EXPERIMENTAL STUDIES ON THE LONG TERM FATE OF THE VEIN AND ARTERY GRAFTS AND ITS CHOICE IN AORTOCORONARY BYPASS SURGERY

KOSHIRO ONO, MAMORU TAGO, KIYOSHI HAMAGUCHI, KENZO OHISHI,
TAKESHI NAKAMURA, YOSHIHIRO ISODA, FUMIO MEGURO,
HATSUZO UCHIDA, SHIGERU TERAMOTO, AND TERUTAKE SUNADA

AORTO-CORONARY bypass surgery has become very popular method for myocardial revascularization.¹⁻⁷ The purpose of this present investigation is to develop experimental model in the dog which may have graft wall changes similar to human being graft wall and to elucidate the short and long term fate of the aortocoronary bypass graft and to discuss on the hydraulic factors.

MATERIALS AND METHODS

Experimental studies were performed in 47 mongrel dogs weighing from 8 to 30 kg and 20 kg in average.

The dogs were anesthetized with Nembutal, 25 mg/kg, and intubated and mechanically ventilated with room air. Surgical exposures were done through the left fourth (for internal mammary artery-circumflex coronary anastomosis) or fifth (for free grafts of A-C bypass) intercostal space.

The experimental dogs were divided into four groups.

Group I was consisted of 20 dogs of which grafts were of hind leg veins in 10 dogs, forearm veins in 5 dogs, external jugular veins in 5 dogs, using as free grafts from ascending aorta or descending aorta just distal to the left subclavian artery to the circumflex coronary artery.

Key Words:

Aorto-coronary bypass graft,
Intimal fibrous proliferation,
Graft-coronary diameter ratio,
Length of graft

Group II was consisted of 7 dogs of which grafts were taken from the superficial femoral artery and interposed with autologous hind leg veins for comparative studies between arterial and venous grafts in the same dogs.

Group III was consisted of 10 dogs of which left internal mammary artery were anastomosed to the circumflex coronary artery.

Group IV was consisted of 10 dogs of which grafts were knitted polyester prosthesis of 4 mm in diameter including 5 composite grafts with veins (Table I).

Most free grafts were 7 to 8 cm in length and the distal end for aortic anastomosis was designed in cobra head beveled in 45 degree that was postulated elsewhere as well as internal mammary-circumflex anastomosis. All procedures were performed under distal coronary perfusion with the use of local Silicone tube shunt, at beating heart under normothermia (Fig. 1). In Group I and II, coronary anastomosis was done first with 7-0 Cardio-Vascular Silk (Nitcho) and then tube was removed out. Aortic anastomosis was done with 6-0 Cardio-Vascular Silk in continuous running stiches. In internal mammary anastomosis, local shunt was introduced from proximal to distal side of circumflex coronary artery and anastomosis was done with 8-0 Silk in same manner as in Group I, II without aid of ocular loupe magnification.

During above procedures, heart was not fibrillated because of distal coronary perfusion with local shunt. External diameter of each vessels were measured with caliber. Graft and coronary

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Department of Surgery, Okayama University Medical School, Okayama, Japan

TABLE I AORTO-CORONARY BYPASS, EXPERIMENTAL SERIES

Group I (Vein Graft)				
Dog	A-C Bypass	Duration	Bypass	Result
39 HV	AA-Cx	380 da.	patent	sacrificed
48 HV	AA-Cx	330 da.	patent	sacrificed
37 HV	AA-Cx	95 da.	occluded	sacrificed
33 HV	DA-Cx	66 da.	patent	sacrificed
25 FV	DA-Cx	20 da.	occluded	dead
34 HV	DA-Cx	13 da.	patent	escaped
35 HV	AA-Cx	14 da.	thrombosed	dead
19 FV	DA-Cx	14 da.	thrombosed	dead
46 FV	AA-Cx	10 da.	patent	dead
49 HV	AA-Cx	10 da.	patent	dead
38 HV	AA-Cx	7 da.	thrombosed	dead
29 HV	DA-Cx	5 da.	thrombosed	dead
45 HV	AA-Cx	4 da.	patent	dead
26 FV	DA-Cx	3 da.	thrombosed	dead
21 FV	DA-Cx	2 da.	thrombosed	dead
32 HV	DA-Cx	2 da.	thrombosed	dead
47 FV	AA-Cx	1 da.	thrombosed	dead
20 FV	DA-Cx	1 da.	thrombosed	dead
30 HV	DA-Cx	1/2 da.	thrombosed	dead
22 FV	DA-Cx	DOT		dead
Group II (Artery Graft)				
Dog	A-C Bypass	Duration	Graft	Result
41 FA	AA-Cx	440 da.	occluded	sacrificed
42 FA	AA-Cx	365 da.	occluded	sacrificed
44 FA	AA-Cx	341 da.	patent	sacrificed
49 FA	AA-Cx	10 da.	patent	sacrificed
40 FA	AA-Cx	4 da.	occluded	dead
43 FA	AA-Cx	DOT		dead
Group III (IMA-Cx Anastomosis)				
Dog	A-C Bypass	Duration	Bypass	Result
IMA 1	IMA-Cx	6 Mo.	patent	living
IMA 2	IMA-Cx	10 da. <	patent	living
IMA 3	IMA-Cx	10 da.	patent	living
IMA 4	IMA-Cx	10 da.	patent	sacrificed
IMA 5	IMA-Cx	10 da.	patent	sacrificed

IMA 6	IMA-Cx	10 da.	patent	dead
IMA 7	IMA-Cx	10 da.	patent	dead
IMA 8	IMA-Cx	10 da.	patent	dead
IMA 9	IMA-Cx	10 da. >	thrombosed	dead
IMA 10	IMA-Cx	10 da.	thrombosed	dead

*Group IV (Prosthetic Graft)**

Dog	A-C Bypass	Duration	Bypass	Result
1G6	AA-Cx	14 da.	thrombosed	sacrificed
2G6	AA-Cx	3 da.	thrombosed	dead
3G6	AA-Cx	24 hrs.	patent	dead
4G6	AA-Cx	24 hrs.	thrombosed	dead
5G6	AA-Cx	24 hrs.	thrombosed	dead
1CG4	AA-Cx	3 da.	thrombosed	dead
2CG4	AA-Cx	24 hrs.	thrombosed	dead
3CG4	AA-Cx	24 hrs.	thrombosed	dead
4CG4	AA-Cx	24 hrs.	thrombosed	dead
5CG4	AA-Cx	24 hrs.	thrombosed	dead

* 40 n.p.i. knitted polyester graft
 HV hind leg vein
 FV fore arm vein
 FA femoral artery
 IMA internal mammary artery
 G prosthetic graft
 CG composite graft

flows were measured with electromagnetic flow meter in all experimental dogs. Velocity of blood flow through the graft and coronary artery were computed using formular of $V = Q/A$ (A: cross sectional area, Q : Flow, cc/min., V = Velocity). All survived dogs were served for studies of long term fate of the graft and hydraulic studies.

RESULTS

Observation was made among the four groups at different time intervals after operation. Bypass grafts which had been in place for the periods of varying from 48 hrs. to more than 1 year were obtained from 47 dogs. In Group I and II, over all patency rate was 35% and early graft occlusion occurred within 2 wks. with 6.5 days of mean. This occlusion was found to be due to thrombosis either in graft or at aortic anastomosis. This might be ascribed to thrombosis resulting from inadequate blood flow or to technically poor anastomosis. In long survived dogs 60% of patency rate were obtained. In

Group III, 80% of it was obtained. In Group IV, all but few dogs could survive more than 24 hours (Table I).

MORPHOLOGICAL STUDIES

Vein grafts in place for 48 hrs. after insertion revealed diffuse mural edema through the entire graft wall and medial necrosis with leukocytes infiltration. Endothelial cell damages were found focally (Fig. 2). In Group II, mural edema and leukocytes infiltration through the wall were recognized. In Group III, no significant alterations in mammary artery grafts were recognized. The vein graft in place for seven to 10 days still had a few cells infiltration at medial and adventitial zones and revealed inflammatory reaction of early phase in most cases (Fig. 3). Myointimal cells, cushion like smooth muscle cells appeared. However discrete subintimal hyperplasia was not recognized. In Group II, high degree of swelling and degenerative changes were markedly seen. The internal mammary artery showed slight

mural edema of the graft but no significant findings recognized as seen at 2 days grafts. Photomicrograph of a free arterial graft implanted for 10 days as shown in Fig. 4; a 14 days

ADA anterior descending coronary artery
Cx circumflex coronary artery

Fig.1. Method of shunt.

graft was also shown in Fig. 5. In the vein graft in place for 3 wks., distinct fibrous intimal proliferation appeared (Fig. 6) and myogenic cells were seen (Fig. 7).

In vein grafts in place for 8 weeks (2 months) after implantation, there was moderate fibrous proliferation of intima to produced stenosis of the vein graft. Collagen deposition, rich in young elastic fibers, myogenic cells in subintimal layer were prominent findings. The venous valve remained intact in shape and endothelial cell was also recognized (Fig. 8).

The vein graft in place for more than 1 year had external diameter of the graft dilated twice as compared to just after bypass, but no aneurysmal dilatation was recognized in this series. Massive subintimal fibrous tissue proliferation was shown in Fig. 9. Collagen deposition, myogenic cells such as fibroblast and fibrocytes were principal elements in this layer. The vein graft media had lost its circular fashion of smooth muscles and could not be determined whether this layer remained changed or completely lost its own structure morphologically. However this intimal proliferation did not result in intraluminal narrowing for the compensatory dilatation of the graft wall (Fig. 10).

Fig.2. Photomicrograph of vein graft in place for 2 days showing inflammatory cells (IC) in media and adventitia (Ad). Note the apparent lysis of structure of media in most part. Internal elastic lamina are seen and external elastic lamina are swollen. (Md) Media, (L) Lumen. (Elastic tissue stain 10 × 40)

Fig.3. Photomicrograph of vein graft, in place for 10 days. Lumen is occluded by fresh thrombus (FT). No discrete findings is seen except mural edema with inflammatory cells. (Azan stain 10 × 40)

Fig.4. Photomicrograph of arterial graft, in place for 10 days showing early graft changes. Mural edema (Ed), external elastic lamina (EEL) and elastic fibers (EF) fragmented and swollen. (L) graft lumen, (IE L) internal elastic lumina. (Elastic tissue stain 10 × 25)

Fig.5. Photomicrograph of vein graft in place for 14 days. Myogenic cells (MC) are abundant in media (Md). Inflammatory cells are also seen. Neither intima nor inner media is present in this specimen. Outer medial muscles are partially preserved. Fibroblasts (FB) are seen adjacent to area of the intact outer medial muscles (OMZ). (Alcian blue + PAS 10 × 40)

Fig.6. Photomicrograph of vein graft in place for 25 days. Note the distinct internal fibrous proliferation (IFP). Elastic lamina (EL) have continuity and no fragmentation at all in this specimen. Longitudinal Section. (L) graft lumen, (Md) Media. (Elastic tissue stain 10 × 40)

Fig.7. Photomicrograph of vein graft showing myogenic cells (MC) in media. This type of cells which currently thought to originate from medial muscle cells takes part in reparative process of vein grafts. (Alcian blue + PAS 10 × 100)

Fig.8. Photomicrograph of vein graft in place for 66 days well preserved silver stained structure. Note the medial (Md) and internal layers. Each fibers are oriented in longitudinal fashion at media and against lumen at intima layer. (L) graft lumen, (Ad) adventita, (FIP) Fibrous intimal proliferation. (Silver stain 10 × 40)

Fig.9. Photomicrograph of vein graft in place for 330 days showing marked intimal fibrous proliferation and collagen deposit without any luminal narrowing. (Md) media, (FIP) Fibrous intimal proliferation (Ad) adventita. (Azan stain 10 × 40)

Fig.10. Photomicrograph of vein graft showing fragmented and proliferated elastic fibers and subintimal hyperplasia (FIP). (Md) Media, (L) Lumen. (Elastic tissue stain 10 × 40)

Fig.11. Photomicrograph of artery graft in place for 341 days showing organized thrombus (OT) protruding into graft lumen (L). The architecture of arterial wall are well preserved. External elastic lamina (EEL) are dense and thick in appearance. No intimal fibrous proliferation could be seen. (Azan stain 10 × 40)

One year arterial free grafts showed minimum degree of intimal fibrous proliferation and architecture of the arterial wall was well preserved. Internal and external elastic layers were still present and hypertrophied (Fig. 11). As shown in Fig. 11, well formed plaque quite similar to that of human atherosclerosis in nature is recognized and then result in intraluminal narrowing. No compensatory dilatations of the graft was marked. In case of #42 dog, lumen of the graft was completely occluded by thrombus in the right of arrangement of collagen bundles (Fig. 12).

HEMODYNAMIC AND HYDRAULIC STUDIES

As shown in Fig. 14, there was little flow difference between the artery and the vein graft of which diameter are large enough for that of coronary artery anastomosis, and were small flow increment of the distal coronary artery after ligation of the circumflex coronary artery. In each vessels, following relationships were obtained.

In the vein graft coronary diameter ratio:

$$1.5 < D_g/D_c < 2.0$$

In the artery graft, graft coronary diameter ratio:

$$1 < D_g/D_c < 1.5$$

In the IMA graft, graft coronary diameter ratio:

$$D_g/D_c < 1.0$$

When above measured values are compared with theoretical values using model of mathematical concepts^{8,9} under the assumption of steady state laminar flow of a Newtonian fluid and constant diameter vessels (Fig. 13).

$$Q_g/Q_d = 1/(1 + R_g/R_c) \dots\dots\dots (1)$$

$$R = L/d^4 \dots\dots\dots \text{Poiseuille's Law}$$

$$R_g/R_c = (L_g/L_c) (D_c^4/D_g^4)$$

$$Q_g/Q_d = \frac{1}{1 + (L_g/L_c) (D_c^4/D_g^4)} \dots\dots (2)$$

$$\frac{V_g}{V_d} = Q_g/Q_d \left(\frac{D_c}{D_g}\right)^2 \dots\dots\dots (3)$$

Q_g .: Blood flow through graft

Q_d .: Blood flow of distal coronary artery

L_g .: Length of graft (cm)

L_c .: Length of proximal coronary artery (cm)

D_g .: Diameter of graft (cm)

D_c .: Diameter of coronary (cm)

V_g .: Velocity of blood flow through graft (cm/min.)

Fig.12. Case #42, with artery graft in place for 440 days. The lumen is completely occluded by organized thrombus (OT). Arterial architecture is well preserved. internal elastic lamina (IEL) are detached each other in which space contain the edematous fluid and inflammatory cells. (EEL) External elastic lumina. (Azan stain 10 x 40)

$$R = 1/D^4 \text{-----(Poiseuille's law)}$$

$$Q_g/Q_d = \frac{1}{1+(L_g/L_c)(D_c/D_g)^4} \text{-----(4)}$$

$$Q = VA, V_g/V_d = Q_g/Q_d(D_c/D_g)^2 \text{-----(5)}$$

- ADA : anterior descending coronary artery
 Cx : circumflex coronary artery
 D_g : diameter of graft (mm)
 D_c : diameter of coronary artery (mm)
 Q_d : distal coronary flow (ml/min)
 Q_g : graft flow (ml/min)
 V_d : velocity of distal coronary flow (cm/sec)
 V_g : velocity of flow through graft (cm/sec)

Fig.13. Model for theoretical analysis.

V_c: Velocity of blood flow through coronary artery (cc/min.)

These equations are plotted in Figure 15 and measured variables are superimposed in this graph as shown in Fig. 15. There is close correlation between experimental data and theoretical laws at graft and coronary flow in terms of graft coronary diameter ratio. When measured graft and coronary flow are plotted, similar trends are also seen at venous and arterial grafts as long as we use any kind of graft available.⁹ From this equations and figures, internal mammary graft may not provide basal flow when proximal coronary artery is clamped or ligated.

When we summarize these hemodynamic and hydraulic studies, optimal sized graft should be limited to as large as possible in range of $1.0 < D_g/D_c < 1.6$. In this circumstances, velocity of blood flow through the graft is able to reach maximum (Fig. 15). Length of the bypass graft should be short enough neither too tight nor any constriction in anastomotic site.

DISCUSSION

There are many reports concerning the mortality rate,¹⁰ graft patency rate,^{11,12} indication for

Fig. 14. The changes of bypass graft flow after ligation of proximal circumflex coronary artery in free grafts. (Q_g) Graft flow before ligation of proximal circumflex coronary artery. (Q_g') Graft flow after ligation of proximal circumflex coronary artery. Open circles mean that grafts were patent at final studies, closed circles, occluded.

surgery,¹³⁻¹⁵ choice of graft¹⁶ and postoperative subjective improvement.¹⁷⁻²¹ On the contrary, experimental works are quite few as for the long term fate of the graft.^{22,23}

In this paper we have discussed on the long term fate of the bypass graft, particularly, late changes of intraluminal narrowing of the bypass graft due to subintimal hyperplasia and flow characteristics of various kind of grafts²⁴ implanted in dogs in term of healing process in the artery and vein in place for more than one year and internal mammary-coronary artery anastomosis in this series. Fibrous proliferation of neointima in reconstructed artery has long been emphasized since Carrel's first report,²⁵ but has not been emphasized as possible causes of failure in late time. There have been many articles in the literature that long term histological changes after insertion of the vein as arterial substitute in short term changes.²⁶⁻³³ They have agreed in

Fig. 15. Relationship between diameter ratio and graft flow percentage to distal coronary flow and velocity through the vessels. Measured values are also plotted.

macroscopic findings of graft wall but have not always been held same views concerning the biological factors in the graft. According to them histological changes of the graft as the lapse of time are mural edema and necrosis with leucocyte infiltration at early time and disruption of elastic and muscle fibers in a few days. After this, fibroblasts and fibrocytes appeared and collagen deposits at subintimal layers.

Endothelial cells are recognized after 7 - 10 days. This leads to late graft change, diffuse subintimal fibroplasia.

In biological components such as medial muscles and elastic fibers, there has been different opinions about the fate of them.

As for the elastic components, there are also different kind of views of reduplication,²⁸ disappearance,²⁹ some stressed that fate of this elastic fiber depends on the kind of vein graft, and surgical handling of the graft.²⁷

When summarized above hypothesis, neither the fresh autologous vein nor preserved homograft is able to reduplicate at early phase reaction period, they are more or less transformed into early graft degeneration, necrosis with cell infil-

Fig.16. Schematic representation of macroscopic healing patterns in each groups. (L) graft lumen, (FIP) fibrous intimal proliferation, (OT) organized thrombus, (FB) fibrin bed.

ration and later replaced by collagenous tissue characterized with a vascular highly cellular connective tissue in due time. These changes can also be found in the patch graft in clinical situation.³² On the other hand, details of the arterial graft in direct coronary artery surgery are known quite few compared to the venous graft except internal mammary anastomosis. Most reports concerning arterial substitutes come from aortic and abdominoiliac arterial surgery before the era of prosthetic surgery. In artery series in this experiment in Group II, the thick wall graft, early graft changes of edema with leukocyte infiltration and swelling of elastic layer membrane were also seen as well. However dilatation of the graft or wall thickening were not noticed. In the free arterial graft, it is of peculiar interest that segmental intraluminal narrowings are quite similar to human arteriosclerotic plaque in the vessels, and to postendoartectomized wall changes. The architectures of the autologous fresh arterial graft wall are well preserved for the

periods of more than one year. Because of availability and hazardness of revascularization of other part of body which artery is taken as a graft, the use of the arterial graft in coronary artery surgery does not become so common.

Internal mammary artery has been well used since early experimental studies.^{1,34-36} As have been often stated, graft wall changes are minimum at later examination compared as the free graft as injuries to the vessel are not occurred during graft handling. However diameter of this artery is considerably small through the entire tapered graft, and arteriosclerotic wall changes are often developed to this artery. Graft flow are hardly enough to maintain the basal coronary flow before bypass at nonobstructed and nonstressed coronary system?

Synthetic arterial grafts were begun to be used from early of 1960 in few institutes but long term results were disappointing.^{38,39} Recently Wesolowski has reported that synthetic graft for coronary artery may be ideal in even smaller caliber graft in future, citing his experimental work done on smaller caliber graft (40 n.p.i. knitted polyester graft) implanted for more than 4 years periods. He stated in his monograph that in ordinary used Gossomer small arterial prostheses, 4 mm in diameter, patency rates were 50% after 3 months implantation in dogs.³⁹ Other prosthesis such as polytetrafluoroethylene prosthesis might be said worth for try.⁴⁰ Schematic representation of graft healing pattern as arterial substitute is summarized in Fig. 16. What is the cause for late change of the graft which might lead to intraluminal narrowing and final obstruction? Can't we prevent the morphological change?

Two hypothesis as for development of sub-intimal thickening are currently presented. The one hypothesis is based on devascularization of free graft wall after insertion of it. This kind of studies mostly come from pathophysiological studies of arteriosclerosis, particularly from field of medial smooth muscles.⁴¹ They stress the structure and function of medial myocytes which pertain to reparative process in arterial injuries induced by ischemia and devascularization. They reported that much of the intimal fibrous thickening and collagen formation may be derived from division and migration of this multifunctional medial mesenchymal cells rather than from pre-existing fibroblast or from the mutation of migration mononuclear inflammatory cells or endothelial proliferation. On the other

hand, there are conflicting debates on devascularization theory. Baird⁴³ raised some question citing his group's experimental work on devascularization studies, the vein graft wrapped with Teflon prosthesis did not show greater degree of intimal thickening than one was not wrapped, and they concluded delayed devascularization was not the cause of intimal thickening.

Another theory comes from hydraulic and hemodynamic point of view and above changes may occur by arterial pressure or physical factors within the segment of the vein. Same as devascularization theory, subintimal proliferation are hemodynamically dependent lesion in intima at least, and metabolic factor as well. Recently a few number of reports concerning the cause of subintimal fibroplasia from the hydraulic stand point of view can be seen^{23,42}. All these physical problem can result in turbulence on subsequent thrombosis, or formation of atheromas. These relationship between subintimal hyperplasia and hydraulic effects have not been proved yet in this series of experiment. Correlation between the graft and coronary artery, ratio of 1 - 1.6 in diameter is the size of choice.⁴⁴

SUMMARY

Experimental studies of aorto-coronary bypass were performed using the technique of distal coronary artery perfusion in 47 dogs to elucidate the flow characteristics at various grafts and long term fate of grafts up to 440 days after operation. On short term results, early graft occlusion seems to occur within 2 weeks with 6.5 days of mean in Group I and II (free grafts) when inflammatory reaction is most prominent. After 2 weeks patency rate was 65% in Group I and II, more than 80% of patency rate were obtained in Group III. In Group IV (prosthetic grafts), all but few (3 cases) could survive for more than 24 hours. In flow characteristic, artery and vein graft of which diameter is larger than that of the coronary artery can maintain enough the basal flow after ligation of the proximal coronary artery. In Group III (IMA-Circumflex anastomosis group), the internal mammary artery must be large enough to carry the blood to coronary artery lest the graft flow becomes below the basal flow. In Group IV, grafts can carry full flow but long term studies were not done because of early graft occlusion. There are much differences between free artery and vein grafts. In artery graft except IMA proper arterial structure is being kept until 440

days but has arteriosclerotic wall changes similar to human being. On the contrary, almost all free vein grafts have subintimal hyperplasia with collagen deposit and fibrous tissue and still progress after one year. These findings demonstrate that ischemia and hydraulic effect in the graft must be important factor for the irreversible graft wall changes.

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