Internal Mammary Artery Versus Autogenous Vein for Coronary Artery Bypass Graft

By Stephen J. Rossetter, M.D., William R. Brody, M.D., Ph.D., Jon C. Kosek, M.D., Martin J. Lipton, M.D., and William W. Angell, M.D.

SUMMARY

Aortocoronary venous graft (ACVG) and internal mammary artery graft (IMAG) are currently the two most popular choices for coronary artery bypass. The morphologic alteration and susceptibility to atheromatous degeneration of the IMAG were compared with the ACVG. Six of 12 surviving dogs with IMAGs were fed a hyperlipidemic diet and six were placed on a regular diet. All dogs were sacrificed 3–15 months after surgery. Twelve of 28 long-term surviving dogs with ACVGS were also on hyperlipidemic diets, and all were sacrificed 3–18 months after surgery. Arteriography and electron microscopy were performed in selected cases, and histology was performed in all cases. All long-term IMAGs remained patent; 83 percent (5/6) "regular" diet arteries were normal, with no intimal proliferation, while 33 percent (2/6) "hyperlipidemic" IMAGs had diffuse atheroma. Eighty-two percent of ACVGS revealed significant atherosclerosis. Severity of arteriosclerotic involvement of the ACVG was far greater than that of the native coronary circulation; this was not true for the IMAG.

It may be concluded that (1) in the normolipidemic condition the IMAG undergoes significantly less severe histologic change than the ACVG, (2) both the IMAG and the ACVG are more susceptible to atheromatous change than the native coronary circulation. In these series, patency was not influenced by severity of histologic changes, and no grafts were occluded by virtue of the arteriosclerotic process.

Additional Indexing Words:
Atherosclerosis
Vein graft

CORONARY ARTERY REVASCULARIZATION procedures are being performed with increasing frequency as treatment for atherosclerotic heart disease. The morphological and functional fate of these bypass grafts is of considerable import. Although atherosclerotic degeneration has been described in peripheral venous grafts in the arterial system, both clinically1–6 and experimentally,7–13 such documentation in coronary artery bypass grafts is meager.

Two major types of coronary artery bypass grafts are commonly utilized: autogenous saphenous vein aortocoronary grafts (ACVG) and internal mammary artery grafts (IMAG). This study deals with the susceptibility of these grafts to atheromatous degeneration in the canine model.

Methods

Group 1 (see table 1): IMAGs were performed on 12 mongrel dogs. The animals were anesthetized with sodium pentobarbital, 30 mg/kg, intubated and ventilated with a positive pressure ventilator. Left thoracotomy in the fourth intercostal space was performed. The left internal mammary artery was dissected free of the chest wall from its innominate origin to the point of transection at the fifth intercostal space. Tributaries were ligated with 4-0 silk and divided. The dogs were systemically heparinized and cardiopulmonary bypass was established by cannulating the right atrium and descending thoracic aorta. Extracorporeal circulation, utilizing a bubble oxygenator, was instituted and the heart fibrillated with cold saline. The middle portion of the left anterior descending coronary artery distal to the first septal branch was isolated and a longitudinal arteriotomy of 1.0 cm made. The internal mammary artery-left anterior descending anastomosis was made with running 6-0 Prolene. The proximal left anterior descending coronary artery was ligated and cardiopulmonary bypass discontinued. Heparin effect was reversed with protamine sulfate.

Group 1 dogs were subdivided into two dietary groups: group 1A (N = 6) animals were fed a standard cane diet until sacrifice or death (mean duration = 2.2 months; range = 2.0–4.5 months); group 1B (N = 6) animals were fed an atherogenic diet, described below, until sacrifice or death (mean duration postop = 6.3 months; range = 3–15 months; time on diet postop, mean = 4.8 months; range = 3–8 months).

Group 2: ACVGS were performed on 28 mongrel dogs.14 A three-inch segment of cephalic vein was isolated and removed from the foreleg. Thoracotomy and anastomosis to
the left anterior descending coronary artery were performed in a manner similar to the IMAG animals. The proximal end of the vein graft was anastomosed to the aorta with running 5-0 Tevdek.

Group 2 dogs were likewise subdivided into two major dietary groups: group 2A (N = 16) were on regular canine diet until sacrifice or death (mean duration = 8.4 months; range = 1½–17 months); group 2B (N = 12) were placed on atherogenic diets, described below, until sacrifice or death (mean duration postoperatively = 3.7 months; range = 1½–9 months; time on atherogenic diet postoperatively, mean = 2.7 months; range = 1½–9½ months).

Pre- and post-diet angiograms and post-diet electron microscopy were performed in several cases. Gross examination plus hematoxylin and eosin histologic examination of all grafts, hearts, coronary arteries and aortae was routinely employed. Sudan lipid stains were utilized selectively.

Diet: A standard atherogenic regimen14,15 was employed for groups 1B and 2B dogs, consisting of a 100 gm mixture of: cholesterol, 20 gm; cottonseed oil, 73 gm; cholic acid, 5 gm and Thiouracil, 2 gm, all added to a two-pound can of dog food (Kal-Kan) daily. Thyroid ablation was not performed. Fasting serum cholesterol and triglyceride levels were obtained pre- and postoperatively at approximately one month intervals.

Results

Serum Lipid Levels

Group 1A and group 2A (regular diet controls, table 2) were considered as one control group for the purposes of blood lipid analysis. There was no significant difference between the two groups. Groups 1A and 2A (control diet): serum cholesterol, mean level = 171 ± 40 (range, 93–245 mg%); serum triglycerides, mean level = 94 ± 64 (range, 35–265 mg%). Group 1B (IMAG atherogenic diet): serum cholesterol, mean level = 522 ± 331 (range 285–1480 mg%), P < 0.05; serum triglycerides, mean level = 160 ± 105 (range, 60–400 mg%), P > 0.05. Group 2B (ACVG atherogenic diet): serum cholesterol, mean level = 398 ± 223 (range, 201–1116 mg%), P < 0.05; serum triglycerides, mean level = 160 ± 99 (range, 25–335 mg%), P < 0.05. The difference in levels between group 1B and group 2B was not statistically significant.

Patency

All of group 1 IMAGs were patent at time of sacrifice (table 3). Eighty-one percent (13/16) of group 2A ACVGs were patent; 19 percent (3/16) had early thrombosis. Eighty-three percent (10/12) of group 2B ACVGs were patent; 17 percent (2/12) had thrombosed, with one recanalized (fig. 1). The difference between group 2A and group 2B patency rates was not significant, nor was the difference in the patency rates between groups 1A and 2A or between groups 1B and 2B (IMAG versus ACVG) significant with these small numbers.

Gross and Histologic Examination

Group 1A (regular diet IMAGs). The majority of internal mammary arteries in this group were histologically normal; 17 percent (1/16) had mural necrosis and intimal sclerosis, probably related to interruption of vasa vasorum. No atheroma or atherosclerotic changes were noted in any group 1A specimen, and all coronary arteries were clean. Intimal fibrosis did not occur in any of the arteries without mural necrosis.

Group 1B (atherogenic diet IMAGs). Thirty-three percent (2/6) of Group 1B IMAGs developed focal atheromas (2+ and 4+) with foam cells and intimal fibrosis. Sudan stains revealed that the lipid was contained mostly in the media of these vessels (fig. 1). One of this group had gross atheromatous plaque in the IMA plus in the native coronary circulation. It should be noted that these two atherosclerotic IMAG dogs were both on atherogenic diet approximately three times longer than the remainder of group 1B animals (10 months versus three months). Seventeen

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Diet</th>
<th>Number of subjects</th>
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<tbody>
<tr>
<td>1 (IMAG)</td>
<td>A Regular</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>B Atherogenic</td>
<td>6</td>
</tr>
<tr>
<td>2 (ACVG)</td>
<td>A Regular</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>B Atherogenic</td>
<td>12</td>
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<tr>
<td></td>
<td>B Atherogenic</td>
<td>6</td>
</tr>
<tr>
<td>2 (ACVG)</td>
<td>A Regular</td>
<td>16</td>
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<td>B Atherogenic</td>
<td>12</td>
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Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Cholesterol (mg %)</th>
<th>Triglycerides (mg %)</th>
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<tr>
<td></td>
<td>Mean ± SD (range)</td>
<td>Mean ± SD (range)</td>
</tr>
<tr>
<td>1A &amp; 2A (Controls — regular diet)</td>
<td>171 ± 40 (93–245)</td>
<td>94 ± 64 (35–265)</td>
</tr>
<tr>
<td>Atherogenic diet IMAG 1B</td>
<td>372 ± 331 (285–1480)*</td>
<td>160 ± 105 (60–400)†</td>
</tr>
<tr>
<td>Atherogenic diet ACVG 2B</td>
<td>398 ± 222 (156–1116)*</td>
<td>160 ± 100 (25–335)*</td>
</tr>
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*P < 0.05, significant compared to controls.
†P > 0.05, not significant compared to controls.
percent (1/6) of the group 1B IMAGs had partial mural necrosis but no atheroma. All other coronary arteries and aortae except the one mentioned in group 1B were grossly and histologically free of atherosclerosis, and Sudan stains in these structures were negative. All other IMAGs were normal and free of atherosclerosis.

**Group 2A.** These vein grafts all demonstrated variable thickening, medial fibrosis with loss of media myocytes, and widespread intimal thickening in the form of focal subendothelial cushions of proliferating myointimal cells and collagen. The severity of medial fibrosis was inversely proportional to the severity of the intimal changes in a given segment of graft.16, 17

No grafts or coronary arteries demonstrated atheroma or foam cells. Sudan stains were negative for lipid.

**Group 2B.** Intimal fibrosis and medial fibrosis occurred in all vein grafts as in group 2A. In addition, 40% (5/12) showed significant histologic evidence of atherosclerosis, with abundant foam cells and focal atheroma (figs. 2, 3). Sudan stains in these vessels revealed the lipid to be contained both in the media and in the intima, and also revealed that the atheroma were mostly concentrated in areas of fibrous intimal proliferation. Two grafts had only minimal atherosclerotic changes and are included in the “nonatherosclerotic” designation. All coronary arteries and aortae were grossly and histologically clear. Sudan stains revealed no lipid in these structures.

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**Table 3**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patency</th>
<th>Graft atherosclerosis</th>
<th>Coronary atherosclerosis</th>
</tr>
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<tbody>
<tr>
<td>1 IMAG A</td>
<td>100% (6/6)</td>
<td>0 (0/6)</td>
<td>0 (0/6)</td>
</tr>
<tr>
<td>B</td>
<td>100% (6/6)</td>
<td>33% (2/6)</td>
<td>17% (1/6)</td>
</tr>
<tr>
<td>2 ACVG A</td>
<td>81% (13/16)</td>
<td>0 (0/16)</td>
<td>0 (0/16)</td>
</tr>
<tr>
<td>B</td>
<td>83% (10/12)</td>
<td>42% (5/12)</td>
<td>0 (0/12)</td>
</tr>
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**Figure 1**

Atheromatous IMAG. Note intimal thickening by cellular fibrous tissue (between arrows), slight and diffuse lipid deposition in intima and massive medial lipid deposition. (Sudan IV lipid stain, about × 200).

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**Figure 2**

Atheromatous ACVG. Note thickened intima (between arrows), and massive lipid deposition (atheroma). (H & E, about × 75).
Atheromatous ACVG. Intima with many lipid-laden ‘foam cells.’ (H & E, about × 400).

Due to the small numbers involved, the statistical test of significance (standard error of the difference between proportions) is insufficiently sensitive to accurately determine the significance of the difference in incidences of atherosclerosis. Despite this shortcoming, the application of this test revealed the following. The difference of IMAG atherosclerosis between groups 1A and 1B is not statistically significant due to the small sample size. Similarly the overall incidence of atherosclerosis in group 1B IMAGs (33%) versus the incidence of atherosclerosis in the native coronary circulation (17%) is not significant statistically.

The difference in incidence of atherosclerosis between groups 2A and 2B is statistically significant ($P < 0.05$), as is the difference in incidence of atherosclerosis in the vein grafts versus the native coronary circulation in both group 2A and group 2B ($P < 0.05$). With the small numbers utilized in this study, the difference between incidence of atherosclerosis in groups 1B and 2B is not significant.

Electron Microscopy.

Electron microscopy of representative vein samples showed fibrosis metaplasia of medial myocytes with consequent mural fibrosis, as well as intimal migration of some of these altered medial cells into the intima, with progressive intimal thickening (fig. 4). The veins of hyperlipemic dogs showed, in addition, frequent dystrophic myocytes, with myelin figures, fat droplets, vacuolation and, occasionally, nuclear pyknosis or karyorrhexis. Endothelial cells often contained lipid droplets as well, and focally were separated from internal elastic lamella by lipid laden and dystrophic myocytes.

The arterial grafts in nonhyperlipemic dogs showed no constant electron microscopic alterations. However, in the hyperlipemic subjects, both endothelial cells and media myocytes frequently contained lipid droplets and, less often, cytoplasmic vacuoles. The middle and outer thirds of the media were most severely involved by the myocyte lipid accumulation in most of the vessels studied.

Angiography.

None of the angiograms obtained revealed discernible radiographic evidence of atheroma. One ACVG which had thrombosed and recanalized was shown to have an irregular and narrowed lumen (fig. 5).

Comments

It appears likely that the difference in susceptibility to atheromatous changes in the ACVG is significantly greater than in the IMAG. The small numbers of subjects involved in this study render statistical tests of significance questionable, and only additional data can prove this belief.

It should be noted that relative to many other studies of atherogenesis in dogs, the atherogenic stimulus in this study was not great. The low incidence (1/40) of systemic arterial atherosclerosis attests to this fact. This is probably related to the relatively short time on diet and the absence of thyroid ablation. However, the nature of this stimulus, which is subminimal for coronary arteries, emphasizes the increased susceptibility of vein grafts to atherogenic changes.

In this study, there was no correlation between graft patency and evidence of atherosclerosis. Whether or not the athero-arteriosclerotic changes seen in these grafts would progress and result in graft occlusion cannot be answered by this relatively short-termed experiment.

Discussion

The atherogenic susceptibility of autogenous vein grafts placed in the peripheral arterial circulation animals has been studied by various investigators. A few initially felt that the vein graft was relatively resis-
tant to the development of athero-artersclerosis.18 They,12 along with others, however, later concluded that the vein graft is at least the equal of the artery in susceptibility to atherosclerosis,9 and is probably more susceptible.7, 10, 11 The milieu of the vessel is the determining factor, not the intrinsic structure of the vein wall.9-11 This experimental evidence is supported by several reports of atherosclerosis developing in human peripheral vein grafts.1-6

Experience with aortocoronary vein grafts (ACVG) is less widespread. Investigators have described intimal thickening, medial hypertrophy, medial necrosis, endothelial damage and aneurysmal dilatation in ACVGs.16, 17, 19, 20 The occasional opportunity to examine ACVGs after implantation emphasizes the propensity for development of these lesions.21-24 The intimal hypertrophy and fibrosis are of concern because of the apparent rapidity of onset and the threat to graft patency which they represent. Lesperance, in a clinical angiographic study of 43 patients with ACVGs, felt that the fibrous hyperplasia does not progress after one year;25 the Cleveland Clinic experience supports this belief.26 The addition of an atheromatous insult in an already compromised vein graft could be intolerable.

The etiology of the degenerative changes in vein grafts is uncertain and is probably multiple. Elevated intraluminal pressure appears to stimulate intimal proliferation, while vein wall ischemia (produced by interruption of vasa vasorum) encourages medial fibrosis.15 Endothelial trauma — from operative injury, anoxia or shear stresses — may result in microthrombi of platelet aggregates and fibrin. Organization of this thrombus and subsequent regeneration of the endothelium may thus produce the subendothelial lesion.20, 25, 27 The myointimal cell20, 28, 29 and/or the macrophage — part of the cellular inflammatory response to the intimal trauma — may then accumulate lipid and become a foam cell, characteristic of the atherosclerotic lesions seen in this study. Hemodynamic factors (vessel size discrepancy, vessel configuration and contour) act to determine the

Figure 4

Left) Atheromatous ACVG. Note widened subendothelial space (s), including fibrinuous material (f) and myocytes (m), some with lipid droplets (l), the central one with karyorrhexis (n), and all with fibrocytic metaplasia. Lumen (l) is at upper left. Electron micrograph about × 4,000. Top right) Portion of a myocyte from atheromatous ACVG at left, showing basement membrane (bm), laminar densities (ld), and microvessels (mc), as well as myofilaments (characteristic features of these cells). Electron micrograph × 25,000. Bottom right) Fibrin from atheromatous ACVG at left. Electron micrograph × 25,000.
sites of focal atheromatous deposition.\textsuperscript{50, 51} Although it seems logical that ACVGs would be susceptible to atherosclerotic degeneration, we are aware of only one report\textsuperscript{29} which documents lipid in the vessel wall, and this was in a thrombosed graft. This and one previous study document susceptibility of ACVGs to atherosclerotic degeneration.\textsuperscript{19}

The structural alterations in ACVGs and attendant threats to patency prompted a search for alternate bypass conduit. In the early 1960s, Goetz\textsuperscript{28} and Spencer\textsuperscript{34} performed experimental internal mammary artery-coronary anastomoses; clinical trials followed by 1968.\textsuperscript{35} More recently, aortocoronary bypasses utilizing free radial artery grafts\textsuperscript{36} and free internal mammary artery grafts\textsuperscript{37} have been utilized with success. Synthetic grafts have thus far been disappointing. Canine experimental studies comparing long-term (up to 48 months) results of internal mammary artery-coronary grafts and ACVGs have been performed.\textsuperscript{38, 39} While the ACVGs suffered the expected sclerotic changes and stenoses, the IMAGs showed no significant histologic changes. Flow rates appeared comparable.\textsuperscript{38, 40} In one study, the IMAG patency rates of 83\textendash88\% compared with ACVG patency of 36\%. (This poor patency rate with ACVGs does not agree with our experience, however.) Clinical comparison of IMAGs and ACVGs is limited; Green found a patency of 97\% for IMAGs and 70\% for ACVGs after 2 weeks to 3 years in 165 patients.\textsuperscript{41}

Wakabayashi et al., in an acute study,\textsuperscript{42} have emphasized the difference in flow characteristics of the IMAG and ACVG, suggesting that the mean flow in IMAG suffers secondary to a rapid fall in diastolic filling pressure (when most coronary flow occurs). Murase has refuted this\textsuperscript{43} in a study with chronic IMAGs and ACVGs, revealing a change in flow characteristics with time.

This study tends to confirm the preference of the IMAG as opposed to ACVG in terms of structural and histologic criteria. It is obvious, however, that the decision concerning which vessel is most suitable for coronary artery bypass must be based on a comprehensive knowledge of the facts; to choose the IMAG merely because of theoretical histologic superiority would be illogical, and extrapolation from this canine study to the human condition is premature.

A variety of arguments supporting the use of IMAGs exists, in addition to the decreased susceptibility to structural alterations: 1) the patient with absent or unsuitable saphenous veins may benefited; 2) only one anastomosis is required; 3) the similarity in size of IMAG and most coronary arteries tends to decrease the turbulent flow and increase the flow rate; 4) the IMAG has an apparently better patency rate than the ACVG; 5) there is less difficulty with kinking and torsion of IMAGs.

Disadvantages of IMAGs with respect to ACVGs have also been suggested: 1) the dissection and anastomosis is more difficult with the small, fragile IMAG; 2) the IMAG is inapplicable to many distal and posterior bypass sites because of its usable length and position; 3) atherosclerotic disease in the IMAG may render the vessel unusable; 4) some have suggested a basic inflow insufficiency, due to small vessel diameter, particularly past the fourth intercostal space.

Certainly, additional experimental and clinical studies are necessary to clarify the situation. In addition, further search for alternate conduits (such as synthetic grafts, preserved homograft and heterograft arteries and veins) is warranted.

Conclusions

This study demonstrates that for the canine model: 1) both IMAGs and ACVGs are susceptible to atheromatous degeneration; 2) the histologic alteration of the normolipidemic IMAG is less severe than the ACVG; 3) the susceptibility of the ACVG to atherosclerotic change is significantly greater than the systemic and coronary arteries; this is not true of IMAGs.
Acknowledgment

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