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Biochemical (Functional) Adaptation of "Arterialized" Vein Grafts

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Canine venous autografts and allografts were interposed in the femoral and carotid arterial positions in 29 dogs; grafts were harvested at three postoperative intervals (1–2 weeks, 4–6 weeks, and 8–10 weeks) for light and scanning electron (SEM) microscopy and lumenal surface prostacyclin (PGI_2) production. Normal veins and arteries were used as controls. Radioimmunoassay for tritiated 6-k-$PGF_{1\alpha}$, the stable metabolite of PGI_2, was performed using a flow surface template incubation chamber during basal and arachidonic acid stimulated conditions. Using SEM, the autografts revealed normal endothelial cell (EC) surfaces at all time intervals; conversely, allografts exhibited extensive EC loss at 1–2 weeks with gradual reparation by 10–12 weeks (such that the EC surface was virtually indistinguishable from that of control veins or autografts). PGI_2 production was significantly greater in control arteries than veins ($p = 0.0001$). At 1–2 weeks and 4–6 weeks, lumenal production of PGI_2 in both the autografts and allografts was not significantly different from control vein; however, PGI_2 production after 10–12 weeks was identical to normal arterial levels (and significantly [$p < 0.0044$] higher than venous levels) in both basal and stimulated conditions. Although the mechanisms responsible for this functional (biochemical) "arterialization" process remain conjectural, increased biosynthesis and/or release of PGI_2 by endothelial cells, acute phase inflammatory cells (allografts) mediated by interleukin-1 or myointimal cells seems most likely. Further elucidation of these sources of PGI_2 is necessary, but these data demonstrate for the first time that venous grafts placed in the arterial circulation undergo complete functional adaptation (in addition to the well known morphological changes).

VEIN GRAFTS placed in the arterial circulation undergo a predictable and characteristic set of morphological changes, including thickening, fibrosis, and subendothelial myointimal cell proliferation. These structural alterations (described by Carrel and Guthrie in 1906[1] and subsequently termed "arterialization") may allow vein grafts to function as effective vascular conduits in the high pressure system but are commonly believed to represent degenerative changes due to repetitive injury and repair presaging accelerated vein graft

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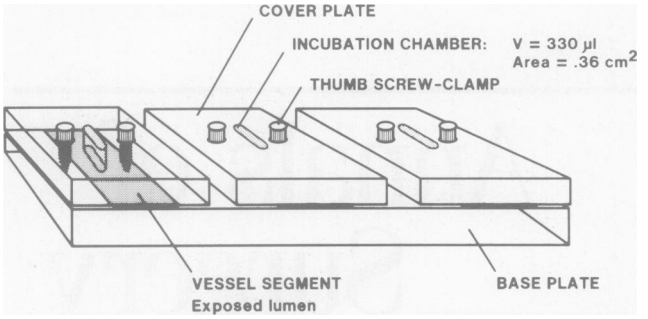


FIG. 1. Special template (3 chamber assay template) designed for measurement of graft and vessel lumenal surface PGI_2 production.

atherosclerosis.[2-9] On the other hand, whether veno-arterial (V-A) grafts also undergo functional (or biochemical) adaptation to the arterial environment in terms of endothelial cell (EC) prostacyclin (PGI_2) biosynthesis and/or release is less well understood, although ECs from some species increase PGI_2 output *in vitro* in response to increased mechanical stress,[10-12] as a result of phenotypic modulation in culture[13] or increased blood-endothelial shear rates.[14] Eldor et al. demonstrated in a canine *in vivo* preparation that V-A grafts recover over a 6-week period the capability to produce only normal venous levels of PGI_2, which are much lower than normal arterial values in dogs[15]; furthermore, recent work has suggested that preservation of venous EC PGI_2 production may be important in terms of the purported increased patency rates of *in situ* vein bypass grafts compared to conventional (reversed) saphenous vein grafts.[16-17] Finally, vein graft and native artery PGI_2 generation has been used as a barometer of acute, iatrogenic functional impairment and/or injury during vein graft harvesting and preparation (18-20) and as an indicator *in vivo* response to increased flow velocity.[21]

Work in this laboratory using canine V-A allografts as a model of accelerated experimental arteriosclerosis led us to examine this question of EC biochemical adaptation in both auto- and allografted veins. V-A allografts are exposed continuously to important, albeit variable, immunologically mediated EC injury,[22-25] but PGI_2 production in these allografted veins has not been investigated. Therefore, we examined the morphological and biochemical characteristics of the lumenal surface of V-A allografts at various times and compared these changes with those seen in conventional (and more clinically relevant) V-A autografts. Additionally, lumenal surface prostacyclin generation in both types of "arterialized" vein grafts was compared with EC PGI_2 production in normal canine veins and arteries.

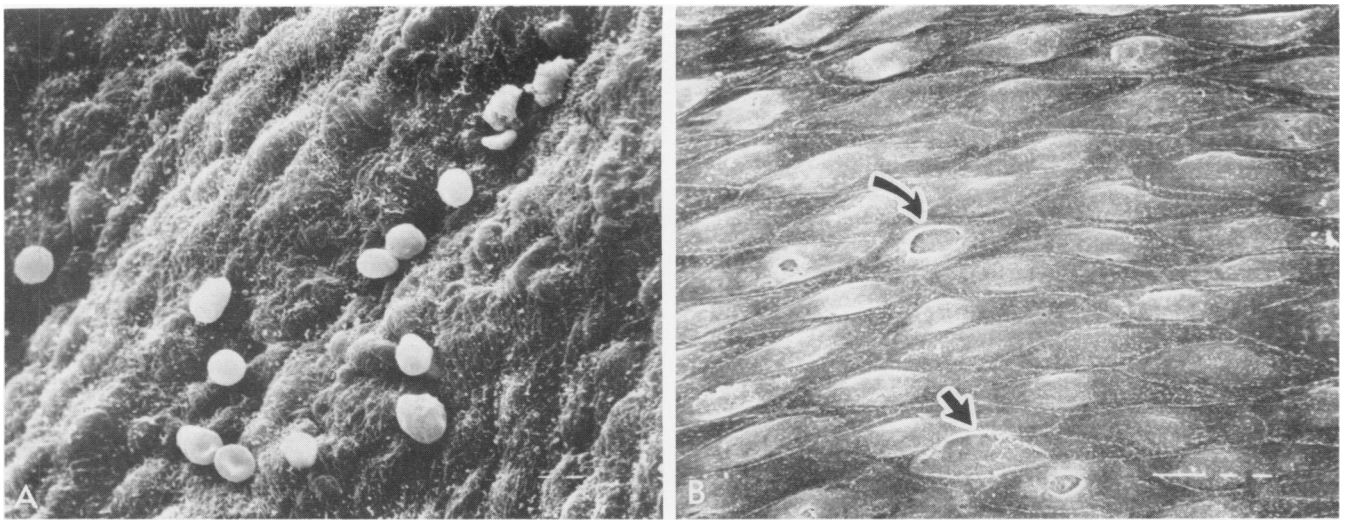
Methods

Twenty-nine adult mongrel dogs of either sex (13-25 kg) underwent reversed femoral vein interposition grafting of the carotid and/or femoral arteries as autografts or allografts. Normal jugular or femoral veins and carotid or femoral arteries were harvested from 15 other dogs to determine control PGI_2 values. Animals were anesthetized with sodium pentobarbital, intubated, paralyzed with succinylcholine, and placed on controlled mechanical ventilation. Using sterile technique, we gently dissected, removed, and divided in half 8 cm segments of both femoral veins. These vein grafts were only gently flushed with and then briefly stored in cold, heparinized lactated Ringer's solution (1000 U/ml); care was taken not to distend or traumatize the veins. They were then reversed and anastomosed end-to-end into either the femoral or carotid arteries or both using continuous 6-0 polypropylene suture. Dogs receiving allograft veins underwent operation in pairs to allow interchange of the four donor vein graft segments between dogs. Systemic heparinization was not employed.

The V-A grafts were harvested at postoperative intervals (1-2 weeks, 4-6 weeks, and 10-12 weeks) for electron and light microscopic examination and determination of lumenal surface PGI_2 production. All animals received humane care in compliance with "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH Publication 80-23, revised 1978), and this protocol was approved by the Palo Alto VA Medical Center Animal Research Subcommittee.

Grafts or vessel specimens not used for the PGI_2 assays were fixed in 10% buffered formalin and dehydrated in graded concentrations of alcohol, critical point dried, sputter-coated with gold, and examined with an ISI scanning electron microscope (International Scientific Instruments, Inc., Milpitas, CA). Other portions were embedded in paraffin and in epon and examined with light and transmission electron microscopy.

Segments from the middle section of patent grafts were used for the lumenal surface prostacyclin assay. Harvested V-A grafts and normal vessels were rinsed immediately with room temperature normal saline, opened longitudinally, and placed in a custom-designed template incubation chamber apparatus (Fig. 1). Each 4×10 mm elliptical hole in the upper lucite plate formed an incubation chamber that exposed 36 mm^2 of lumenal surface for assay of PGI_2 production using a radioimmunoassay according to the method published by Weksler's group.[26] A 0.25 ml aliquot of Tris-NaCl buffer (pH = 8.6) was placed in the incubation well for 2 minutes, quickly transferred to a polypropylene centrifugation tube, and then frozen at −20 C. A second incubation was then performed using Tris buffer containing 20 μM arachidonic acid (AA) for stimulated PGI_2 measurements. All vessel specimens were



FIGS. 2A and B. *A*. Lumenal surface of 7-day-old veno-arterial autograft. In marked contrast to the allograft vein (Fig. 3A), the endothelial cells are essentially normal with prominent microvilli (SEM × 1700). *B*. Scanning electron micrograph (SEM) (×1000) of lumenal surface of control canine femoral vein illustrating uniform endothelial cells, average appearance of microvilli, distinct intercellular junctions, and no leukocyte adherence. The absence (arrows) of occasional endothelial cells is consistent with normal cell turnover.

immediately processed in this manner with an average of 10 minutes elapsing from the time of vessel harvest to completion of the lumenal surface incubation period. Lumenal surface PGI_2 production was measured in duplicate for both the basal and the AA stimulated samples by radioimmunoassay of tritiated 6-k-$PGF_{1\alpha}$ (New England Nuclear, Boston, MA). Standard curves were constructed for each assay using known amounts of 6-k-$PGF_{1\alpha}$ (500, 250, 100, 50, 25, and 10 pg/0.1 ml). Values of 6-k-$PGF_{1\alpha}$ are expressed as ng/ml of incubation fluid.

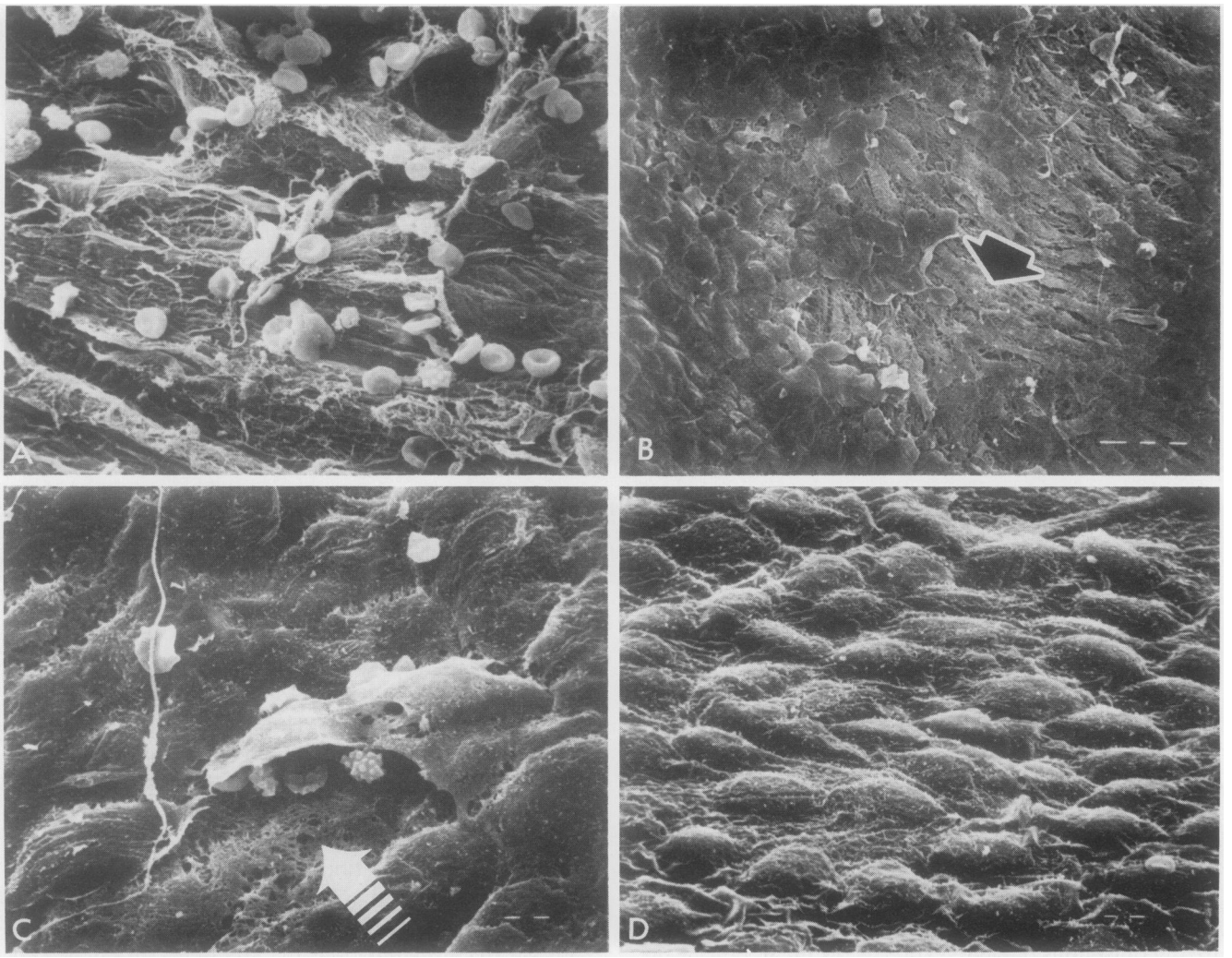
All continuous data are expressed as mean plus or minus one standard error of the mean (SEM). Differences in 6-keto-$PGF_{1\alpha}$ levels were assessed using analysis of variance followed by either the Scheffe or Bonferroni multiple range test and nonpaired t-tests. A two-tailed p value less than 0.05 (adjusted for multiple comparisons) was considered to be statistically significant.

Results

Scanning electron microscopy revealed that the V-A autograft specimens generally had intact, normal appearing EC surfaces, regardless of time of implantation (Fig. 2A). Only a few isolated ECs were missing, consistent with normal EC turnover as seen in control veins (Fig. 2B). Conversely, most V-A allograft specimens had variable degrees of EC loss and/or damage. The 1–2 week V-A allografts exhibited the greatest extent of changes, with extensive endothelial ulceration leaving large areas of exposed subendothelial surface covered by platelet, leukocyte, and fibrin masses (Fig. 3A). The ECs in the allograft specimens at 90 days were generally hypertrophied, consistent with ongoing cell division (Figs. 3B and 3C) in areas where desquamation was not present. There was progressively less endothelial ulceration in the allografts over time; after 90 days, restoration of the flow surface in the allografts was virtually indistinguishable in many areas from that seen in the autografts and the control vein specimens (Figs. 3C and 3D). There were, however, occasional small denuded zones, but with less platelet, fibrin, and leukocyte aggregation than seen in the 1–2 week allografts (Figs. 3B and 3C).

Light microscopy also demonstrated distinct differences between the autografts and the allografts; although both types of V-A grafts had developed some degree of subendothelial fibrosis, myointimal cell proliferation, and/or medial fibrosis by 10–12 weeks, these processes were all more consistent and much more severe in the allografts than in the autografts. Extensive, diffuse granulocyte infiltration (with fewer lymphocytes and macrophages) characterized the media and adventitia of the allografts at 1–2 weeks, while lymphocytes and plasma cells, in smaller numbers and in a more focal distribution, were seen after 3 months.

Table 1 and Figure 4 summarize the results of the graft and vessel lumenal surface 6-k-$PGF_{1\alpha}$ assays. Normal canine arteries produced significantly more PGI_2 than did veins ($p = 0.00001$ for both the basal [Fig. 4A] and the AA stimulated [Fig. 4B] samples). Moreover, the V-A autografts as well as the V-A allografts produced normal arterial levels of PGI_2 after 10–12 weeks; additionally, these values were significantly higher than venous levels ($p < 0.00001$ and $p = 0.0039$ [basal] and $p = 0.0044$ and $p = 0.0038$ [AA stimulated] for the autografts and the allografts, respectively). Figure 4 illustrates these changes



FIGS. 3A–D. *A.* Lumenal surface of veno-arterial allograft at 7 days. Note total loss of endothelium and adhesion of fibrin and erythrocytes (SEM × 1700). *B.* Low power SEM (×500) of the endothelial surface of an allografted vein at 90 days. The endothelial surface is intact in most areas, but there is extensive ulceration without much adherence of formed blood elements (arrows). *C.* High power (×3000) SEM of the endothelial surface of an allografted vein after 90 days in the arterial position. There is focal endothelial cell slough with ulceration (arrow) along with an adherent fibrin strand and erythrocytes. *D.* Endothelial surface of veno-arterial allograft after 90 days. Note the intact endothelial cells with ordinary microvilli, which is indistinguishable from that seen in control veins (Fig. 2B) (SEM ×1600).

as a function of time. Both types of V-A grafts generated PGI_2 at all sampling times, but a substantial increase occurred only after 4–6 weeks. The differences in PGI_2 production between the autografts and the allografts were not statistically significant at any sampling time.

Discussion

Autogenous vein grafts interposed into the arterial circulation undergo characteristic morphologic alterations in their wall structure.[3,4,6] The stress of the high pressure, high flow arterial system in conjunction with the obligatory vessel wall ischemia attendant with graft harvesting and preparation is associated with thickening of the vein graft wall. These changes become apparent within 1 month of graft implantation, but the early edema, hemorrhage, and cellular infiltrate later evolve into subendothelial myointimal cell proliferation and medial fibrosis.[3,4] Fonkalsrud et al.[5] demonstrated that canine V-A autografts generally recover from iatrogenic EC trauma within 1 month; moreover, the ECs appeared to be morphologically identical to those of the original vein (including the presence of microvilli, as shown in Figure 3D). If considered to be a compensatory adaptive response, this process appears to be effective, since the rate of clinical graft aneurysm formation or rupture is low ([3–6]) unless the autogenous vein graft is placed in a very high flow position, *e.g.,* aortorenal bypass graft. On the other

TABLE 1. *Summary of Lumenal Surface Prostacyclin Production in Normal Artery, Normal vein, and Veno-arterial Autografts and Allografts*

Specimen	N	1–2 Weeks	N	4–6 Weeks	N	10–12 Weeks
Basal						
V-A allograft	10	1.8 ± 0.5	8	1.3 ± 0.2	7	3.3 ± 1.3*
V-A autograft	4	1.0 ± 0.3	5	1.2 ± 0.4	9	4.8 ± 1.1†
Normal vein	15	0.47 ± 0.1‡	—	—	—	—
Normal artery	15	3.8 ± 0.7‡	—	—	—	—
Arachidonic acid stimulation						
V-A allograft	10	3.8 ± 0.8§	5	2.4 ± 0.7§	2	9.7 ± 0.7*
V-A autograft	4	1.7 ± 1.1§	5	2.3 ± 0.5§	9	6.5 ± 2.0*
Normal vein	15	2.7 ± 0.7‡	—	—	—	—
Normal artery	15	8.6 ± 0.6‡	—	—	—	—

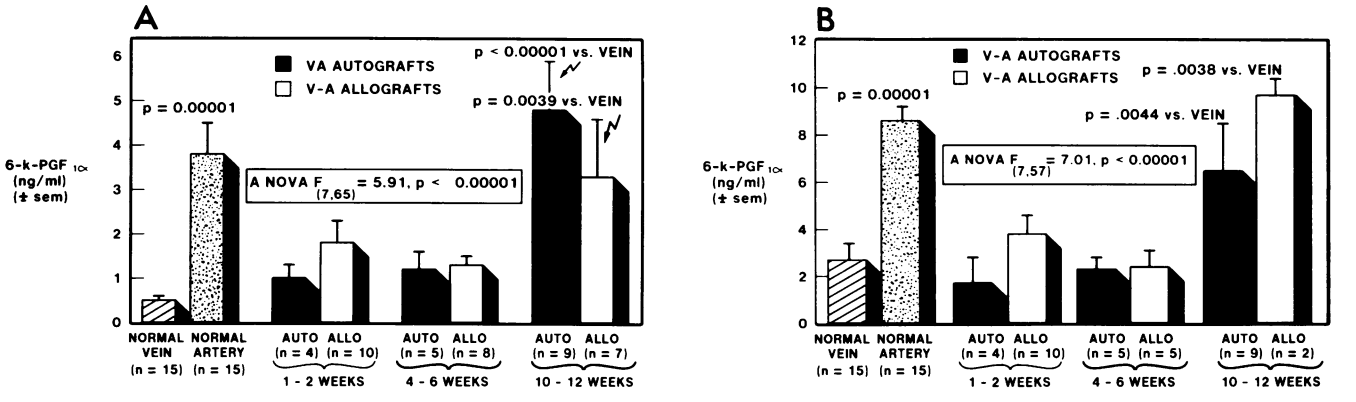
Data are expressed as ng/ml of 6-k-$PGF_{1\alpha}$ (mean plus or minus one SEM).
ANOVA: Basal—$F_{(7,65)} = 5.91$, $p < 0.00001$.
Arachidonic acid stimulated—$F_{(7,57)} = 7.01$, $p < 0.00001$.

* $p < 0.05$ *vs.* normal vein.
† $p < 0.0002$ *vs.* normal vein.
‡ $p < 0.00001$ (vein *vs.* artery).
§ $p < 0.01$ (Allograft) or < 0.05 (Autograft) *vs.* normal artery.

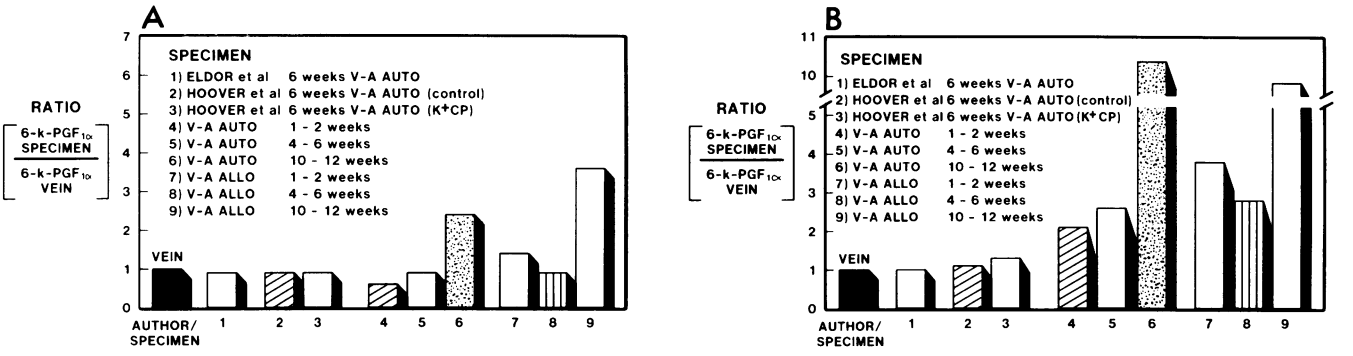
hand, these morphological changes probably represent repetitive injury and repair and thereby reflect graft degeneration that *pari passu* may become the precursor of accelerated graft atherosclerosis.[7–9,19,27]

Whether such V-A grafts also undergo concomitant biochemical adaptation in the form of increased EC prostacyclin production is less clear.[15,28] Arterial ECs produce more PGI_2 than do venous ECs, at least in rats,[11] human tissue studies *in vitro,*[12] and dogs.[15] The reason for this difference is not completely understood but may relate to augmented platelet-vessel wall interaction in the arterial circulation as a result of higher flows, pressures, and shear stresses.[14,21] Venous ECs are morphologically different than arterial ECs,[5] but it is unknown whether this represents different cell types or structural (and/or biochemical) phenotypic modulation of EC function as a result of the different hemodynamic environment.[13] It has been demonstrated that arterial ECs adapt to increased physical and mechanical stress by increasing PGI_2 biosynthesis and/or release,[10,11,21] which teleologically inhibits platelet adhesion and platelet-endothelial cell interactions.[29–31] Arterial ECs from spontaneously hypertensive rats produce more PGI_2 than do ECs from nonhypertensive rats.[10] Rat aortic rings exposed to increased mechanical stresses *in vitro* increase PGI_2 synthesis,[10] and cultured ECs from several species respond to mechanical stretch or shear by producing more PGI_2.[10,21,28,32]

Eldor et al.[15] showed that the lumenal surface of "arterialized" segments of autogenous canine jugular vein exposed to arterial flow and pressure for a 6-week period did not produce significantly greater quantities of PGI_2 than did control (normal) vein. This finding was also observed after arachidonic acid stimulation; furthermore, full thickness vessel wall homogenates of the V-A autografts actually produced significantly less PGI_2 than did normal vein under unstimulated conditions.[15] Both normal vein and the V-A autografts produced significantly less 6-k-$PGF_{1\alpha}$ than did carotid artery. These observations suggested that the EC surfaces of arterialized V-A autografts are repopulated by venous ECs that do not undergo any substantial functional adaptation to the high flow and pressure arterial environment. It must be re-emphasized,



FIGS. 4A and B. Results of basal (*A*) and arachidonic acid stimulated (*B*) prostacyclin production (assessed as 6-keto-$PGF_{1\alpha}$) by normal (control) veins, normal arteries, V-A autografts (AUTO), and V-A allografts (ALLO) at various sampling times.



FIGS. 5A and B. Graft, venous, and arterial prostacyclin generation in the perspective of previous observations reported by others: Eldor et al.[15]; Hoover et al.[18] To adjust for differences in analytical techniques and incubation template chamber size, these measurements are expressed as a ratio compared to normal vein production (6-keto-$PGF_{1\alpha}$ produced by the graft divided by that produced by control vein). *A*. The basal measurements are illustrated; maximal (arachidonic acid) stimulated values are shown in *B*. AUTO = veno-arterial autograft; ALLO = veno-arterial allograft; K^+CP = potassium cardioplegia infusion.

however, that these experiments were only performed after 6 weeks of graft implantation. Similar findings have also been reported subsequently from Weksler's laboratory in studies of various modes of vein graft injury[18,20]; again, only 6 week specimens were analyzed.

We have demonstrated that lumenal surface PGI_2 production of both V-A autografts and allografts is significantly greater than that in normal canine veins after 10–12 weeks (Table 1 and Fig. 4). Importantly, the amount of PGI_2 generated by both types of grafts at this time was not significantly different than that produced by normal canine artery. Since our serial data demonstrated a marked increase in 6-k-$PGF_{1\alpha}$ production between 6 and 12 weeks (Fig. 4), the apparent discordance between the results of Eldor et al.[15] and Hoover et al.[18] and those reported herein is probably simply a function of the time elapsed since graft implantation. This hypothesis is graphically illustrated in Figure 5, where data from all three investigations (normalized as a ratio of normal vein PGI_2 production) are shown as a function of graft implantation time.

The fact that both types of reversed (ischemic) V-A grafts recovered the capability to produce PGI_2 over time probably does not detract from the utility of using such measurements minutes to hours after vein harvesting and preparation to assess the magnitude of iatrogenic trauma incurred and to compare methods designed to minimize this injury.[16–21] Our findings do, however, call into question the practical and clinical long-term relevance and significance of such data, especially in regard to the purported superiority of *in situ* saphenous vein grafts for femoral-popliteal and femoral-tibial bypass grafting.[17] Indeed, recent work from Bush's laboratory (using a different analytical approach) appears to confirm our observation that any early difference in lumenal surface PGI_2 generation between *in situ* and reversed canine V-A autografts diminishes over time.[33]

It is interesting that the severely denuded flow surface of the V-A allografts (Fig. 3A) generated similar amounts of PGI_2 compared to the relatively normal autograft EC lumenal surface (Fig. 2A) at the early sample time (Figs. 4 and 5); indeed, PGI_2 production by V-A allografts was statistically indistinguishable from that in V-A autografts at all three sampling times. Explanations for this observation include the possibility that the few remaining ECs in the allografts at 1–2 weeks produce more PGI_2 per cell[13,28] (compared to the relatively normal ECs in the autografts) or that local release of interleukin-1 (IL-1) during this rejection phase is responsible for augmented PGI_2 synthesis.[34] As a corollary, the origin of the ECs repopulating these V-A allografts (host or donor) was not examined; however, we suspect that the majority of the ECs lining these (relatively short) V-A allografts was of host origin within several weeks after implantation. Nevertheless, the allograft ECs did appear to be somewhat hypertrophied compared to those in the autografts. If so, this might indicate EC adaptation consistent with the *in vitro* response demonstrated in several species.[10–14,21,28,32] Another explanation entails PGI_2 generation from sources other than endothelial cells. This hypothesis is consistent with findings in rats after balloon catheter injury[26] and suggests a salutary role for myointimal cells in "arterialized" V-A autografts and allografts vis-à-vis platelet adhesion and degranulation.

Our observations clearly demonstrate that EC production of prostacyclin is responsive over time to the altered environment associated with autogenous or homologous vein grafts interposed into the arterial circulation. The mechanism responsible may be increased biosynthesis and/or release of PGI_2 from venous ECs, repopulation of the graft with arterial ECs, PGI_2 production by cells other than ECs (*e.g.*, myointimal cells and other cells [mediated by IL-1 during the inflammatory response]), or a combination of these mechanisms.[5,6,8–15,17,21,26–28] Although electron microscopic studies have shown different mor-

phologic characteristics of venous and arterial ECs,[5] it remains to be determined whether these differences reflect truly different cell populations or simply various degrees of phenotypic modulation induced by the different hemodynamic environment.[13,14,28] In either case, the V-A bypass grafts examined in this study demonstrated significant changes in PGI_2 generation as a function of time of implantation; we believe such behavior represents functional, biochemical adaptation to the mechanical stresses imposed by the arterial circulation. Despite the fact that Carrel and Guthrie did not actually mention the word "arterialization" in their seminal 1906 paper,[1] the data presented herein amplify the meaning of this word, whether its connotations be positive or negative. Veno-arterial bypass grafts, whether they are of autologous or homologous origin, become "arterialized" in both functional as well as morphological terms.

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