Review of the Literature

Pedicled or Skeletonized?

A Review of the Internal Thoracic Artery Graft

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The internal thoracic artery is the gold-standard conduit for coronary artery bypass surgery. Until recently, it was used almost exclusively as a pedicle, with construction of 1 distal anastomosis. Skeletonization of the internal thoracic artery has recently been advocated in order to increase the number of arterial anastomoses and decrease the occurrence of sternal wound infections. When skeletonized, the vessel loses its "milieu", which raises the question of whether this technique sacrifices the superior longevity of the conduit. The current status of research on the effects of skeletonization (depriving the internal thoracic artery of vasa vasorum, innervation, and lymphatic and venous drainage, together with creating an imbalance between vasoconstricting and vasodilating substances) appears to support the superiority of the pedicled graft. Long-term patency studies of the skeletonized ITA, with meticulous follow-up and confirmation by angiography, are not currently available. Theoretically, skeletonization of the ITA might adversely affect its long-term resistance to atherosclerosis. More data are needed before this technique can be universally recommended. If the skeletonized ITA has decreased long-term patency, bypass surgery may be at a disadvantage when compared with the new generation of drug-eluting stents. ***(Tex Heart Inst J 2003;30: 170-5)***

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The internal thoracic artery (ITA) graft has the best long-term patency rates of all conduits currently used for myocardial revascularization. Its superiority is due to its high resistance to atherosclerosis.[1,2] The left ITA was originally used for coronary artery grafting with a single distal anastomosis to a single coronary artery, most commonly the left anterior descending (LAD). Recent technical developments have enabled surgeons to construct multiple distal arterial anastomoses using both ITAs[3,4] and sequential grafting.[5-7] Free ITA grafts have been used by some investigators to reach more distal areas of the native coronary arteries[8-10] in an attempt to achieve complete or near-complete arterial revascularization in selected patients. These new techniques have not been free from added complications. The use of bilateral ITAs has been associated with an increased occurrence of sternal wound infections, probably as a consequence of the decrease in the blood supply to the sternum.[11-14] Hypothetically, skeletonization of the ITA preserves collateral blood flow to the sternum.[15] This has been confirmed by Cohen and colleagues,[16] and skeletonization appears to have decreased the occurrence of sternal wound infections. Skeletonization of the ITA may also increase its length and allow for sequential grafting, more distal anastomoses, or both. However, the effect of skeletonization of the ITA on its long-term patency has not been established. Calafiore's group reported that the long-term patency rate of skeletonized and pedicled IMA grafts in human beings was similar.[6] However, his patients underwent a mean of only 9 years of follow-up, and long-term studies of the pedicled ITA at 15, 17, and 20 years are currently available.[17-19] Furthermore, the angiographic follow-up in Calafiore's series was limited to one third of the patients at a mean of only 17.5 months, with a wide standard deviation (± 18.4). It is not clear how patients were selected for repeat angiography.

The superiority of the ITA over other conduits may be due to several morphologic differences, most importantly its blood supply from the vasa vasorum, in in addition to its well developed internal elastic membrane, its innervation, and a comparatively low number of smooth muscle cells in its media.

Although there are important morphologic reasons why arteries have better patency rates than veins when used as conduits, biochemical factors may also have significant impact. The supply of nutrients to the wall of the conduit, the removal

of metabolites, and the production of vasoactive substances are among these.

When the saphenous vein is used as a coronary bypass conduit, it has to be used as a free graft, whereas the ITA gives us the option of using it as a pedicle, a skeletonized graft, or a free graft. It is possible that long-term patency rates of the ITA are affected either positively or negatively, depending on whether the graft is pedicled or skeletonized.

The rate of sternal wound infections is higher when both ITAs are used[13] but appears to decrease when the ITAs are skeletonized.[15] For this reason, skeletonization is gaining popularity. However, skeletonization deprives the ITA of the theoretical advantage hypothesized by Green[20] 35 years ago: that the ITA is a better conduit for coronary bypass because the pedicled graft carries its homeostatic milieu with it.

Patency Rate

The superior resistance to atherosclerosis of the ITA, over the coronary arteries, has been reported.[2]

A 20-year follow-up study,[19] with angiographic confirmation in 90% of the survivors, demonstrated an 89% patency rate in pedicled ITA grafts. A significant decrease in patency (96.3% vs 86.5% [*P*=0.02]) was demonstrated during 10 years of follow-up in patients who had received the ITA as a free graft.[14] Cheanvechai and colleagues[21] reported the superiority of the in situ ITA over the ITA as a free graft. Yamashiro and coworkers[22] concluded that results obtained with the free ITA were comparable to those obtained with the pedicled ITA, but their study included only 41 patients with free ITA grafts—only 17 of whom were restudied angiographically at more than 5 years. The effect of skeletonization of the ITA on its long-term patency has not been established. Calafiore's group[6] reported its results at 9 years; however, during the first 3 years the group's patients received pedicled ITAs, and during the following 6 years patients received skeletonized ITAs. Of 3,196 patients, only 88 were studied with late angiograms. The patency rates of pedicled ITA grafts at 7 to 9 years appear to be only slightly reduced from those at 6 and 13 months, which demonstrates a slow progression of disease.[23] The skeletonized ITA has not been used long enough to establish whether a decline in patency will occur after several years.

Technical Aspects

Experience with distal lower-extremity bypasses to the femoral artery and its branches using the saphenous vein taught us that interruption of the vasa vasorum is one of the reasons for early structural changes to the graft;[24,25] therefore, a technique was developed for use of the saphenous vein in situ. This technique yielded superior durability.[26]

Long-term changes due to the lack of vasa vasorum are likely to take longer in the ITA than in the in situ saphenous vein graft, because other factors are involved. The wall of the ITA is more resistant to atherosclerosis than is the wall of the venous conduit because of differences in muscular layers and in the lamina elastica interna. In free harvested vein grafts, endothelium lost to sloughing—in both human beings and experimental animals—requires up to 3 months to be repopulated by blood elements.[26] Furthermore, the degree of subendothelial hypertrophy appears to be related to the number of vasa vasorum of the vein wall.[27,28] There is a higher risk of damaging an ITA during skeletonization than in preparing a pedicled graft, especially in regard to intraluminal hematoma. If the ITA is partially denuded of the adventitia and its vasa vasorum during skeletonization, patchy areas of degeneration may develop. Arterial free conduits anastomosed to the ascending aorta have lower patency rates than do pedicled ITA grafts.[29] It is not known whether this is due to the construction of the proximal anastomosis alone or to physiologic changes.

Histology

Daly and coworkers[30] demonstrated in dogs that skeletonized ITAs stripped of the adventitia had a higher incidence of thrombosis, intimal thickening, and medial injury than did pedicled and free ITA grafts. Furthermore, the vasa vasorum in 4 out of 6 skeletonized ITA grafts failed to fill with contrast material during arteriography and subsequent histologic examination. They concluded that this was likely due to early vascular wall ischemia as a result of poor early perfusion of the vasa vasorum.[30] The vasa vasorum of vascular grafts is eventually perfused by collateral vessels that arise from surrounding tissues, and later by regeneration across anastomotic lines.[31-35] However, the time elapsed until this occurs, usually 1 week, may suffice to produce medial necrosis and stimulation of subintimal hyperplasia.[36,37] Daly's findings were challenged by Sasajima and coworkers[38] when they found, in dogs, no histologic evidence of detrimental effects in skeletonized ITA. In their study, the ITA was dissected but not transected, and anastomoses were not constructed; therefore, the experimental design did not meet the full conditions of clinical use. The vasa vasorum appeared to be preserved, but this was not shown by angiography, so revascularization of the vasa vasorum was not proved. Sasajima did not use a sensitive method other than histology to demonstrate endothelial integrity. In an immunohistochemical study that used polyclonal antibody to factor VIII to assess the integrity of the endothelial layer after surgical preparation, Gaudino and colleagues[39] concluded that there was no difference between skeletonized and ped-

icled IMAs in 40 randomized patients. In 2 cases of skeletonized ITA (but in none of the pedicled), microthrombi were found on electron microscopic examination. Contradictory conclusions were reached by Choi and Wendler[40,41] and Sasajima[38] regarding the effect of skeletonization of the ITA. The former claimed that freeing the vessel from the endothoracic fascia increases flow and is an acceptable strategy for that purpose; however, Sasajima observed a reduction in flow rate through the ITA, probably from closure of all mural branches. Corson and coworkers[42] demonstrated in dogs that even in the absence of intraluminal flow the vasa vasorum is able to maintain endothelial integrity in "in situ" vein bypasses and that the endothelium is very sensitive to the loss of vasa vasorum blood supply. Intimal proliferation might be expected to increase dependence on nourishment by vasa vasorum.[43]

Arterial Wall Metabolism

Metabolic exchange occurs at the capillary level. Capillaries are always low-pressure conduits, because they would rupture at higher pressures. For this reason, arteries cannot have capillaries in their inner layer. Oxygenation and nourishment of the arteries, and removal of waste products, must occur through the capillary bed that lies predominantly in the adventitia—specifically, through the vasa vasorum. If the adventitia is removed, metabolic exchange is limited to diffusion from blood traveling in the arterial lumen. Oxygen has a great deal of difficulty diffusing through the thick arterial wall, and waste products cannot enter the lumen against high arterial pressure until they have reached a very high concentration within the wall, sufficient to create a diffusion gradient. Furthermore, it has been suggested that a local or anatomic factor (perivascular lymphatic drainage) may play an important role.[2] Lymphatic capillaries have an even lower intraluminal pressure and are present only in the outer layers of the muscular arteries. Angouras and coworkers[44] have shown that interruption of the vasa vasorum of the aorta in an experimental model leads to abnormal morphology of elastin and collagen fibers of the outer media, which results in arterial wall stiffness within 15 days. The vasa vasorum of coronary arteries in arteriosclerotic monkeys increases its blood flow toward the intima and media;[45] if the adventitia is removed, this compensatory mechanism will be absent.

Another reason why the ITA has a better long-term patency rate than does any other conduit may be that when used as a pedicle it retains the internal thoracic vein, which drains into the subclavian vein. If the internal thoracic vein is able to remove waste products from intact connections with the vasa vasorum of the ITA, it may retard or prevent the formation of atheroma in the ITA. When the ITA is skeletonized, it is also deprived of its drainage via the vasa vasorum.

Because atherosclerosis secondary to these waste deposits may take some time to develop, its contribution to the formation of plaque with hemodynamic consequences may not be detected for years. It is also possible that this process may be accelerated in patients with diabetes or patients with previous minimal disease of the ITA. When the ITA is used as a free graft with an intact surrounding pedicle, its patency rate approximates that of in situ ITA grafts.[29,46-48] It is possible that vessels in the intact pedicle may perfuse the vasa vasorum of the free ITA. This has been shown in experimental models, in which no histologic differences between in situ and free pedicled ITA grafts were found.[30] Lipoproteins might accumulate in the arterial wall as a result of diminished adventitial flow.[49]

Arterial Tone Regulation

Sympathetic unmyelinated fibers from the autonomic nervous system are situated in the adventitia of arteries and supply the muscular layers. Vasoactive agents that are normally released from nerve endings in the adventitia of the ITA—norepinephrine and vasoactive intestinal peptide,[50,51] for example—may no longer be available in the skeletonized ITA. We do not know how their absence affects the balance with potent vasodilators like endothelium-derived relaxing factor (EDRF,[52,53] now called nitric oxide or NO), prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF), or with vasoconstrictors such as endothelin-1.[37,54,55] Nitric oxide is synthesized in the endothelium and acts on smooth muscle cells to induce vasodilation. Acetylcholine, serotonin, thrombin, and bradykinin stimulate NO release. Endothelial NO also inhibits smooth muscle cell proliferation, reducing the chance of vascular intimal thickening.[56] The human ITA releases more NO in response to vascular endothelial growth factor than does the human saphenous vein.[56] Patients with severe atherosclerosis exhibit ITA endothelial dysfunction,[57] so purely theoretical assumptions regarding endothelial function in either pedicled or skeletonized ITA are likely to be inaccurate. Singh and Sosa demonstrated angiographically that the pedicled ITA changes its caliber in response to changes in the size of the coronary vascular bed. This phenomenon of autoregulation is absent in saphenous vein grafts.[58] The intact ITA is highly sensitive to endothelin-1-induced vasoconstriction.[59] This is likely to be accentuated by the absence of NO. The vascular endothelium of pedicled ITA grafts plays an important modulatory role by releasing NO,[60] and the resistance of these grafts to atherosclerosis may be partly due to superior prostacyclin secretion.[61] Pedicled and free ITA grafts produce similar amounts of prostacyclin.[62]

Flow-induced vasodilation of arterial conduits is mediated by the release from endothelial cells of endothelium-derived relaxing factor (EDRF).[52,53] This response may be abolished by removal of the endothelium.[52,53,63-66] Whether the ITA loses its ability to autoregulate flow when skeletonized or is able to respond to humoral changes alone is not clearly known. Dysfunctional or denuded endothelium leads to intimal hyperplasia in the vascular wall, platelet adhesion, and release of potent growth factors.[67] On the other hand, skeletonized ITA grafts have a higher free-flow capacity than do pedicle grafts as measured intraoperatively;[41] this may be due to the resulting periarterial sympathectomy and may reduce the risk of ITA hypoperfusion syndrome. It is not known whether this effect is permanent. Nitric oxide is also known as an antithrombotic agent.[68] Because coronary artery disease is associated with an interruption of the production of NO,[69] coronary disease could by that mechanism contribute to thrombosis. Increasing blood flow produces endothelium-dependent vasodilation of angiographically normal epicardial coronary arteries in human beings. Hanet and colleagues[70] found this property to be preserved in the grafted and in situ ITA but not in saphenous vein grafts after bypass surgery. They concluded that the ability of the ITA's endothelium to modulate vasomotor tone could be a major factor in the long-term patency of the ITA graft.[70,71]

Conclusions

How should we balance the risks of problematic healing of the sternotomy, length of the ITA, bilateral grafting, and multiple arterial anastomoses versus the benefit of the ITA's long-term patency? The ultimate goal of coronary revascularization is to achieve the longest patency rate for each individual conduit and to avoid preventable conduit failure. If skeletonizing the ITA produces more arterial anastomoses but fails to achieve this goal, this approach should be reconsidered.

Long-term comparative studies are needed, with complete or near-complete angiographic and freedom-from-reintervention data. Until prospective, randomized studies of pedicled versus skeletonized ITA grafts are conducted, with follow-up periods of 15 to 20 years, we cannot conclude that skeletonization does not adversely affect patency. In the meanwhile, retrospective comparative studies could give us some indication of whether a substantial decline in patency occurs over a long period, similar to the slow deterioration and calcification of heart valve bioprostheses. Because octogenarians are likely to die of causes other than coronary artery disease before structural changes in the ITA are clinically or radiologically detectable, the true long-term effects of these technical changes are best evaluated in younger patients with longer life expectancies. Ironically, this is also the group that will be affected the most if the skeletonized ITA proves to have lower patency rates. If, on the contrary, the skeletonized ITA exhibits patency equal to that of the pedicled graft at 15 years or longer, this information will seriously challenge our current concepts concerning the process of graft atherosclerosis. Should the patency of the ITA be decreased by skeletonization, the forthcoming availability of drug-eluting stents, which promise longer patency than current stents, may deter cardiologists from referring patients for coronary artery bypass grafting. Regardless of such speculation, the ultimate verdict will be determined by the proven long-term patency of the conduit.

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