

Does denervation affect the performance of blood vessels used as coronary artery bypass grafts? A mini-review.

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Abstract

The saphenous vein (SV), a blood vessel superficially located in the leg, is the most commonly used graft in patients requiring coronary artery bypass surgery (CABG). Using conventional surgical methods of preparing the SV this vessel is subjected to considerable trauma that influences graft performance. While much interest has focussed on reducing damage to the veins' innermost surface (the endothelium) during CABG, preservation of its outer layer (the adventitia) has been largely neglected. Within the adventitia are located the vascular nerves and vasa vasorum, a microvascular network providing the vessel wall with oxygen and nutrients. An atraumatic, no-touch, technique of harvesting the SV has been introduced that dramatically improves the performance of this vessel when used in patients undergoing CABG. When preparing the SV by the no-touch technique the vessel is removed complete with its cushion of surrounding tissue and in doing so the vein's normal architecture is maintained and the adventitia remains intact. There is evidence that the improved patency of no-touch grafts is associated with preservation of structures in the SV adventitia. In this mini review we discuss the preparation of vessels used as bypass grafts in patients with heart disease, the use of synthetic and tissue-engineered graft materials and the potential importance of retaining or mimicking normal vessel structure.

Key words: Adventitia, bypass graft, saphenous vein, vasa vasorum, vascular nerves

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Introduction

The two vessels most frequently used as bypass grafts in patients requiring revascularization of ischaemic myocardium are the saphenous vein (SV) and the internal mammary artery (IMA). These vessels are often prepared in such a way that they are separated from their surrounding tissue and isolated to form a tube, or conduit, suitable for restoring blood supply to the affected region of the heart [1-3]. More recently, synthetic or tissue-engineered materials have been prepared in an effort to provide alternative means of restoring arterial blood flow to ischaemic tissues i.e. dog carotid and femoral arteries or primate abdominal aorta [4, 5]. If successful, such materials would reduce the undesirable effects of harvesting vessels required for i.e. coronary artery bypass surgery (CABG) (scarring, cosmesis and infection at the site of vein harvesting) and provide readily available 'connectors' that may be used for revascularisation procedures.

Autologous grafts

The SV is the most commonly used conduit for CABG yet its performance is poor compared with the IMA, the 'gold standard' [6, 7]. The major advantage of the SV is that it is expendable as deeper vessels maintain blood flow to superficial tissues after its removal; the extensive length of this vein allows for multiple grafts; its superficial position renders it easily accessible. The major cause of early SV graft failure is due to thrombotic occlusion following endothelial damage caused by surgical trauma at harvesting [8].

Here, endothelial denudation exposes the vein intima basement membrane to the circulating blood and platelet aggregation occurs as a result of reduced endothelium-derived factors such as NO and prostacyclin [9].

During conventional preparation of the SV in patients undergoing CABG the vessel is stripped of its surrounding cushion of tissue including the adventitia (**Figure 1**). Within this layer are situated the vascular nerves and the vasa vasorum [10-21], which play an important role in maintaining a healthy vessel. The question therefore arises, does the damage to SV innervation during harvesting effect graft performance and therefore tissue perfusion?

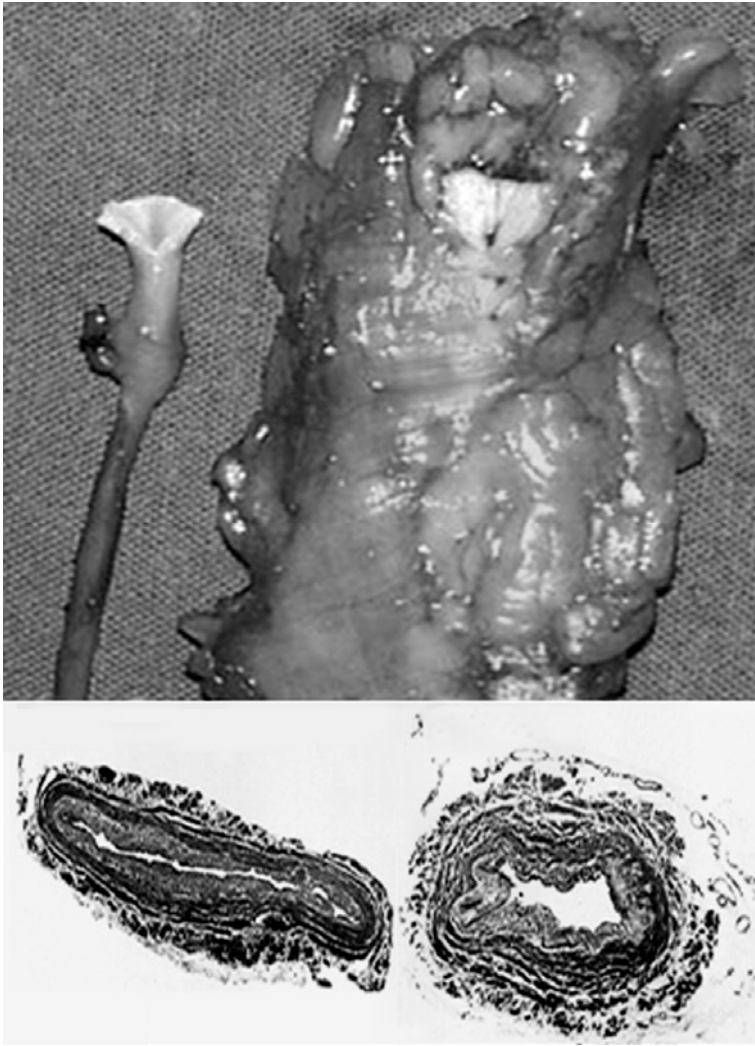


Figure 1. Comparison of SV preparations for CABG.

Top image. An example of a conventionally-prepared SV (left in top image) for use in CABG. The surrounding tissue has been removed. A branch that has been tied off can be seen on the left side of the main vessel just below the vessel lumen. A no-touch harvested SV (right in top image) that has been removed complete with its surrounding cushion of tissue, much of which is perivascular fat.

Lower images. These show transverse sections of conventional (left) and no-touch (right) harvested SV that were stained for collagen. The lumen of the conventional vein is collapsed and the media is thin due to the high-pressure intraluminal distension used to overcome spasm. In addition, a high proportion of the vessel's outermost layer has been damaged or removed. The no-touch vein retains a normal architecture where the intima is thrown into folds (as it has not been distended), the media remains thick and the pronounced adventitial layer remains intact. Adventitial vasa vasorum that can be clearly seen in these veins are absent or damaged in conventional vein preparations.

In SV, perivascular nerves are usually located in the vicinity of the vasa vasorum system, suggesting a functional relationship between these two networks. Figure 2 demonstrates a close anatomical relationship between vasa- vasorum and perivascular nerves in the adventitia of the SV wall [also see 21].

Adventitia: vasa vasorum: perivascular nerves

Our understanding of the influence of the vasa vasorum and the perivascular nerves within the adventitia and on the physiology of SV is still limited. Nonetheless, recent studies strongly suggest that preservation of the nutrient role of the vasa vasorum might be crucial to the performance of the SV as an autologous graft in the early stages after implantation into the coronary circulation [15]. Previous experimental studies showed that occlusion of the vasa vasorum e.g. of rabbit carotid artery [22] causes neointimal hyperplasia and a reduction in lumen diameter, features observed in coronary artery disease, stroke and peripheral artery disease. It has also been shown that adventitial removal of the rabbit carotid

artery caused early signs of atherosclerosis and that this was reduced on the appearance of a 'neoadventitia' [23]. Therefore, preservation of the adventitia in conduits used as grafts may play an important role in their ability to restore and maintain blood supply to ischaemic tissue. In this respect, preservation of the perivascular nerves, the vasa vasorum and vasa nervorum may be crucial to the performance of autologous grafts, in particular the SV, which as an intact vessel possesses a pronounced adventitia containing an extensive network of vasa vasorum and vascular nerves.

It is highly possible that the adventitial perivascular nerves of human SV contribute to the "healthy" functioning of the vasa vasorum, and hence the vein wall. It has been shown that the sympathetic signalling in human SV is complex [24-34]. The vasa vasorum of the SV is densely innervated by sympathetic nerves [21] the presence of vasa vasorum-associated vascular smooth muscle cells implies that the vasa vessels actively regulate their own tone. However, when harvesting the SV for CABG perivascular nerves are disconnected from their autonomic ganglia (mostly pelvic ganglia) during vein dissection from the leg. It is also unclear whether these nerves remain intact after harvesting procedures and what impact this denervation may have on SV graft performance. According to commonly accepted opinion such denervation would be expected to lead to nerve degeneration. Our own observations suggest that both damaged and undamaged varicosities, at least of the sympathetic nerves showing positive reaction for tyrosine hydroxylase (TH), are observed in the SV wall during harvesting [21]. Recent observations also suggest that SV graft patency is improved when mechanical damage to the vein is minimised during harvesting for CABG. These facts strongly support the importance of preserving all vein wall components, in particular the adventitia and associated structures such as the vasa vasorum and perivascular nerves. It is likely that, apart from surgical trauma at harvesting, distension-induced trauma causes constriction of the vasa vasorum

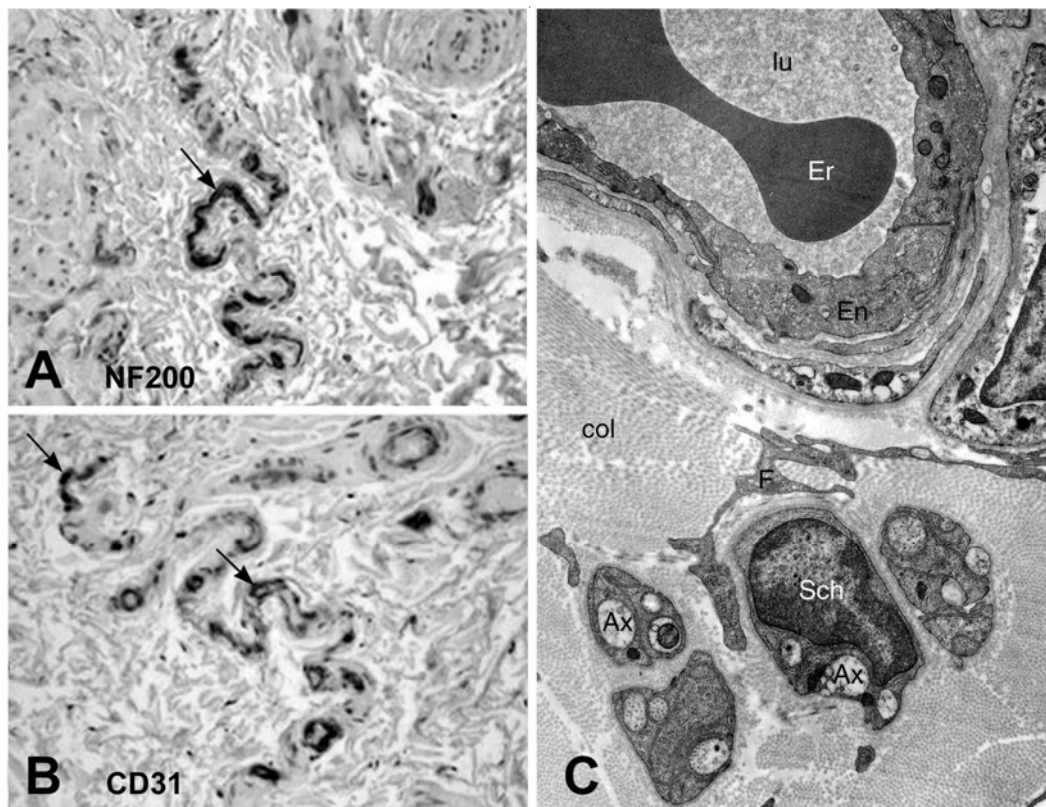


Figure 2. SV adventitial perivascular nerves and vasa vasorum. Images A and B show light microscopy of adventitial perivascular nerves and vasa vasorum immunolabelled (arrows) for NF200 and CD31, respectively (x 40 original magnification). Image C illustrates the proximity of adventitial vasa vasorum vessel (venule) and autonomic perivascular nerves as seen at the electron microscope level. In the vessel note endothelium (En), lumen (lu) and an erythrocyte (Er). Note that the autonomic nerves consist of Schwann cells (Sch) and enclosed axon profiles (Ax); fibroblast (F) and collagen (col) are also seen. x 11,500. Image C is from [18], which is kindly acknowledged.

and subsequent reduction in blood supply to the SV graft wall [35].

While present attention is generally focussed on the vessel's innermost surface and maintaining a non-thrombotic/patent lumen, how might the preservation of the outermost vessel layer impact on graft performance? Certainly while there is

increasing evidence that this may be an important consideration when using autologous grafts, there is little, if any, attention to the potential importance of adventitial influences on synthetic graft materials.

Synthetic graft materials

Since the outermost layer of autologous grafts, including the adventitia, of SV effects graft performance should this be considered when developing synthetic materials? An intriguing and important question is, can the SV (and also the internal mammary and gastroepiploic arteries) harvested “with normal architecture” for CABG, be substituted by synthetic grafts?

There has been considerable interest in recent years into the potential use of ‘manufactured’ graft materials. Clearly, synthetic grafts that can be used ‘off the shelf’ are desirable since the need for surgical removal or in situ grafting of blood vessels is obviated. The most popular synthetic materials that are already used in cardiovascular surgery including bypass surgery are polymers: Dacron™ and polytetrafluoroethylene (PTFE) with the more recent introduction of nanotechnology as a potential technique for producing grafts. In addition to these approaches considerable effort has been spent into the study of tissue-engineered conduits using a variety of cell types harvested from patients requiring imminent revascularisation due to atherosclerotic occlusion of coronary, carotid or popliteal arteries. To this end the main focus has been coating potential graft materials with endothelial cells (‘seeding’) in an attempt to prevent thrombotic occlusion that frequently occurs soon after implantation. While such attempts at improving graft patency concentrate on the development of a non-thrombotic intima, its outer surface - the adventitia - receives little attention.

So far, studies into the use of prosthetic grafts in CABG patients requiring regrafting have proved disappointing primarily due to their thrombogenicity and subsequent intimal hyperplasia particularly at regions of anastomosis. Patency rates using PTFE in CABG patients were only 14% at 45 months [36]. The formation of intimal hyperplasia is believed to be a result of compliance mismatch at the anastomoses between the viscoelastic blood vessel and the comparatively non-elastic grafts. These disappointing results have prompted the development of superior grafts made with polymers such as polyurethanes (PU) that are said to be more compliant and reseal after use. These materials are still under clinical trial, so far with no long-term patient data available.

Tissue Engineering

This approach involves the development of “fully engineered grafts made from a scaffold and mixtures of VSMCs/collagen and endothelial cells” [5]. This technique takes several weeks to prepare a potential graft and cannot therefore be applied within a time frame suitable for emergency procedures. This method has not as yet undergone clinical trial and the long-term effectiveness and patency rates are not yet known. However, it has been suggested that this method of vascular tissue engineering will not be accepted until results superior to autologous grafts have been demonstrated in clinical trials. At present, a combination of prosthetic grafts with two-stage seeding appears to produce optimal results. The development of a more rapid endothelial cell lining for the graft is needed before these grafts are a realistic option in emergency cases.

Interestingly, there are several reports of the appearance of vasa vasorum in experimental tissue-engineered grafts [4, 5]. As in the SV these microvessels become evident once the graft wall reaches a critical thickness. Although there may be a gradual change in the lumen size of the vasa vasorum of tissue engineered grafts it is not clear if such grafts become innervated or if these vasa vasorum are simply passive channels. Consequently, the second by second neural influences that occur in native vessels may or may not influence the vasa vasorum of tissue-engineered vessels. This is a similar situation to SV grafts for used for CABG as these vessels are also denervated at harvesting. It is not known what effect this denervation has on graft performance although there is evidence that “neoinnervation” occurs in close proximity to areas exhibiting neovascularization in a porcine vein graft model [37, 38]. Perhaps there is eventual re-growth of host vessel nerves (e.g. coronary artery) with the graft and that this “reconnection” influences the long-term outcome of CABG. Studies into the innervation of autologous bypass conduits as well as synthetic graft materials are to be recommended.

Conclusions

We are still at the very early stages regarding the development of synthetic/tissue-engineered graft materials suitable for CABG. The main obstacles are associated with the thrombogenicity, compliance and other factors that affect the potential of these would be grafts when compared to autologous vessels that are currently in use. The SV is therefore the vessel of choice when the IMA is unsuitable or has already been used for the purpose. When handled with minimal vascular trauma at harvesting the SV may well serve as a conduit providing an improved graft patency in the coming years until suitable synthetic grafts are developed for patients requiring bypass surgery.

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