

# The future of saphenous vein graft for coronary artery bypass surgery

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Coronary artery bypass graft surgery (CABG), developed in the late 1960s by Favaloro and using saphenous vein grafts dramatically changes the treatment and the prognosis of patients with ischemic coronary artery disease.

The aim of the surgical procedure is to improve patients' quality of life alleviating anginal symptoms and restore physical activity, as well as increasing survival in certain groups of patients, especially in those at higher risk. However, inherent factors to both procedure and basal disease affect and even suppress the long-term benefits provided by coronary artery bypass graft surgery. Among these factors, the venous graft degeneration is yet one of the greatest drawbacks.

The coronary artery bypass graft surgery success is, to a great extent, related to the type and quality of the graft employed. However, this continues to be our dilemma, once the only graft which has been shown excellent long-term outcomes and considered to be the gold standard in coronary artery bypass graft surgery is the pediculated left internal thoracic artery, when it is anastomosed to the anterior descending artery.

Nevertheless, the complete myocardial revascularization is the goal to be achieved, treating all severely stenosed coronary arteries causing ischemia, assuring the remission of symptoms and increasing survival. Thus, the use of saphenous vein grafts is still vital to accomplish this goal. Moreover, up to the present time, there is no demonstration of the superiority of arterial grafts (except the internal thoracic artery grafts) over the saphenous vein grafts. Techniques and strategies to better preserve structurally and functionally the saphenous vein could safely contribute to a better outcome, once the increased patency grafts correlates to an increased survival in the long-term.

The superior outcomes achieved by means of the internal thoracic artery are due partly to the scrupulous caution devoted by the surgeon to the dissection and the minimal surgical trauma of this conduit, thus avoiding traumas that could jeopardize its patency. However, this same caution is not addressed to the saphenous vein graft,

which often undergoes wounds and injuries during its dissection, such as tractions and sprains leading to structural integrity alteration, endothelial lesion, platelet deposition, and induction and acceleration of atherosclerotic process.

With the success of internal thoracic artery grafts attaining excellent patency on the long-term and the demonstration of poor outcomes of venous grafts, from the early 1980s on, there has been an intensive search for other types of arterial grafts to be concurrently used with one or both internal coronary arteries and, therefore, to achieve a complete revascularization of the myocardium.

The right gastro-omental (gastro-epiploic) artery and the inferior epigastric artery, introduced in the early 1990s by Suma et al. and Puig et al., respectively, did not displayed late satisfactory and comparable outcomes with the internal thoracic artery [1]; currently, these vessels are used only in special cases.

The radial artery proposed by Carpentier et al. in the early 1970s, which was shortly after abandoned, currently, has been widely used by cardiac surgeons around the world. There are several studies designed to convince us that the radial artery is a graft of quality when it is used in selected cases [2,3], even though randomized prospective studies are needed to perform a better analysis and discernment of this conduit.

Regarding synthetic grafts, up to the present none of them are capable of replacing autologous vascular grafts with the same efficacy.

Therefore, there is no question about that the saphenous vein continues to be a necessary and crucial graft for surgical myocardial revascularization. Notwithstanding, in order to keep being used as a conduit in this type of surgery, the three most important pathological alterations causing failure and decrease of patency (thrombosis, intimal hyperplasia, and atherosclerosis [4]) have to be attenuated, delayed, or prevented.

Thrombosis is the main mechanism responsible for the early occlusion of the saphenous vein grafts, which occurs in 3% to 12% of the patients in the first week

postoperatively. The injury to the vein wall, usually during its removal in surgery, stimulates the activation of the coagulation cascade system, resulting in thrombosis formation.

Intima hyperplasia is recognized as the leading cause of venous graft failure in the middle-term (2 to 24 months). Intimal hyperplasia is represented by an increase in number of normal smooth muscle cells in the vein wall that afterwards migrate from the tunica media to the tunica intima, resulting in a stricture of the lumen of the vein. In venous grafts, this is followed by an increased deposition of cell matrix. Despite the efforts to reduce intimal hyperplasia and its clinical outcomes, the impact of hyperplasia regarding the setting of vascular interventions is relevant, once it forms the substrate to the development of atherosclerosis, which is the end-stage of the graft occlusion process.

The recidivation of myocardial ischemia symptoms caused by the *atherosclerosis* of venous graft is not usually noticed before 3 years of surgery. The development of atherosclerosis in native arteries requires a 50- to 60-year period, whereas in the venous grafts it takes only 5 to 10 years. One of the basic causes of the accelerated status of the disease in venous grafts is injury and cellular dysfunction triggered during surgical management. Additionally, atherosclerotic plaques build up within the venous grafts present high numbers of inflammatory and spongy cells, as well as other morphological marked differences when compared to the arteries [4,5].

## CURRENT STRATEGIES TO REDUCE VENOUS GRAFT FAILURE

### Pharmacological agents

Several pharmacological interventions have been introduced in an attempt to improve the vein patency. The use of statins postoperatively along with antiplatelet agents is already an established strategy to reduce occlusion of the saphenous veins grafts. Recently, a clinical investigation has shown that the use of lovastatin significantly reduces the occlusion rate of the coronary artery saphenous vein bypass grafts [6].

Aspirin increases vein patency up to one year after surgery, when compared to placebo. However, after the first year, the benefit of aspirin action disappears, suggesting that its primary effect is to reduce early thrombosis [7].

There are evidences that the concentration of the enzyme nitric oxide synthase (NO synthase) is reduced in areas of vascular injury and that the nitric oxide (NO) is involved in graft failure. Particularly, vasospasm and thrombotic occlusion can be the result of a decreased NO activity in the venous graft. NO prevents platelet and leukocytic adhesion, inhibits proliferation of smooth muscle

of the vein wall, and has antioxidant activity. Nitric oxide donor drugs causing vasodilation and inhibition of platelet deposition in the saphenous vein, such as S-nitrosoglutathione, have been investigated [8]. Substances reducing neointimal hyperplasia are also being studied as a potential pharmacological strategy to prevent the saphenous vein occlusion graft. Thapsigargin has been evaluated in an attempt to inhibit the neointimal formation in saphenous vein grafts, once it acts increasing intracellular sodium concentration and regulating migration and proliferation of smooth muscle cells [9].

### Gene therapy

The fast advances in molecular biology in recent years lead to the development of gene therapy techniques aiming at identifying the methods to reduce venous graft hyperplasia [10,11]. Clinical trials of the gene therapy use are expected as a potential application in clinical practice in order to improve patency of saphenous vein grafts. The three first processes involved in the development of graft failure, that is, early thrombosis, intimal hyperplasia, and accelerated atherosclerosis, all represent potential targets to agents with antithrombotic, antiproliferative, antimigratory, pro-apoptotic, and antiinflammatory properties.

However, a recent large randomized multicenter study, the PREVENT IV [11], that has analyzed more than 3000 patients undergoing coronary artery bypass grafting surgery, did not show benefit from the gene therapy application. The occlusion rate of saphenous vein grafts was > 40% in the angiographic exam performed between 12 and 18 months, both the group receiving treatment and group control, thus raising the hypothesis that vein minimal surgical trauma, wound, and injuries before its implantation are, unquestionably, the triggering mechanisms of the processes leading to the loss of patency.

### External stents

Experimentally, external stents, both synthetic and biodegradable, have decreased the formation of neointima in porcine veins, which were interposed in carotid arteries. Mehta et al. [12] demonstrated that both the Dacron synthetic graft and the biodegradable polyglactin grafts decrease the thickening of tunicae media and intima. Perivenous support reduces endothelial lesion and other alterations in studies carried out with human veins perfused with blood (*in vitro*) [13]. However, the randomized study performed in patients receiving saphenous vein grafts treated with external polyester stent showed that all veins were occluded 6 months after surgery [14].

### Synthetic grafts

The most tested and used artificial grafts in

cardiovascular surgery were both Dacron and polytetrafluoroethylene (PTFE) grafts. Studies in patients with recurrent myocardial revascularizations who have received such grafts due to the lack of autologous grafts showed disappointing outcomes, mainly because of the thrombogenicity and subsequent intimal hyperplasia, especially in regions of anastomoses. The patency of polytetrafluoroethylene (PTFE) grafts in coronary artery bypass grafting surgery is 14% at 45 months [15].

Attempts of endothelialisation of artificial grafts by means of seeding of the graft lumen with endothelial cells also did not improve the outcomes, resulting in a patency of only 60% at 4 years [15].

### **Tissue engineering**

This procedure involves the development of grafts constructed with a mixture of vascular smooth muscle, collagen, and endothelial cells [15], requiring several weeks of graft preparation and, thus, it cannot be used in emergency surgery. This method was not yet clinically assessed; its long-term efficacy and patency rate remain unknown. It has been suggested that this method of vascular tissue engineering will not be accepted until superior outcomes, or those comparable to autologous grafts have been demonstrated in clinical trials. At present, the combination of endothelial cells implantation with gene therapy vascular endothelial nitric oxide synthase (eNOS) seems to present a great potential to be used in synthetic grafts.

### **Refining the paradigm: the technique of vein preparation**

With the disappointing outcomes provided by the alternative grafting strategies discussed above, there is no doubt about that all efforts should be driven in order to avoid injury of the vein wall during its preparation and, consequently, improving the outcomes. Several studies demonstrated that the injury occurring during vein preparation is one of the major factors of its failure when it is used as a graft in coronary artery bypass graft surgery [16]. It is interesting to notice that the vein continues to be prepared with the same conventional technique formally approved since the beginnings of coronary artery bypass graft surgery, over 40 years ago, that is, the vein is denuded and distended before being implanted. This could have been a critical failure and might have entailed its relative failure in face of the internal thoracic artery grafts.

It has been acknowledged for many years that the high pressure applied to distend the saphenous vein to the effect of reversing the spasm during its preparation and checking for leaks is the main cause of loss of endothelial layer and medial damage [17]. This is the main triggering factor of

pathological events, which are responsible for grafting occlusion.

Recently, the introduction of a novel technique of the saphenous vein preparation, the technique “no-touch”, in which the vein is harvested with a pedicle (1 cm) of surrounding fatty tissue and minimal surgical trauma, represents an advance in the maintenance of graft physiological and structural integrity [18]. A randomized study comparing both techniques – “no-touch” vs conventional – has shown a significant vein patency improvement, both in the short-term (18 months, 89% conventional vs 95% no-touch;  $p<0.0025$ ) and in the long-term (8.5 years, 76% conventional vs 90% no-touch;  $p<0.01$ ) [19,20].

Some mechanisms have been proposed to explain the success of this technique. First, in the no-touch technique, the occurrence of vein spasm can be avoided or reduced, thus, the vein in this particular case does not to be dilated. The fatty tissue can function as an external biological stent, providing support against the detrimental effect of arterial pressure on the ascending aorta over the vein wall. Also, fatty tissue protects against injury caused by direct manipulating of the vein wall with surgical instruments. Recently, a significant number of adipose-derived peptides have been identified, among them the adipocyte-derived relaxing factor secreted into the plasma, which plays an important vascular regulation and hemostasis role [21]. Particularly, perivascular fat is an important source of NO, contributing to improve the patency of the vein prepared using intact fatty tissues. Vein segments harvested from patients undergoing coronary artery bypass graft surgery have demonstrated that the perivascular tissue-derived enzyme eNOS plays a crucial role in improving the patency of the saphenous vein graft prepared atraumatically [22]. The denudation of perivascular fat, used in the conventional technique, can substantially reduce eNOS levels, thus contributing to the worsening of the saphenous vein patency.

It has been demonstrated that the vein endothelium treated with the no-touch technique remains intact [23], preserving the enzyme eNOS, which represents an additional mechanism to improve patency [23,24]. Besides preserving the endothelium, it has been suggested that the protection of the “vasa vasorum” network plays a fundamental role in the success of this novel technique. It has been demonstrated that this network of nourishing microvessels penetrates deeply into the tunica media, ending up into the vein lumen, thus providing a retrograde filling of the vasa vasorum [23]. The preservation of the vasa vasorum network aims at providing the restoration of blood flow through the vein wall, thus reducing ischemic injury. These outcomes suggest that the preservation of the tissue surrounding the vein by the no-touch technique, including perivascular

fat, not only provides structural support and minimizes surgical trauma, but also plays an important role in modulating vascular tonus, preserving the endothelial function, and reducing neointimal thickening [22]. A matter of great concern to this evidence is the previous study published by Gao et al. [25] that reported the potential of perivascular adipose tissue preservation in the internal thoracic artery grafts, reducing the occurrence of vasospasm of the graft vessels.

## CONCLUSION

Despite all the advances verified in the last decades in coronary artery bypass graft surgery, the use of the saphenous vein graft continues to be critical in achieving a complete coronary artery bypass graft goal in the majority of the patients, but venous graft failure still represents a severe issue that needs to be solved.

Most of the current breakthrough strategies used to improve the saphenous vein graft outcomes, both in experimental and clinical studies, have been attempting to fix the effects of surgical trauma by means of replacement, restoration, or inhibition of the factors released by vascular trauma during vein preparation.

Notwithstanding, there is no question about the better approach to prevent vascular injury instead of trying to repair it after its occurrence, which should be started at the surgery room using atraumatic surgical techniques to graft preparation.

Therefore, the use of no-touch technique associated with up-to-date pharmacological strategies could contribute to further improve the outcomes of the saphenous vein grafts.

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