case balloon advancement fails, it is recommended to use another improved support catheter and/or a new guide wire. In particularly difficult cases, techniques of intraluminal material removal can be applied, such as Rotablator or Excimer Laser for angioplasty. The use of small range Rotablator or Laser catheters is enough to create an adequate initial lumen and to modify the malleability of the obstructive plaque so that the advancement of the angioplasty system and stent is possible.

3) Maintaining patency of the recanalized vessel

As mentioned before, CTO angioplasty is associated with a high restenosis and vessel reocclusion rate[3,6,7]. Long term administration of vasodilators is recommended during the early postoperative period in order to restore the endothelial function of the occluded segment of the vessel as well as the administration of antiplatelet agents. Several studies have shown that stent implantation contributes to achieving successful recanalization with a long-term result and reduces restenosis rates. Thus, in the SICCO[31] study, restenosis rates in CTOs where stents were implanted were found to be significantly lower in comparison to lesions which were treated with conventional angioplasty (32% versus 74% respectively). Consequently, a repeat revascularization was required at a lesser extent (24% vs 53%). Furthermore the GISSOC[5] study reported similar results with respect to reduced restenosis (32% vs 68% respectively), vessel reocclusion (8% vs 34%), recurrence of ischemia (14% vs 46%) and need for repeat revascularization (5.3% vs 22%). A recent study (STOP Study)[32] confirms these results and shows a significantly lower restenosis rate (42.1% vs 70.9%) and vessel reocclusion rate (7.9% vs 16.1%) with stent implantation compared to conventional angioplasty, after the recanalization of chronic total occlusions. In the same study, a need for repeat revascularization of the target lesion was reported in 41% of the patients in the conventional angioplasty group and only in 25% of the stent group during the 6-month follow up. It is clear, therefore, that following a successful recanalization and CTO angioplasty, stent implantation is necessary in order to optimize the immediate results and preserve long-term patency. Covering the full length of the occlusion with the use of one stent is the preferred method when the occlusion length is not particularly large whereas in longer length occlusions the method of choice is implantation only in the most angiographically adverse segment with simultaneous administration of GP IIb/IIIa inhibitors.

Complications

Two types of complications particularly characterize CTO angioplasty: burdening or elimination of collateral circulation and vessel perforation. There are many mechanisms which are harmful to collateral circulation: peripheral embolization by plaque material, extensive diffusion which obstructs collateral vessel entry points, lesions of the neovessels that are connected to the vasa vasorum of the adventitia. In such cases the attempt is interrupted and the patient is conservatively treated or even subjected to immediate surgery depending on the extent of ischemia and his hemodynamic condition. Vessel perforation is caused by an intramural course of the wire or the balloon which exits through the adventitia, balloon dilatation intramurally or in a small distal lateral branch or by a serious lesion - rupture of the neovessels. It is treated with prolonged obstructive dilatation of a balloon proximal to the rupture site, implantation of a stent with autologous venous or arterial graft coating or PTFE membrane coating, inhibition of administered heparin with protamine sulphate and rapid pericardiocentesis if cardiac tamponade phenomena occur. On rare occasions urgent surgical treatment may be required.

Long-term outcome of patients after CTO angioplasty

In a large meta-analysis incorporating a total of 4400 cases, Freed et al report a long-term success rate of 69% (restriction of ischemia recurrence, improvement of left ventricular function, higher event-free survival rate) with a major cardiovascular events rate of 2%[33]. The majority (80%) of failures were complication-free and were due to an inability to cross the occlusion with the guide wire, a fact which underlines the importance of material selection as well as the potential benefits of the "vibrating wires" technique. It seems that the favorable results are maintained through stent implantation, as the SICCO[31] study showed, in which the major cardiovascular event rate during 3 years of follow-up was found to be 24% in patients with stents, compared to 59% in conventional angioplasty patients.

Future trends

There are two new techniques, which if extensively developed, could significantly contribute to the improvement of the initial successful recanalization of CTOs. These are forward applied laser energy and plaque rupture by means of ultrasound at the site of the occlusion. Both these techniques however are still at an experimental stage of application. A new type of guide wire incorporating a sensor with the ability for prospective spectral analysis of the tissue that comes into contact with its end, was recently introduced (Safe Steer wire®) and this could significantly contribute to achieving a safer, successful percutaneous recanalization of chronic total occlusions.

In conclusion, successful angioplasty of chronic total coronary artery occlusions poses a technical challenge even today and depends to a large extent on the experience and expertise of the physician. Despite the progress achieved, results depend directly upon the operator, the selection of patients and the available material, and consequently the comparison of recanalization methods requires the existence of large randomized studies. Due to the high cost of the intervention, the radiation exposure of both patients and physicians who perform the procedure and the relatively higher long-term restenosis-reocclusion rate, the choice of a percutaneous treatment, at least until we can extract safe conclusions from large trials, should be based on strict and well-documented criteria with a clear distinction between individual cases. New wire types and interventional techniques contribute to a higher success rate either through the recanalization of the underlying lumen or by creating a new, parallel lumen within the occlusion. The implantation of coronary stents at the lesion site is mandatory for preservation of the long-term patency of the vessel.

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