New Prospects in Myocardial Surgical Revascularization

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Myocardial revascularization with coronary bypass graft surgery or angioplasty is the conventional treatment for ischaemic heart disease. The progressive refinement of both techniques (eg, use of arterial grafts and drug eluting stents) has improved clinical outcomes but the elucidation of which of the two treatments is more effective would require well designed randomised studies. While the utility of off-pump as compared to on-pump coronary bypass graft surgery is still debated, the evidence for the exclusive use of arterial conduits for surgical revascularization is compelling. Patients with diffuse coronary artery disease that cannot be treated by conventional revascularization treatments remain a challenge for the control of angina and a variety of alternative treatments, including transmyocardial laser revascularization and cardiac denervation, have been applied. However, these treatments do not eliminate angina and the benefit obtained is transient. The angiogenic therapy using stem cells and modification of gene expression is a new treatment which potential, in spite of the promising animal studies and the initial clinical trials, is still unclear. The introduction of less invasive surgical techniques and robotics could play an important role for the delivery of these treatments in the future.

Key words: *Myocardial revascularization. Coronary bypass graft surgery. Angioplasty. Angiogenic therapy.*

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Nuevas expectativas en la revascularización miocárdica quirúrgica

La revascularización miocárdica con injertos coronarios o angioplastia constituye el tratamiento convencional de la enfermedad coronaria isquémica. El refinamiento progresivo de ambas técnicas (p. ej., el uso de injertos arteriales y *stents* farmacoactivos) ha mejorado los resultados clínicos, pero aún no está claro cuál de estos tratamientos es más eficaz y, para ello, es necesario realizar estudios aleatorizados y adecuadamente diseñados. Mientras la utilidad de la revascularización quirúrgica sin circulación extracorpórea no está definida, hay evidencia a favor del uso exclusivo de injertos arteriales (p. ej., arteria mamaria interna, arteria radial). Los pacientes con enfermedad difusa coronaria que no pueden recibir el tratamiento convencional son todavía un reto para el control de la angina de pecho y, con este fin, se ha utilizado una variedad de tratamientos alternativos, incluidos el láser transmiocárdico y la denervación cardíaca. Sin embargo, estos tratamientos no eliminan la angina por completo y el beneficio obtenido no es duradero. La terapia angiogénica con células madre y genes es un nuevo tratamiento cuyo potencial es actualmente desconocido, aunque las investigaciones en animales y los estudios clínicos iniciales son prometedores. No cabe duda de que la introducción de técnicas quirúrgicas menos invasivas y los avances en la cirugía robótica podrían contribuir a la aplicación de la terapia convencional de revascularización miocárdica y a la difusión de nuevos tratamientos.

Palabras clave: *Revascularización miocárdica. Injertos coronarios. Angioplastia. Terapia angiogénica.*

INTRODUCTION

Ischemic coronary artery disease is the greatest cause of mortality in developed countries. Recent decades have witnessed great progress in the understanding of the pathophysiology and treatment of coronary artery disease holding out the promise of greater efficacy in controlling it. This article discusses the current state of the different conventional approaches to myocardial revascularization and the

most recent antiischemic therapies, such as angiogenic therapy using stem cells and growth factors.

MYOCARDIAL SURGICAL REVASCULARIZATION OR PERCUTANEOUS ANGIOPLASTY?

It is widely accepted that myocardial surgical revascularization with coronary artery bypass grafts is an effective method for eliminating angina. Furthermore, this kind of surgery also improves life expectancy in patients with severe coronary disease and reduced left ventricular function.[1] Surgical risk is relatively low, with hospital mortality no higher than 2%, despite the increase in patients reaching an advanced age and with greater severity of coronary disease.

Percutaneous angioplasty was introduced later than surgical revascularization and applied initially to cases of 1- or 2-vessel coronary disease. Coronary restenosis, which has a frequency of 25%-35%, has been the greatest drawback in angioplasty but this has been reduced significantly with the introduction of the stent (10%-15%) and stents coated with slow-release immunosuppressive agents (e.g., sirolimus-eluting stents) or antineoplastic ones (e.g., paclitaxel).[2-6] These advances have made it possible for percutaneous coronary interventions to be applied to patients with more severe coronary disease, including patients with 3-vessel disease and left main coronary artery disease. As a result, many patients who were previously treated surgically, now undergo percutaneous coronary intervention which is a less invasive method that does not require anesthesia, shortens hospital stay and enables a swift return to work. However, is it possible to know which of these two treatments is really the more effective? The randomized clinical trials carried out to date have mainly been done in patients with 1- or 2-vessel coronary disease, and in a small percentage of patients with 3-vessel disease. It is known that surgery does not improve the prognosis of patients with 1- or 2-vessel coronary disease[1] and, thus, it is not surprising that in these studies there are no differences in survival rates between the 2 groups. Despite this limitation, these studies show that surgery significantly reduces the need for new myocardial revascularization interventions,

decreasing from 20% in patients undergoing angioplasty to 5% in those treated with surgery.[7] In patients with severe coronary disease, mortality at 5-year follow-up is 2.5 times higher in those treated with angioplasty than in those treated with surgery,[8] and in diabetic patients with 3-vessel disease mortality is also twice as high with angioplasty compared to that with surgery.[9] As mentioned, the results of angioplasty with stents have raised new hope regarding reducing coronary restenosis and the treatment of coronary disease. Thus, new randomized studies are needed to compare the most advanced techniques in relation to both types of myocardial revascularization (e.g., angioplasty with drug-eluting stents versus coronary artery bypass grafts).

CORONARY GRAFT: ARTERIAL VERSUS VENOUS

The results obtained with myocardial surgical revascularization are excellent in the short- and medium-term, but these benefits decrease in the long term due to the progressive failure of venous grafts. The most widespread practice is to use the internal mammary artery (IMA) to revascularize the anterior descending coronary artery and the internal saphenous vein to revascularize the remaining coronary arteries. Despite the lack of randomized studies, it is clear that using the IMA to revascularize the anterior descending artery improves survival and reduces the frequency of new myocardial infarctions, the recurrence of angina and the need for new cardiac interventions.[1,10,11] Some 90%-95% of left IMA grafts remain patent 10 years after surgery, whereas 70% of veins are occluded or present severe disease.[12] The failure of the venous graft is the cause of the recurrence of angina and of new myocardial infarctions, as well as the need for new myocardial revascularization interventions.[13] It can be argued that the better outcomes with the IMA stem from the fact that this is anastomosed to the anterior descending artery, that is, the artery with greater coronary flow. However, this hypothesis is unsound as it has been demonstrated that the patency of the IMA used to revascularize other coronary arteries different from the descending anterior is equally high (>95%) and higher than that observed with venous grafts.[14,15] Recently, the Cleveland Clinic group has confirmed the higher patency of the IMA compared to venous grafts in all coronary territories except in lesions in the right coronary artery (<70%).[16]

If the advantages of anastomosing an IMA to the anterior descending artery are clear, the benefits of using 2 IMA remain a matter of debate. The studies published up to now[17-29] were not randomized and this makes their interpretation difficult. Furthermore, the 2 IMA have mainly been used in young individuals carrying lower surgical risk and, thus, any observed benefit could be attributed to patient selection more than to a beneficial effect stemming from using the 2 IMA. Bearing these

considerations in mind, an analysis of the published reports demonstrated that the use of both IMA[30] reduces mortality compared to using just one IMA. Survival improves when both IMA are anastomosed to the left coronary system[31,32] and worsens when one IMA is anastomosed to the right coronary artery,[31] probably due to greater development of atherosclerotic disease in the distal third of this artery. Although the use of the 2 IMA does not increase surgical risk, it is possible that, due to the lack of randomized studies and greater technical difficulty, the use of the 2 IMA has not become widespread. Resistance to using the 2 IMA in patients with diabetes is based on the greater risk of sternal wound infection,[33] but it is precisely this group of patients which can benefit enormously from the use of the 2 IMA.[34-37] It is important to point out that the risk of infection can be reduced when, instead of being dissected as the pedicle, the IMA is skeletonized.[38,39]

Based on the results of using the IMA, it is reasonable to surmise that other arterial grafts, such as the radial, gastroepiploic, and epigastric grafts, could be better than venous grafts. The good clinical results obtained in the short-, medium-, and long-term using the radial artery[40-43] have been matched by excellent patency rates (>95%).[42] As in the case of the IMA, it seems that the patency of the radial artery is less when anastomosed to the right coronary artery[44] and, thus, using the radial artery for revascularization of coronary vessels with stenosis <70% is not recommended.[45,46] Despite the good results with the radial artery, a group of researchers has recently reported that this has lower patency than the IMA and venous grafts, especially in women.[47]

The radial artery offers great versatility (it is close to all coronary territories and can be used as a coronary artery bypass graft or anastomosed to the IMA) and is easy to harvest. The use of this artery as a graft anastomosed proximally to the left IMA avoids manipulation of the aorta and enables complete revascularization, a configuration that produces better clinical results than the use of the IMA and venous grafts in the short- and medium-term.[48] The tendency to spasm observed in this artery at the beginning of its use,[49] meant that its reintroduction to clinical practice was undertaken with great caution and included the use of antispasmodic agents. Even though such agents are frequently used, their clinical usefulness has not been demonstrated. Although we have systematically used the radial artery for 9 years, initially with calcium antagonists, and for the last 3 years without administering antispasmodic drugs, we have never observed spasms in this artery of any clinical importance (unpublished personal experience).

ON- OR OFF-PUMP CORONARY ARTERY BYPASS GRAFT SURGERY

The patients who undergo cardiac surgery with cardiopulmonary bypass (CPB) have a systemic inflammatory response that is believed to cause an increase in postoperative complications and hospital stay.[50] Several interventions, such as the use of corticosteroids[51] or aprotinin,[51] heparin-coated circuits[52] and hemofiltration,[53] reduce the inflammatory response produced by CPB, as well as its consequences. A more radical and effective way of combating the effects of CPB would be to avoid its use. Our group has proven in a randomized study that off-pump coronary bypass graft (CABG) operations on the beating heart reduce oxidative stress and the inflammatory response associated with CPB.[54] However, is there any evidence that operations without CPB reduce postoperative complications? The initial outcomes of off-pump CABG show a reduction in stroke,[55] reduced blood loss and transfusions,[56] and a lower incidence of atrial fibrillation[57] and renal dysfunction.[58] However, an analysis of the literature has not demonstrated that off-pump CABG is associated with a reduction in the incidence of atrial fibrillation,[59] and follow-up studies have not shown significant differences between on- and off-pump CABG.[60-62]

The methods used to expose coronary arteries in beating-heart surgery have improved steadily and this has enabled a rapid increase in off-pump CABG, but there is still controversy regarding the quality of the anastomoses carried out and graft patency. A randomized study demonstrated that 3 months after the operation graft patency is greater with on-pump CABG than with off-pump CABG,[63] whereas in another randomized study, patency at 1-year follow-up was similar with and without CPB.[64]

Surgical access to the lateral and inferior walls of the left ventricle during off-pump CABG is difficult in the presence of ventricular hypertrophy and in dilated hearts with reduced function, which means that incomplete revascularization is more frequent in this procedure than when CPB is used. It is well known that incomplete revascularization determines the surgical outcomes in the short-, mid- and long term[65-67] and, thus, survival is also reduced in patients undergoing off-pump surgery[68,69] since they frequently have a greater incidence of incomplete revascularization. Incomplete revascularization is precisely the causative factor behind the increase in myocardial revascularization reoperations in patients undergoing off-pump CABG.[69,70]

The outcomes of on- or off-pump CABG in high-risk patients are also unclear and, whereas some researchers have reported that off-pump CABG reduces operative mortality,[71] others have not observed benefits.[72] The results in patients with diabetes are even more contradictory, since some studies show that off-pump CABG reduces perioperative complications,[73] whereas others have found greater perioperatorive risk.[74] It is clear that detailed randomized studies with sufficient statistical power and suitable follow-up should be carried out to identify the type of patients and clinical conditions that can really benefit from off-pump CABG.

ALTERNATIVES TO CONVENTIONAL MYOCARDIAL REVASCULARIZATION

Patients with severe diffuse coronary artery disease and refractory angina that cannot be treated with CABG or angioplasty present a difficult challenge and represent 12%-15% of candidates for myocardial revascularization.[75,76] A series of alternative treatments for these patients have been described and are discussed below.

Transmyocardial Laser Revascularization

Several researchers, including our group, have observed in randomized clinical studies that transmyocardial laser revascularization reduces angina and improves exercise tolerance.[72-82] A recent metaanalysis that included 7 randomized studies and 1053 patients treated with transmyocardial laser demonstrated that after 1-year follow-up there is a significant improvement in angina, but not in survival.[83] It should be noted that in all these studies the reduction in the degree of angina was quite modest and of limited duration, lasting no more than 42 months after surgery.[81]

Transmyocardial laser revascularization has also been used as a complementary therapy in CABG to revascularize myocardial areas with small coronary arteries unsuited to receiving a graft and, thus, obtain complete revascularization.[84,85] In a randomized study, Allen et al[84] did not find a reduction in angina or improvement in exercise tolerance, but did find a reduction in operative mortality and an improvement in survival at 1-year follow-up. In our study, also randomized,[85] transmyocardial laser revascularization combined with CABG also failed to reduce the degree of angina compared to the control group, but exercise tolerance improved during the first months following the operation, later disappearing at 36-month follow-up.

The mechanism causing the modest benefit obtained with transmyocardial laser revascularization has been a cause for debated topic. Initially this was thought to be due to idea that the effect was due to increased blood flow directly from the ventricle to the ischemic area through the channels created with the laser.[86,87] However, it has been demonstrated that such channels are occluded soon after their creation.[88] Neither is there agreement, in experimental or clinical studies, on whether the effects of the laser are associated with angiogenesis or improved perfusion. Thus, whereas some researchers have been unable to demonstrate an improvement in blood flow,[80,81,86,89-91] others have observed an increase.[79,92-94] It has been speculated that cardiac denervation could play a role in the laser's effect,[95,96] but this idea has also been called into question.[97,98] In a study conducted by our group, the degree of reduction in angina was smaller with thoracic sympathectomy than

with transmyocardial laser revascularization.[81] The lack of a powerful and lasting clinical effect together with the lack of knowledge regarding the mechanism of action probably account for the loss of interest in this technique. Despite this, some enthusiasts continue to carry out transmyocardial laser revascularization, sometimes with less invasive endoscopic methods,[99,100] and in combination with other techniques, such as stem cell injection.[101] In recent experimental studies the efficacy of transmyocardial laser revascularization combined with gene therapy has also been explored.[102]

Cardiac Denervation

Left thoracic sympathectomy reduces angina,[103] but is only practiced in very few centers in cases of severe coronary disease when there is no possibility of CABG or angioplasty. Our group has shown that this reduction in angina is transitory, and 42 months after thoracic sympathectomy the patients return to a similar degree of angina that they presented before the intervention.[81] Thus, the benefit of thoracic sympathectomy is limited and only should considered as a last resort.

Arterialization of the Coronary Venous System

Coronary veins do not have valves, which allows retrograde flow, nor do they undergo atherosclerotic changes. Thus, the arterialization of the venous system, consisting of connecting the aorta to the vein adjacent to the artery with coronary disease with a graft, could be a way of irrigating specific regions of the heart. Animal studies have demonstrated that the arterialization of the cardiac veins only slightly reduces the size of the infarction[104] and the few studies carried out in humans have not shown clinical benefit.[105,106] Our group has found that the grafts connected to the venous system do not endure[106] and, thus, it is unlikely that the arterialization of the coronary venous system is a useful technique for the revascularization of the ischemic myocardium.

Direct Communication of the Left Ventricle to the Coronary Arterial System

This approach to myocardial revascularization was proposed almost 50 years ago by Goldman[107] and later studied in detail by other researchers.[108-110] In principle, if anterograde coronary flow occurs preferably during diastole, it is difficult to understand how communication between the left ventricle and a coronary artery can result in adequate blood flow. Arguing against this, experimental studies have shown that regional myocardial blood flow can be preserved at rest and under conditions of increased oxygen demand,[111] and the first published study in humans has recently shown that the technique of implanting a left

ventricle-to-coronary artery stent is feasible.[112] At present, it is difficult to assess the future of this myocardial revascularization technique and it is clear that more research is needed to determine its viability and efficacy.

Stimulation of the Formation of New Blood Vessels With Stem Cells and Genes (Angiogenic Therapy)

Angiogenic therapy is a new and promising method of increasing blood flow to ischemic areas by stimulating either the formation of new blood vessels or the development of the collateral blood vessels available.[113] It has been shown that a great variety of angiogenic factors administered in the form of proteins or genes can induce angiogenesis and the growth of collateral arteries, leading to an improvement in regional blood flow and the preservation of tissue.[114-116] Despite promising laboratory outcomes, the preliminary clinical studies carried out to date have not shown a clear benefit.[117-121] Vessels whose growth has been induced by the overexpression of a single angiogenic growth factor do not seem to have the morphological and functional characteristics of mature capillaries.[122] Thus, for example, vascular endothelium growth factor (VEGF), which is a strong stimulator of the proliferation and migration of endothelial cells, generates vessels that are frequently patent, irregular and unstable and, in addition, can develop hemangiomas.[123,124] This suggests that after inducing stimulation there should be a process of maturation and stabilization of the new blood vessels. Most of the proposed proangiogenic therapies are based on the administration of a single factor, such as VEGF, that, by itself, cannot be sufficient to obtain the desired effect. Moreover, the premature withdrawal of VEGF leads to the regression of most of the newly formed blood vessels, which restricts the usefulness of this therapy based on a short stimulus duration,[125] whereas overproduction of VEGF causes an intense edema that can be harmful.[125] It is clear that, regarding angiogenesis, the role played by each growth factor and their interactive effects needs to be specified, as well as the timing, duration, and dose of each growth factor in isolation and in combination such that stable, normally functioning blood vessels are obtained. The use of stem cells as growth factor vectors could help modulate the duration and levels of their expression. The question of whether angiogenic therapy with growth factors still has real clinical potential remains unresolved and awaits the results of third-phase studies currently underway.

Stem cells can differentiate into practically any type of cell and, in theory, offer great potential to generate new blood vessels in the myocardium. Recent experimental and clinical trials have shown that, after a myocardial infarction, bone marrow cells injected into the myocardium can induce a significant degree of tissue regeneration and functional improvement.[126-128] Bone marrow cells transplanted into the heart increase the expression of angiogenic factors[129] and improve ventricular function and the formation of new vessels.[130] The formation of new myocytes, arterioles and capillaries, via the mobilization of bone marrow stem cells, yields similar results.[131] The idea that primitive cells can migrate through the systemic circulation has been substantiated by the observation of a high degree of chimerism in female-to-male transplanted hearts.[132] Against this argument, it has been found that the mobilization of stem cells with hematopoietic growth factors in a nonhuman primate model does not produce detectable myocardial infarct repair, although a certain degree of angiogenesis can be observed in the infarction area.[133]

Other types of cells have also been used in myocardial repair to improve blood perfusion with promising results. Thus, for example, the injection of peripheral blood mononuclear cells into hibernating myocardium of pig improves collateral perfusion and regional function.[134] The administration of human umbilical cord blood cells in myocardial infarction in the mouse also contributes to angiogenesis and favorably influences the process of cardiac remodeling.[135] Other types of cells, including embryonic stem cells, have also been shown to have angiogenic potential. There is no doubt that the use of stem cells and genes has opened up new horizons in angiogenic therapy, but it is still in its infancy and the road could be long and hard before we attain full understanding of its potential and are able to apply this in clinical settings. This is a task where the ethical problems and side effects involved in this therapy should not be underestimated.

ROBOTIC SURGERY

The success of robotic surgery within several surgical specialties has not been matched in cardiac surgery. There is still no evidence that robotic surgery can be carried out safely, quickly and effectively. Although anastomosis of the IMA to the anterior descending artery is possible[136] and the development of endoscopic stabilizers has enabled beating heart surgery, there are still serious problems, such as persistent movement in the area of the coronary anastomosis[137,138] and limitations regarding manual control, identification and follow-up.[139,140] For these reasons, robotic surgery has not become widespread and still remains the province of a few groups who continue to investigate and refine its use. It is possible that progress in other areas of surgery, such as carrying out coronary anastomosis without needing conventional sutures, will facilitate the incorporation of robotics into daily practice. Without doubt, such

research and the development of new technologies will lead to safe, quick and efficacious myocardial revascularization with CABG and the other therapies discussed in this article.

CONCLUSIONS

The results of myocardial surgical revascularization are similar to or better achieved with percutaneous coronary interventions, depending on the type of patient. Despite this, the number of angioplasties with coronary stent placement is greater than myocardial revascularization with CABG, a trend that has increased with time. It is difficult to change this trend since the cardiologist is the person who performs the percutaneous intervention and, at the same time, the one who offers this procedure to the patient, but it is important to recognize that the capacity of drug-eluting coronary stents to offer local delivery adds a new dimension to the control of coronary restenosis. Thus, it is conceivable that better knowledge of the mechanisms of coronary restenosis and the arrival of new technical advances will improve the clinical outcomes of angioplasty in the future.

The outcomes of myocardial surgical revascularization with CABG are better than those of venous grafts regarding the elimination of angina symptoms, survival and the need for new revascularization interventions. The selection of the type of arterial graft and graft configuration depends on each surgeon's experience and personal skill but, currently, there is no reason not to use arterial grafts. Despite enthusiasm for off-pump CABG, the results obtained to date have not shown clear advantages over on-pump CABG. On the contrary, the possibility of a reduction in graft patency and the high rate of incomplete revascularization in off-pump CABG represent a serious limitation to this technique. The clearest indication for off-pump CABG may be atherosclerosis and calcification of the ascending aorta, where the non-handling of the aorta is fundamental in preventing embolic complications.

The patients with diffuse coronary disease and refractory angina who cannot receive CABG or angioplasty can be treated with a series of alternative therapies. Unfortunately, however, some of these are not effective or do not completely eliminate angina in the way conventional therapy can and sometimes the modest benefit obtained is not permanent. Stimulating the growth of new vessels with stem cells and genes to overexpress growth factors is a promising therapy, but this treatment is in its infancy and there is still a long way to go before clarifying its clinical efficacy.

ACKNOWLEDGEMENTS

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