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Growth factors and experimental arterial grafts

Antonio V. Sterpetti, MD, FACS, FRCS, Sandro Lepidi, MD, Valeria Borrelli, PhD, Luca Di Marzo, MD, Paolo Sapienza, MD, Alessandra Cucina, PhD, and **Marco Ventura, MD,** *Rome, Italy*

Background: **The production of growth factors from several experimental arterial conduits was determined.**
Methods: **We implanted 105 experimental arterial grafts that were 1 cm long in the abdominal aorta of Lewis rats (average weight, 250 g). Five different types of grafts were analyzed: arterial isografts, vein grafts, arterial allografts, and polytetrafluoroethylene (PTFE) grafts with normal or decreased compliance. Animals were killed humanely 4 weeks after surgery and the production of platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor-β, tumor necrosis factor-α, and interleukin-1 was analyzed.**
Results: **Myointimal hyperplasia (MH) was evident in vein grafts, arterial allografts, and PTFE grafts, but not in arterial isografts. Growth factor production was increased for grafts prone to develop MH like vein, PTFE grafts, and arterial allografts. PDGF and bFGF were increased significantly for PTFE and vein grafts, but not for arterial allografts. The importance of bFGF and PGDF was confirmed by the capability of antibody to PDGF and to bFGF to reduce the mitogenic activity of smooth muscle cells, in vivo and in vitro, for PTFE and vein grafts, but not for arterial allografts, in which a predominant role was played by interleukin-1 and tumor necrosis factor-α.**
Conclusions: **Agents able to neutralize this increased production of growth factors, either directly or by competition with their receptors, can prevent MH formation. (J Vasc Surg 2016;64:1444-9.)**

Clinical Relevance: **Arterial grafts release growth factors, which can lead to myointimal hyperplasia formation and atherosclerosis progression in the arterial tree. Both phenomena can cause graft occlusion. Inhibition of growth factor release by arterial grafts can improve their clinical effectiveness.**

Myointimal hyperplasia (MH) and atherosclerosis progression are major obstacles to the clinical success of arterial grafting.[1] MH formation at the level of the anastomoses, and atherosclerosis progression in the distal arterial tree, are more common in synthetic grafts than in autologous grafts.[2-4] Clinical results in coronary artery bypass surgery have shown that MH and atherosclerosis formation are less common in arterial grafts like the internal mammary artery than in the reversed saphenous veins.[5,6] Several growth factors have been implied in the genesis of MH in the clinical and experimental setting.[7-12]

A series of animal experiments was performed to establish the correlation between MH formation and the biological and physical characteristics of experimental arterial grafts. MH is also a common clinical problem in transplantation,[13,14] and experiments were performed to compare growth factors release in arterial autografts and allografts.

METHODS

Experimental design. We implanted 105 experimental arterial grafts that were 1-cm long in the infrarenal abdominal aorta of Lewis rats (average weight, 250 g). The same anastomotic technique was used in all animals: a continuous suture was fashioned with starting points, at 180°. We used 10-0 monofilament nylon sutures (Ethicon Inc, New Jersey). Seven animals died in the early postoperative period from occlusion of the graft, and they were excluded from the study; 78 animals were humanely killed 4 weeks after surgery. All grafts were patent at the time of the killing. Patency was tested opening the graft and observing the inflow and outflow separately. Growth factor release (platelet-derived growth factor [PDGF], basic fibroblast growth factor [bFGF], tumor necrosis factor [TNF]-α, and interleukin (IL)-1) by the grafts was studied in organ culture. This group of arterial grafts consisted of 15 syngeneic arterial grafts, 15 syngeneic vein grafts, 30 polytetrafluoroethylene (PTFE) grafts (15 with normal compliance, 15 with reduced compliance), and 18 arterial allografts.

In 20 animals, PTFE grafts were inserted in the abdominal aorta, and they were randomised to receive either polyclonal antibody to bFGF (10 animals) or nonspecific immunoglobulin (10 animals). Fourteen animals (seven animals in each group) were killed humanely 7 days after surgery, 24 hours after intraperitoneal injection of bromodeoxyuridine (BrdU) to label proliferating smooth muscle cells. The remaining six animals (three in each group) were humanely killed 4 weeks after surgery to determine the average thickness of the distal anastomotic site.

Type of anesthesia and operative procedures. The animals were anesthetized with intramuscular xylazine (3 mg/kg) and intramuscular ketamine (50 mg/kg), supplemented with intraperitoneal ketamine for maintenance. The same drugs were used at the time of the killing of the

From the Istituto Pietro Valdoni, University of Rome Sapienza.
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Correspondence: Antonio V. Sterpetti, MD, FACS, FRCS, Policlinico Umberto I, Viale del Policlinico, 00167 Rome, Italy (e-mail: antonio.sterpetti@uniroma1.it).
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animals. No heparin was used intraoperatively or postoperatively. No antiaggregant drugs were given to the animals.

Animal care complied with the Principles of Laboratory Animal (National Institutes of Health publication 80.23, revised 1996).

Vein grafts group. A 1-cm-long segment of supra diaphragmatic inferior vena cava was obtained from donor syngeneic Lewis rats, and it was transplanted in the infrarenal abdominal aorta of syngeneic Lewis rats recipients.

PTFE grafts. A 1-cm-long segment of nonreinforced PTFE graft (30 microns fibril length, 2 mm internal diameter, 0.39 mm thick; W. L. Gore Associates Inc, Flagstaff; Ariz) was inserted at the level of the abdominal aorta in 15 animals. In another 15 animals a low-compliance PTFE graft was inserted in a similar way at the level of the abdominal aorta. The original PTFE graft was wrapped with a rigid nylon sheet. The graft in a previous study showed a reduction in compliance of 50%.

Isogenic arterial grafts. A 1-cm-long segment of abdominal aorta was obtained from donor syngeneic Lewis rats, and it was transplanted in the infrarenal abdominal aorta of a syngeneic Lewis rat recipient.

Allogenic arterial grafts. We used 18 Brown Norway rats as donors of the abdominal aorta. This inbred strain of rats was chosen for its immunologic incompatibility with Lewis rats, which were used as recipients of the arterial grafts. A 1-cm-long segment of abdominal aorta was obtained from donor Brown Norway rats and transplanted in the infrarenal abdominal aorta of Lewis rats.

Animal treated with anti-bFGF antibodies or aspecific immunoglobulins. In 20 Lewis rats, a 1-cm-long segment of PTFE graft was inserted at the level of the abdominal aorta with the standard technique described. In 10 animals, 0.5 mg of anti-bFGF-specific antibody (in a 1-mL solution) was injected intraperitoneally just after surgery, and at 24 and 48 hours after the operation. In the control group, nonspecific globulins were inoculated. Fourteen animals (seven in each group) were humanely killed 7 days after surgery. In all 14 animals, an intraperitoneal injection of BrdU, at the dosage of 100 mg/kg, was performed 24 hours before humane killing.

The remaining six animals (three in each group) were humanely killed 4 weeks after surgery. At humane killing, the carotid artery was cannulated and perfused with formaldehyde at a pressure of 100 mm Hg. The graft and the aorta below and above the graft were excised to measure the thickness of the aortic wall near the anastomoses.

Histology and histochemistry. Tissues (n = 2 for each group) were prepared analysis of the different growth factors and of α-actin with frozen section techniques, as previously described.[2,13-15]

Organ culture. The grafts and the control ungrafted aortas and veins were opened longitudinally, and rinsed thoroughly for 10 minutes with Dulbecco's modified Eagle's medium supplemented with antibiotics (gentamycin 200 μg/mL, streptomycin 100 μg/mL, penicillin 100 IU/mL). The specimen were maintained for 5 days at 37°C in a 5% CO_2 atmosphere (n = 12 for each group). The viability of the organ culture was assessed by incorporation of tritiated thymidine and by cytofluorometry.

Assay for mitogenic activity. Serum-free media (20 μL) from grafts conditioned for 72 hours, and from aortic conditioned media (n = 12 for each group) were added to Swiss 3T3 cells. The positive control group consisted of Swiss 3T3 cells which received an equivalent volume of Dulbecco's modified Eagle's medium plus recombinant growth factors (bFGF, PDGF, TNF-α, transforming growth factor-β, IL-1; Boehringer Mannheim, Germany). The negative control group received only Dulbecco's modified Eagle's medium.

After 2 days, tritiated thymidine (0.5 μCi per well plate) was added, and the serum cultures were incubated for 18 hours and collected on Skatron filters (Skatron Instruments, Sterling, Va) for radioactivity determination in a scintillation counter (LKB Instruments Inc, Gaithersburg, Md).

Analysis of reduction of mitogenic activity by antigrowth factor antibodies. Measurement of Swiss 3T3 cells DNA synthesis-stimulated activity of the conditioned media from explanted grafts was repeated in presence of an excess of monospoecific antibodies to bFGF (produced in our laboratory; n = 12 for each group), PDGF AA and BB, transforming growth factor-β, TNF-α, and IL-1 (Genzyme CO, Boston, Mass). Tritiated thymidine was again added, and the cultures were incubated for 18 hours. After further processing, the radioactivity was measured.

Assay of growth factors in the conditioned media. The presence of growth factors in the conditioned media was determined by inhibition antibody-binding assay, as previously described (n = 12 for each group).[2,13-15] A dilution of anti-bFGF mouse monoclonal antibody was incubated with various dilutions of the grafts conditioned media, in 400 μL/tubes precoated with phosphate-buffered saline gelatine 2%. After 20 hours of incubation at 4°C, *Staphylococcus aureus* was added, and the immunoaggregate was removed by centrifugation. The residual antibody-binding activity in the supernatant was measured by enzyme-linked immunosorbent assay.[2,15]

BrdU labelling index. In animals treated with antibodies to bFGF and control animals, an intraperitoneal injection of BrdU at the dosage of 100 mg/kg, was performed 24 hours before humane killing. Sections were stained using anti-BrdU antibody (BU 33 Sigma St Louis, Mo), diluted to 1:50. Antifactor VIII polyclonal antibody, at a dilution of 1:300, to highlight endothelium, and antimuscle actin antibody, diluted to1:100, to identify smooth muscle cells, were used. The total number of neointimal-labeled and unlabeled cells, in each high-power field along the whole section length, was used as the BrdU-labelling index. The BrdU-labeling index was assessed as the mean percentage of neointimal smooth muscle-labeled cells (labeled nuclei/total nuclei × 100).

Statistical analysis. Data were expressed as mean values ± standard deviation. The χ^2 test, analysis of variance, and Student *t*-test were used where appropriate. Differences were considered significant at the 5% critical level.

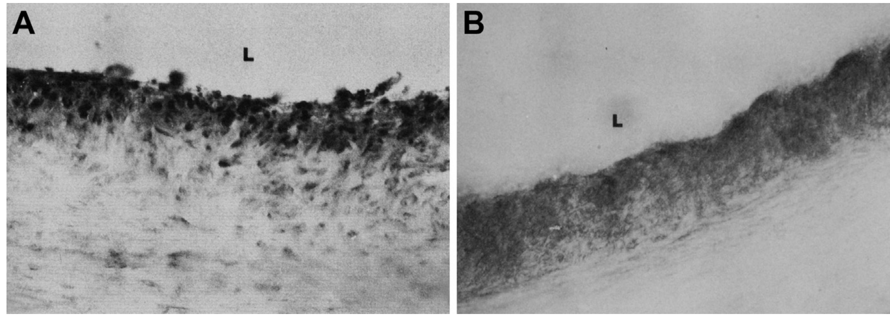

Fig 1. **A,** Histochemical localization of basic fibroblast growth factor (bFGF) in arterial vein grafts explanted 4 weeks after surgery (transverse section): localization of bFGF in smooth muscle cells which form the area of myointimal hyperplasia (MH; original magnification ×400), *L,* Lumen. **B,** Histochemical localization of platelet-derived growth factor (PDGF) in arterial vein grafts explanted 4 weeks after surgery (transverse section): localization of PDGF in smooth muscle cells which form the area of MH (original magnification ×400).

RESULTS

Histology. PTFE grafts showed evidence of MH at the level of the anastomoses. The midgraft portion was covered by thrombin and fibrin. Vein grafts were completely covered by endothelial cells. In the vein grafts, the thickness of the intima-media layer was significantly greater than that of ungrafted control veins (230 ± 40 vs 50 ± 20 microns; $P < .01$). Isogenic arterial grafts showed only minimal evidence of MH, and the thickness of the intima-media layer was similar to that of ungrafted arteries. Allogenic arterial grafts showed evident signs of rejection, with diffuse cellular infiltration in the adventitia. The intima-media thickness was greater in allografts than in isografts (250 ± 30 vs 100 ± 25 microns; $P < .01$).

Histochemistry. In vein grafts examined 4 weeks after implantation in the arterial system, the area of MH was positive for bFGF and PDGF (Fig 1, *A* and *B*). Lymphocytes heavily infiltrated the allografts, as demonstrated by panleukocytes antibody, and they were found in all layers. In allografts examined 4 weeks after implantation, the area of MH was positive for IL-1 and TNF-α (Figs 2 and 3) but not for PDGF and bFGF.

Growth factors and cytokine assay by enzyme-linked immunosorbent assay. In PTFE grafts and vein grafts, there was a significant release of PDGF and bFGF, which led us to hypothesize that these two growth factors were responsible for MH formation (Tables I and II). In ungrafted veins and aortas, the production of PDGF and bFGF was minimal ($P < .01$). Similarly, in arterial isogenic grafts PDGF and bFGF release was minimal ($P < .01$). PTFE grafts with decreased compliance had a greater release of growth factors than PTFE with higher compliance ($P < .05$) In arterial allografts, production of PDGF and bFGF was minimal. There was a significant release of IL-1 and TNF-α ($P < .01$).

Mitogenic activity of the conditioned media. Addition of serum-free conditioned media from PTFE, vein and arterial allografts collected at 72 hours (n = 12 for each group) produced a significant increase of tritiated thymidine uptake of Swiss 3T3 cell cultures, in comparison with conditioned media from control ungrafted veins, control ungrafted aortas, and arterial isografts. These differences were statistically significant ($P < .01$). The increased tritiated thymidine uptake (correlated with DNA synthesis and, thus, with cell proliferation) was greater for conditioned media from PTFE grafts, than for those from vein grafts ($P < .05$).

Reduction of mitogenic activity by anti-bFGF and anti-PDGF antibody in vitro. Addition of monospecific anti-bFGF antibody to the medium of 3T3 cells cultures exposed to conditioned media from PTFE and vein grafts decreased the uptake of tritiated thymidine by 65% ($P < .001$). Addition of monospecific anti-PDGF antibody to the medium of 3T3 cells cultures exposed to conditioned medium from PTFE and vein grafts decreased the uptake of tritiated thymidine by 20% ($P < .05$). Addition of both antibody to bFGF and anti-PDGF had only a minimal effect on the tritiated thymidine uptake of 3T3 cells cultures exposed to conditioned media from allografts.

BrdU labeling index. From the previous experiments, bFGF seemed to have a fundamental role in the genesis MH in vein and PTFE grafts. Polyclonal anti-bFGF antibody was used to inhibit the in vivo proliferative response of smooth muscle cells after grafting. The labelling index was decreased significantly ($P < .01$) in animals treated with anti-bFGF in comparison with animals treated with aspecific antibodies. The difference was evident at the level of the proximal anastomosis, distal anastomosis, and the PTFE graft. Four weeks after surgery, there was a significant decrease in MH at the level of the distal anastomosis of PTFE grafts in animals treated with anti-bFGF antibodies compared with the control group ($P < .05$).

DISCUSSION

Several factors are responsible for MH formation in arterial grafts, and an increased production of growth factors is probably the final biological mechanism leading to smooth muscle cell proliferation.[1-4,16-19] We found that PTFE grafts produce a high quantity of PDGF and bFGF, which can lead to anastomotic myointimal and

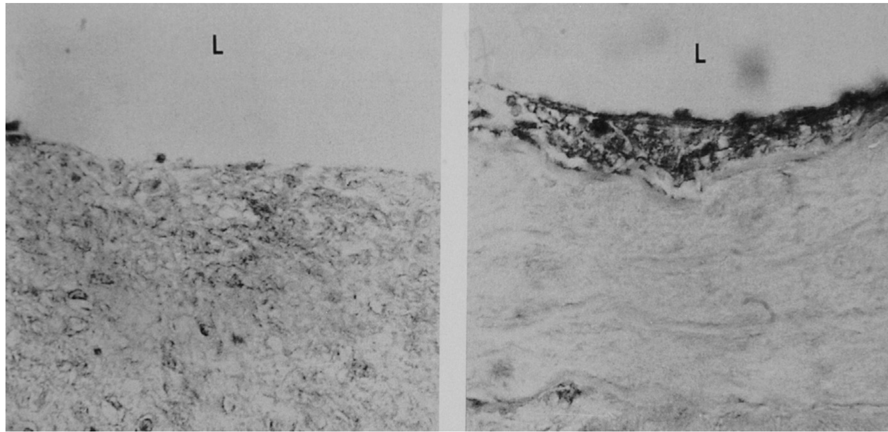

Fig 2. Histochemistry for interleukin (IL)-1 in arterial isografts **(left)** and arterial allografts **(right)** explanted 4 weeks after surgery (transverse sections). No detectable localization of IL-1 in isografts **(left)**. Evident localization of IL-1 in the area of myointimal hyperplasia (MH) in aortic allografts (original magnification ×200). *L,* Lumen.

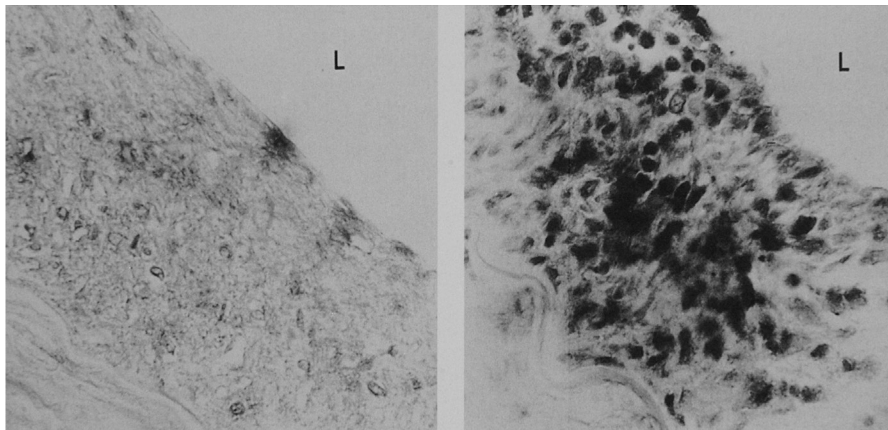

Fig 3. Histochemistry for tumor necrosis factor (TNF)-α in arterial isografts **(left)** and arterial allografts **(right)** explanted 4 weeks after surgery (transverse sections). No detectable localization of TNF-α in isografts **(left)**. Evident localization of TNF-α in the area of myoinitmal hyperplasia in aortic allografts (original magnification ×200). *L,* Lumen.

atherosclerosis progression in the distal arterial tree. The source of these two growth factors is poorly defined. Platelets, endothelial cells, and smooth muscle cells are able to release PDGF and bFGF. Platelet deposition on synthetic grafts is well-documented.[18] In vitro studies suggest that activated endothelial and smooth muscle cells produce a high quantity of PDGF and bFGF. A similar activation of endothelial and smooth muscle cells can be expected at the level of the anastomoses for the initial surgical trauma as well as for the mechanical stress caused by the different elastic characteristics of the synthetic graft and of the host artery.[20] As initially showed by Abbott et al,[21] grafts with lesser compliance are at greater risk for occlusion. In our study, PTFE grafts with reduced compliance produced a greater quantity of growth factors.

The relationship between PDGF and bFGF and myiontimal hyperplastic reaction in balloon traumatized arteries has been studied in detail. The possibility to reduce MH in this experimental setting with the administration of antibodies to bFGF and PDGF has been shown in several studies.[8,9,22] In our study, antibodies to bFGF decreased significantly the proliferation rate of smooth muscle cells at the level of the anastomoses, with decreased formation of anastomotic myoinitmal hyperplasia 4 weeks after graft implantation. This finding demonstrated a direct cause−effect correlation between increased production of bFGF and myointimal reaction. We tested only bFGF, which was the growth factor released in greater quantities in the PTFE grafts.

This evidence supports the theory that prevention of anastomotic MH in synthetic grafts, should be based on two main therapeutic approaches: (1) grafts with physical characteristics similar to the host artery and (2) pharmacologic intervention to reduce platelet deposition on the graft

Table I. Growth factor production (ng/cm^2/72 hours)

	PDGF AA	*PDGF BB*	*bFGF*
Arterial isografts	9 ± 3	30 ± 5	79 ± 6
Vein grafts	7 ± 2	62 ± 6[a]	295 ± 20[b]
PTFE (normal compliance)	28 ± 4[c]	66 ± 7[c]	404 ± 22[b]
PTFE (low compliance)	32 ± 4[c]	73 ± 8[c]	455 ± 20[d]
Arterial allografts	6 ± 3	9 ± 5	19 ± .02
Control ungrafted aorta	7 ± 4	25 ± 4	46 ± 8
Control ungrafted vein	7 ± 3	4 ± 2	55 ± 6

bFGF, Basic fibroblast growth factor; *PDGF,* platelet-derived growth factor; *PTFE,* polytetrafluoroethylene.
[a] $P < .95$.
[b] $P < .01$.
[c] $P < .05$.
[d] $P < .001$.

Table II. Growth factor production (ng/cm^2/72 hours)

	IL-1	*TNF-α*
Arterial isografts	0.3 ± 0.04	48 ± 5
Vein grafts	0.2 ± 0.04	50 ± 6
PTFE (normal compliance)	0.3 ± 0.02	49 ± 6
PTFE (low compliance)	0.3 ± 0.02	49 ± 8
Arterial allografts	1.1 ± 0.13[a]	500 ± 45[b]
Control ungrafted aorta	0.16 ± 0.02	60 ± 7
Control ungrafted vein	0.17 ± 0.02	65 ± 8

IL, Interleukin; *PTFE,* polytetrafluoroethylene; *TNF,* tumor necrosis factor.
[a] $P < .05$.
[b] $P < .001$.

(through antiaggregants or anticoagulation therapy) and to block the action of PDGF and bFGF, either directly or through their receptors. MH occurs in the wall of veins implanted in the arterial circulation. This is a physiologic adaptation of the vein to the new hydraulic system, with high pressure and high wall shear stress. The increased thickness of the vein is an adaptation that can prevent vein rupture.[23] In specific, traumatized segments, or near the valves, the myohyperplastic reaction can go further and can lead to stenosis and occlusion. In the clinical setting, in coronary artery bypass surgery and in lower limb arterial reconstruction, the saphenous vein undergoes serious occlusive changes.[24-27]

In our study, veins grafted in the arterial circulation produced a high quantity of PDGF and bFGF. This phenomenon, which was not seen in isogenic arterial grafts, could explain the clinical differences between venous and arterial coronary grafts. These findings support the view that pharmacologic intervention directed at decreasing PDGF and bFGF production might be beneficial in preventing occlusive changes in the wall. The biologic mechanisms leading to MH in arterial allografts seem different from those at the basis of the same phenomenon in vein and PTFE arterial grafts. Accelerated MH has emerged as a major and life-threatening complication in long-term survivors of heart and kidney transplantation.[13,14] In this study, we found that aortic allografts of rats are heavily infiltrated by lymphocytes that produce high quantities of IL-1 and TNF-α. These molecules are powerful mitogens for endothelial and smooth muscle cells. IL-1 and TNF-α can initiate a cascade action of T-lymphocyte activation, either directly or through expression of surface antigens and, thus, promote local amplification by positive feedback.[28] The nature of this positive feedback can explain the rapidity with which MH forms in this setting.

Agents able to neutralize these cytokines and growth factors either directly or through their receptors can be beneficial in preventing MH, often seen after heart and kidney transplantation.[29-31] New and specific immunosuppressive treatments can decrease lymphocyte and macrophage infiltration of the transplanted artery, and prevent growth factor production.

We conclude that agents able to reduce the release of these growth factors or able to neutralize their action, either directly or through blockage of their receptors, may contribute to the prevention of MH. The growth factors and cytokines are specific to each clinical setting.

AUTHOR CONTRIBUTIONS

Conception and design: AS
Analysis and interpretation: AS, SL, VB, AC
Data collection: AS, SL, VB, AC
Writing the article: AS
Critical revision of the article: AS, SL, PS, LD, MV, AC
Final approval of the article: AS, SL, VB, PS, LD, MV, AC
Statistical analysis: AS
Obtained funding: AS
Overall responsibility: AS

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INVITED COMMENTARY

Ravi R. Rajani, MD, *Atlanta, Ga*

Although improvements in operative technique, adjunctive maneuvers, local drug delivery, and systemic pharmacotherapy have improved outcomes after arterial reconstruction, durable clinical improvement continues to be limited by the development of intimal hyperplasia and progressive native atherosclerosis. These limitations have been successfully mitigated in the setting of coronary artery bypass grafting because of the availability of an easily accessible native arterial conduit. Unfortunately, no such native conduit of sufficient length is readily usable for lower extremity arterial bypass, and reversed vein conduits remain a marginally acceptable substitute.

The authors here present a series of 105 aortic replacements in rats, using a variety of available grafts. Postoperative growth factor measurements were assessed, and the effect of conduit compliance is also separately evaluated in an attempt to summarize the pharmacologic and mechanical stressors felt to contribute to late graft failure. Their findings highlight several of the important advances made in bypass outcomes during the last 20 years: local pharmacotherapy to reduce early response to injury in vein grafts, local drug delivery to improve patency after angioplasty, systemic pharmacotherapy to suppress midterm hyperplasia, and adjunctive anastomotic techniques in an attempt to mitigate compliance change across an anastomosis.

As evidenced by the outcomes presented here, the basic mechanism by which hyperplasia progresses is clearly multifactorial and also dependent on the type of conduit present. That a single silver bullet solution will present itself remains unlikely; interventions that are beneficial for vein grafts may not automatically improve outcomes for prosthetic conduits. Rather, the postoperative management of these patients will likely continue to require graft-specific maintenance therapy within the framework of broad scientific guidelines.