Alteration of Reactivity of Native Arteries Induced by Venous Graft Placement

Dale E. Bjorling, Ricardo Saban, Mark W. Tengowski, Suzann M. Gruel, and Venkat K. Rao

Occlusion of aortocoronary venous grafts can be due to thrombosis, atherosclerosis, or vasospasm. Investigations have focused on properties of the graft itself, and little is known about the vascular reactivity and function of the native arteries proximal and distal to the vein graft, although spasm of the native artery distal to the graft site has been observed in patients. We hypothesized that the function of the endothelium of the native arteries may be altered after surgery. Autogenous venous grafts were placed in femoral arteries of rabbits to study the reactivity of the native arteries after grafting. Four weeks after graft implantation, the vein graft, ipsilateral vein, and native artery proximal and distal to the graft were removed for in vitro studies. Morphological evaluation by scanning electron microscopy and fluorescence microscopy after labeling with acetylated low density lipoprotein labeled with 1,1'-dioctadecyl-3,3,3',3'-tetramethyl-indocarbocyanine perchlorate indicated the presence of an intact, metabolically active endothelial layer. There was no alteration in the contractile responses to phenylephrine of the arteries, vein grafts, or veins. Precontracted vein grafts, veins, and arterial segments proximal to the grafts relaxed when exposed to endothelium-dependent vasodilators (acetylcholine, arachidonic acid, and substance P), but the native arteries distal to the grafts did not. In bioassay cascade experiments, the distal artery did not release any measurable relaxing factor when exposed to acetylcholine. We conclude that the endothelium of the distal artery did not function normally. The extent and reversibility of altered endothelial function remain to be determined. This observation may help to explain the occurrence of myocardial infarction after aortocoronary bypass grafting in some patients. (Circulation Research 1993;72:319–329)

Key Words • venous grafts • arachidonic acid • endothelium-derived relaxing factor • vascular failure

Despite advances in surgical techniques and medical therapy, occlusion of autogenous vascular grafts used to bypass arterial obstruction remains a frequent occurrence. Occlusion of autogenous venous grafts is most often due to thrombosis in the early postoperative period or atherosclerosis 1 month or more after graft implantation.1-3 Thrombosis of vascular grafts does not completely account for graft failure in the early postoperative period.4 Vasospasm of aortocoronary venous bypass grafts has been observed,5,6 and in vivo and in vitro studies of vascular grafts placed in experimental animals have demonstrated significant changes in the reactivity of the smooth muscle of these tissues.6,7 Aggregation of platelets causes a direct reduction of flow and a local increase in thromboxane A2, which can contribute to vasospasm and further platelet aggregation. The interposition of a bypass graft creates new hemodynamic conditions in both the native circu-

From the Department of Surgical Sciences (D.E.B., R.S., M.W.T.), School of Veterinary Medicine, and the Department of Surgery (S.M.G., V.K.R.), School of Medicine, University of Wisconsin, Madison.

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Address for correspondence: Dale E. Bjorling, DVM, MS, Department of Surgical Sciences, School of Veterinary Medicine, 2015 Linden Dr. West, Madison, WI 53706.

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dilated in response to ACh administration, whereas
the coronary arteries distal to the graft contracted in
84% of the patients, reaching complete occlusion in
some individuals.20

Most experimental work has focused on the morphol-
y and function of vascular grafts, with little attention
devoted to the morphology and reactivity of the adja-
cent native arteries. With the exception of the work of
Werner et al.19,20 the reactivity of the native vasculature
has not been described after graft placement. The
purpose of this study was to investigate endothelium-
dependent responses of native arteries proximal and
distal to the graft and the vein graft to vasoactive
substances.

Materials and Methods

Thirty-eight albino New Zealand rabbits (2.5–3.5 kg)
were used. Animals were obtained and housed accord-
ing to standard procedures for care of laboratory ani-
mals (facilities are accredited by the American Associ-
ation for Accredited Laboratory Animal Care, and this
work complies with licensing requirements for working
with laboratory animals).

Anesthesia was induced and maintained with keta-
mine hydrochloride (60 mg/kg i.m.), xylazine (6 mg/kg
i.m.), and acepromazine maleate (1.5 mg/kg i.m.). Sur-
gery was performed using a double-headed operating
microscope (Zeiss Universal S-3). In 32 rabbits, the left
 femoral artery was dissected free from adjacent tissues,
and a 2–3-cm segment of the artery was isolated with
vascular forceps and removed. A 2–3-cm segment of the
contralateral femoral vein was interposed in the femoral
artery in an end-to-end manner by using 9–0 microva-
scular nylon suture in an interrupted pattern. The vas-
cular forceps were removed in all rabbits within 1 hour
of application. In six rabbits used as sham-operated
controls, a similar length of the artery was isolated from
adjacent tissues, and a vascular forceps was applied to
the artery for 1 hour. The point of application of the
vascular forceps was marked with a single suture of 9–0
polypropylene placed through the adventitia.

Four weeks later, the rabbits were anesthetized, and
tissues were harvested for study using the operating
microscope. The ipsilateral femoral vein, contralateral
femoral artery, graft, and native femoral artery proxi-
mal and distal to the graft were removed. Tissues within
3 mm of the anastomoses were discarded, and the
remainder of the graft tissue was left intact for cascade
studies or divided into proximal (within 8 mm of the
proximal anastomosis) and distal (within 8 mm of the
distal anastomosis) portions for ring studies. Two to 3
mm of artery adjacent to the suture marking application
of vascular forceps to the arteries that did not receive
grafs was discarded, and the remainder was divided
into proximal and distal portions.

Functional Studies

Segments (4–5 mm long) of the vein graft, ipsilateral
femoral vein, contralateral femoral artery (correspond-
ing to the segments of femoral artery proximal and
distal to the graft), femoral artery proximal and distal to
the graft, and femoral artery proximal and distal to the
point of application of the vascular forceps from control
animals were suspended as rings between two stainless-
steel stirsups in water-jacketed (37°C) tissue baths. The
tissue baths contained 10 ml physiological salt solution
(PSS) of the following composition (mM): NaCl 119,
KCl 4.7, NaH2PO4 1.0, MgCl2 0.5, CaCl2 2.5, NaHCO3
25, and glucose 11, gassed continuously with 95%
O2–5% CO2. Mechanical responses were measured
isometrically and recorded on a polygraph (Grass In-
strument Co., Quincy, Mass.) via isotonic force trans-
ducers (Grass FT-03). Data acquisition was carried out
using a LabMaster board (Tekmar Co., Cincinnati,
Ohio) in an IBM compatible PC computer and Data
Collection Program V1.0 (developed by Paul Kaarakka,
Smooth Muscle Laboratory, Department of Surgical
Sciences, University of Wisconsin, Madison).

All vessel segments were stretched to the tension
found to maximize responses (usually 1.5–2.0 times the
relaxed diameter) and allowed to equilibrate for 1.5
hours before any manipulation. The vessels were
washed with fresh PSS solution at 15-minute intervals
during the period of equilibration. Cumulative concen-
tration–response curves were determined for phenyl-
ephrine by increasing the concentration by a factor of
approximately 3 after maximal contraction developed
to the previous concentration.21 The concentration of
phenylephrine that produced 50% of the maximal con-
tractile response (EC50) was determined from each
experiment, and the geometric mean was calculated
according to Fleming et al.22 After washing out the
phenylephrine for 60 minutes with PSS, tone was in-
duced with phenylephrine (EC50). In separate experi-
ments, it was found that phenylephrine produced a
consistent contraction of sufficient duration to reliably
obtain a cumulative relaxation–response curve for va-
sodilators. Endothelium-dependent vasodilators were
added to the tissue bath in a cumulative fashion,21 and
only one substance was tested in each tissue. Subse-
quently, the tissues were washed with PSS and precon-
tracted with phenylephrine (EC50), and substance P (1
μM) was added. Relaxation in response to substance P
confirmed the presence of functional endothelium.
Papaverine (1 mM) was added at the end of the exper-
iment to produce maximal relaxation of the vessels.

Cascade Experiments

A superfusion system modified from Elliott and Ad-
olfs23 was used for cascade experiments. Briefly, side
branches of vessels used in this experiment were ligated
during removal. The proximal and distal femoral seg-
ments and the vein graft were cannulated with polyeth-
ylene tubes (PE50, 1.5-mm inside diameter, Clay Ad-
ams) and placed in organ baths containing PSS at 37°C
to serve as donor segments. They were perfused intralu-
minally at constant flow rate (2 ml/min) with gassed
(95% O2–5% CO2) PSS (37°C) delivered by a multi-
channel roller pump (Gilson Minipuls 2). Indomethacin
(5 μM) was added to the perfusate to prevent synthesis
of prostanoids. To bioassay intraluminally released
EDRF, a ring of endothelium-denuded pulmonary lar-
y artery (3–5 mm wide) was positioned directly below
the muscle bath by means of two stainless-steel stirsups
passed through the lumen. The bioassay tissue was
superfused with an isolated system that delivered PSS at
a rate of 2.1 ml/min. This allowed the delivery of drugs
(phenylephrine and substance P) directly to the bioas-
say tissue, bypassing the donor tissue. Isometric tension
generated in the pulmonary arterial segment was mea-
sured by a force transducer (Grass FT-03) attached to one of the stirrups. The transit time between the distal end of the donor tissue and the bioassay tissue was 4 seconds. Before the actual experiment, the bioassay ring was stretched in a stepwise manner until the optimal tension for active contraction of this vessel was reached (approximately 6 g). All assay rings were tested for complete removal of endothelium by inducing contraction with phenylephrine (EC_{50}, 0.2 μM) delivered through the isolated superfusion circuit distal to the donor tissue followed by brief exposure to substance P (1 μM). Any rings that relaxed in response to substance P were considered to have some functional endothelium and were discarded. After 1 hour of equilibration, assay tissues were precontracted with phenylephrine (EC_{50}), and the donor tissues were exposed intraluminally to ACh (1 and 10 μM). After completion of cascade studies, papaverine (1 mM) was used to induce endothelium-independent relaxation of the assay tissues.

**Morphological Studies**

**Labeling with DiI-Ac-LDL.** Segments of all vessels were placed in 1 ml aerated (95% O₂–5% CO₂, pH 7.4) PSS (37°C), and acetylated low density lipoprotein (LDL) labeled with 1,1'-dioctadecyl-3,3,3',3'-tetramethyl-indocarbocyanine perchlorate (DiI-Ac-LDL; final tissue bath concentration, 10 μg/ml) was added and kept in contact with the tissues for 4 hours, with replacement of PSS and DiI-Ac-LDL after 2 hours. After 4 hours, excess DiI-Ac-LDL was removed by 10 washes with PSS. Samples were frozen, sectioned (4 μm) on a cryostat, evaluated by fluorescence microscopy, and photographed.

**Scanning electron microscopy.** Representative cross sections of the endothelial surface of the vessels were viewed by scanning electron microscopy. Arteries and veins were incised longitudinally, fixed in 2.5% glutaraldehyde in phosphate-buffered saline (pH 7.4) for 24 hours at 4°C, washed in buffer, and postfixed in 0.1% osmium tetroxide. The tissues were rinsed in buffer before being dehydrated through a grased series of ethanol and dried by the critical-point method. The tissue blocks were mounted on silicon chips with colloidal carbon and rotary platinum coated in a vacuum system. The specimens were examined and photographed with a low-voltage high-resolution Hitachi S-900 scanning microscope (Integrated Microscopy Resource, University of Wisconsin, Madison).

**Drugs Used**

A stock solution of arachidonic acid was made in ethanol, and further dilutions were made with 0.9% sodium chloride. All solutions were gassed with argon, and the solutions used on each study day were stored on ice. DiI-Ac-LDL was purchased from Biomedical Technologies, Inc., Stoughton, Mass. Phenylephrine hydrochloride, substance P acetate salt, ACh, osmium tetroxide, papaverine hydrochloride, and indomethacin were purchased from Sigma Chemical Co., St. Louis, Mo. Substance P was dissolved in saline containing sodium metabisulphite (0.05%). Indomethacin was dissolved in 95% ethanol and diluted directly to the final concentration in the stock PSS; final ethanol concentration in the tissue bath was 0.01%.

**Statistical Analysis**

Statistical analysis of the results was performed with STATWORK software using analysis of variance and Student’s t test for paired or unpaired data. All values are expressed as mean±SEM, and a value of p<0.05 was considered significant.

**Results**

**Morphology**

Four weeks after placement, the vein grafts were twice the diameter of the adjacent femoral artery. There were no differences in the appearance or size of the unoperated control arteries, arteries proximal and distal to the grafts, and the sham-operated control arteries. Four weeks after graft placement, the endothelial surfaces of the grafts and arteries examined by scanning electron microscopy appeared intact (Figure 1). Fluorescence micrographs of segments of the vessels that had been incubated with DiI-Ac-LDL in vitro confirmed that at 4 weeks after implantation the endothelial cells lining all vessels examined were capable of metabolizing acetylated LDL (Figure 2). These results demonstrate that at 4 weeks after implantation endothelium was present and metabolically active, since only viable endothelial cells metabolize acetylated LDL.

**Mechanical Responses**

The responses of isolated vessels to phenylephrine are shown in Figure 3. There were no differences in the maximal contractile responses of the native arteries proximal and distal to the grafts (mean contraction, 2.5 g). Concentration–response curves to phenylephrine described as a percentage of maximal contraction for each individual tissue were similar for the native femoral arteries proximal and distal to grafts (EC_{50}, 1.4±0.3 μM). The responses of the arteries proximal and distal to the grafts did not differ from the responses obtained from contralateral (unoperated) femoral arteries or the proximal and distal arterial tissue from sham-operated control arteries. Venous grafts, divided in two portions (proximal and distal), did not differ in response to phenylephrine from control veins, but both were 100-fold less sensitive to phenylephrine (EC_{50}, 100±0.2 μM) than the arteries.

When the tissues were precontracted with phenylephrine (EC_{50}), ACh induced a concentration-dependent relaxation of the vein graft and the native artery proximal to the graft (Figure 4). Not only were the responses of distal native artery to low concentrations of ACh (0.1–10 μM) significantly reduced in comparison with the proximal arteries, but these vessel segments also exhibited contraction (Figure 4) in response to the addition of higher concentrations of ACh (100 μM). The contralateral femoral veins and arteries and the proximal and distal sham-operated arteries also relaxed in response to ACh (data not shown). Arachidonic acid (0.1–100 μM) induced relaxation of precontracted proximal artery and vein grafts (Figure 5). The distal artery was practically insensitive or exhibited contraction (Figure 5). Although the distal arterial segments had morphologically normal endothelium, they were functionally insensitive to endothelium-dependent vasodilators. The absence of relaxation in response to substance P (0.01–1 μM) confirmed the fact that the distal femoral
arteries were incapable of endothelium-dependent relaxation (Figure 6). All segments relaxed in response to the addition of papaverine (10 mM), demonstrating that the smooth muscle cells were functional. There were no differences between the responses of the contralateral control arteries and the sham-operated arteries proximal and distal to the point of application of the vascular forceps, nor were there any differences between the responses of the sham-operated proximal and distal arteries.

In another set of experiments, the effect of cyclooxygenase blockade was investigated. Each segment of the proximal and distal arteries and vein grafts was divided into two adjacent rings; one of them served as a control, and the other was incubated in vitro with Krebs' solution containing indomethacin (5 μM) for 1 hour before obtaining concentration–response curves. The contractile effects of phenylephrine on the vein graft and proximal and distal femoral arteries were not altered by the presence of indomethacin (data not shown). Indomethacin did not alter the relaxant responses of the vein grafts (data not shown) nor the responses of arterial segments to ACh (Figure 7) but reduced relaxation of the proximal artery in response to arachidonic acid (Figure 8). Therefore, in the presence of cyclooxygenase blockade, the response of the distal artery was similar to that of the proximal femoral artery.

Cascade Experiments

Although the endothelium of the distal artery appeared morphologically normal, the distal artery did not relax when exposed to endothelium-dependent vasodi-
lators. Cascade studies were performed to further characterize the functional status of the endothelium.

Intraluminal perfusion of the proximal artery and the vein graft with ACh (1 M and 10 μM) induced relaxation of precontracted endothelium-denuded rings of pulmonary artery. The perfusate from the distal artery failed to induce relaxation of the bioassay tissues (Figure 9). All bioassay tissues relaxed when exposed to papaverine (1 mM), but none responded to the addition of substance P (1 μM). These results demonstrate that both the proximal femoral artery and the vein graft were able to produce EDRF when exposed to ACh, but the arteries distal to the grafts were unable to produce EDRF.

Discussion

Despite the normal histological appearance of the endothelium of the native arteries distal to the grafts and the fact that this endothelium metabolized Dil-AcLDL, these vessel segments did not dilate in response to endothelium-dependent vasodilators, nor did they produce EDRF. Spasm of the distal coronary artery after bypass grafting has been regarded as paradoxical.5,6,27 Werner et al19,20 found that the administration of ACh to patients after placement of arterial or venous bypass grafts can cause contraction rather than dilation of the distal coronary artery. This could contribute directly to graft occlusion, because contraction of the native artery distal to the graft will decrease flow, facilitating occlusion of the graft by thrombosis.

Although there are no previous reports of alterations in the vasoactivity of native vessels adjacent to vascular grafts, it has been observed that the vasodilatory mechanisms controlled by the endothelium may be abnormal in venous grafts, contributing to spasm or occlusion of the graft.28 Cross et al15 evaluated venous grafts in rabbits 4 weeks after graft placement and found that the grafts failed to produce EDRF in response to ACh and histamine but were able to relax when exposed to exogenously applied EDRF. Venous grafts in that study were placed in an end-to-side manner in the carotid artery, and it is possible that this technical difference may account for the observation that the endothelium of grafts in that study did not appear to produce EDRF, whereas those in our study did.

Venous grafts that were examined in vitro 6 weeks after placement in dogs also failed to relax when exposed to ACh after tone was induced with norepinephrine, regardless of the presence or absence of endothelium.27 Prostacyclin production by the endothe-
The reasons for failure of adaptation of grafts or distal native vessels are unclear. Possible explanations for abnormal function of these vessels include 1) altered endothelial function in response to changes in shear stress, 2) structural alterations in the vascular wall (such as intimal thickening) that physically limit the ability of the vessel wall to respond normally, 3) alteration of vasoactivity of distal vessels that is due to release of humoral substances by upstream vessels, and 4) altered function of the endothelial muscarinic receptors or some other primary dysfunction of the endothelium or vascular smooth muscle.

The most likely explanation for the observed changes in reactivity of the arteries distal to graft implantation appears to be altered endothelial function. Handling of grafts during surgery may result in the loss of as much as 85% of endothelial prostacyclin production. A major-
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Graft-Induced Alteration of Vasodilation

Figure 2. Phosphorgraph of a frozen section (4 µm) viewed by differential interference contrast microscopy with epifluorescence of tissue labeled in vivo with acetylated low density lipoprotein labeled with 1,1'-dioctadecyl-3,3',3'-tetramethylindocarbocyanine perchlorate (DiI-Ac-LDL). Panel A: Differential interference contrast photograph of the artery distal to the graft. Panel B: Differential interference epifluorescence of the same tissue as in panel A. The endothelium (arrow) is seen as a continuous fluorescent layer. Panel C: Photomicrograph of a frozen section of the artery proximal to the graft incubated with DiI-Ac-LDL. Intact endothelium (arrow) is clearly visible. Nonspecific uptake of DiI-Ac-LDL by adventitia is also visible.
3. Graph showing the effect of increasing concentrations of phenylephrine on the contractile responses of proximal and distal femoral arteries and the proximal and distal segments of the vein grafts harvested 4 weeks after implantation (n=8).

4. Venous or arterial endothelium within the adjacent native artery is also lost and replaced after surgery. This neoendothelium may function in a manner that is inconsistent with either venous or arterial endothelium. Several factors that may influence functional adaptation of venous grafts have been identified. These factors include denervation, devascularization, and trauma of the graft, which occur during surgery, increased oxygen content of arterial blood, and altered hemodynamic conditions that follow placement of venous grafts in the arterial circulation. These factors probably all combine to induce the characteristic morphological changes observed in venous grafts. At least two investigators have noted functional differences that occur along the length of venous grafts in dogs. In one study, segments of the distal portion of venous grafts demonstrated decreased endothelium-dependent relaxation in response to thrombin and contraction in response to arachidonic acid (segments from the proximal areas of the grafts relaxed in response to both these compounds), whereas in the other study, PGI2 production in the distal portion of the venous grafts was significantly less than that observed in the proximal areas of the grafts. In the first study, changes in reactivity were correlated with increased myointimal thickening. We compared the distal and proximal segments of venous grafts and failed to identify functional or morphological differences. We also did not identify significant myointimal thickening of the native femoral arteries distal to the grafts. However,
the spatial differences observed in the function of the grafts suggests that relative distance from suture lines and changes in vessel diameter may profoundly affect endothelial function. It is still possible that humoral substances released from injured vessels or devascularized grafts may affect downstream endothelial function.

The histological appearance of the endothelial surfaces of venous grafts and native arteries in our study was identical to that previously reported in rabbits. Although a layer that appears to be endothelium the vessels, it is difficult in some instances to clearly identify these cells as endothelium. Acetylated LDL is specifically taken up by monocytes, macrophages, and endothelial cells by a receptor that is distinctly different from the receptor for unmodified LDL. A variety of markers have been attached to acetylated LDL to allow critical identification of endothelial cells. Uptake of acetylated LDL requires that the specific receptor be present and that the cells be metabolically active. Non-specific tissue uptake is minimal, and uptake by monocytes or macrophages is easily distinguished from metabolism by the endothelium by the intensity of the marker and physical location of uptake.

In the presence of cyclooxygenase blockade, the responses of the proximal femoral artery and control artery to arachidonic acid were similar to those observed in the artery distal to the graft (Figure 8). This suggests that in the femoral artery a component dependent on cyclooxygenase, probably PGI₂, is at least partially responsible for relaxation induced by arachidonic acid and that, in addition to significantly reduced EDRF production, the endothelium of the artery distal to the graft produced less PGI₂. It has been previously demonstrated that in vitro exposure of rabbit femoral arteries to arachidonic acid stimulates PGI₂ production, and although the rabbit aorta is relatively insensitive to the vasodilatory effects of PGI₂, it causes vasodilation of other peripheral arteries (including the femoral) of the rabbit. Indomethacin did not alter the relaxant responses of any vessels to ACh (Figure 7), indicating that the major component of ACh-induced relaxation was not a prostaglandin.

Endothelium-dependent relaxation of vessels in response to arachidonic acid has been attributed to
EDRF release, but recent reports indicate that this relaxation is primarily due to PG1 production. Endothelium-dependent contraction in response to arachidonic acid has been observed in canine veins, and this response was blocked by indomethacin. However, at least two metabolites of arachidonic acid cause a contraction of a variety of canine systemic arteries that is insensitive to indomethacin. An enzyme present in normal and atherosclerotic vessels, 15-lipoxygenase, causes the metabolization of arachidonic acid to several compounds, including 15-hydroperoxyeicosatetraenoic acid (15-HPETE) and its hydroxy derivative 15-hydroxyeicosatetraenoic acid (15-HETE). Segments of canine coronary, splenic, femoral, and renal arteries exposed to 15-HPETE and 15-HETE in vitro exhibited a slight relaxation followed by contraction at higher concentrations. Indomethacin enhanced contractions in response to these two compounds, whereas thromboxane A2 receptor antagonists blocked contraction in a concentration-dependent manner. Under certain conditions, relaxation that was in part endothelium dependent and indomethacin sensitive was induced in these arteries. These responses are very similar to those we observed when vessels in our study were exposed to arachidonic acid, and it is probable that the responses we obtained were due to activation of thromboxane A2 receptors. Another possible explanation for contraction initiated by arachidonic acid is the production of leukotrienes by the 5-lipoxygenase pathway. It has been shown that cultured rabbit endothelial cells are capable of producing leukotrienes from arachidonic acid, and vasoconstriction in response to leukotrienes is well documented. Further clarification of the contractile responses we observed in response to arachidonic acid would require the evaluation of tissues in the presence of blockers of thromboxane A2 receptors and 5-lipoxygenase.

In our experimental model, relaxation of the distal artery in response to arachidonic acid is dependent on the cyclooxygenase pathway, not EDRF, and arachidonic acid may actually cause contraction. The results of this experiment and those of Werner et al suggest that the functional characteristics of native arterial endothelium distal to the site of graft implantation may be altered in a manner that predisposes the graft to occlusion.

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