Original Article

Aortic Root Necrosis after Surgical Treatment Using Gelatin-Resorcinol-Formaldehyde (GRF) Glue in Patients with Acute Type A Aortic Dissection

Shinichi Suzuki, MD, Kiyotaka Imoto, MD, Keiji Uchida, MD, and Yoshinori Takanashi, MD

Background: Although gelatin-resorcinol-formaldehyde (GRF) glue is used for surgical repair of acute type A aortic dissections, late complications possibly ascribed to toxic effects of GRF glue have been reported. We analyzed the benefits and risks of using GRF glue.

Patients and Methods: Between January 1990 and August 2003, 269 consecutive patients underwent emergency operations for acute type A aortic dissection. GRF glue was not used in 47 patients (non-GRF group) who were operated on until May 1995 and was used in the 222 (GRF group) who underwent operation subsequently.

Results: The rate of in-hospital mortality was significantly higher in the non-GRF group (31.9%) than in the GRF group (12.6%) ($p<0.0001$). In the GRF group, false aneurysms were found in 31 patients (31/194 survivors, 16.0%) 1–65 (mean, 30±18) months after initial operation. Reoperation was done in 24 of these patients. At reoperation, the site to which GRF glue was applied had degenerated, and the anastomosis between the aortic root and prosthesis had opened widely, creating a false aneurysm and resulting in aortic regurgitation with prolapse of the coronary cusps. The mortality rate of reoperation was 4.2% (1/24).

Conclusion: The use of GRF glue improved the short-term outcome of surgery for acute type A aortic dissection, but was associated with a high incidence of false aneurysms forming at the site of proximal anastomosis, where GRF glue had been applied. Patients in whom GRF glue has been used should be carefully followed up after surgery. (Ann Thorac Cardiovasc Surg 2006; 12: 333–40)

Key words: aortic root necrosis, gelatin-resorcinol-formaldehyde glue, acute type A aortic dissection

Introduction

Dissection of the aortic root causes aortic regurgitation and impairs the coronary circulation in patients with acute type A aortic dissection. Although successful reconstruction of the aortic root is an important determinant of the outcome of surgery for acute type A aortic dissection, the surgical technique of choice remains controversial.

Gelatin-resorcinol-formaldehyde (GRF) glue was first used for aortic root reconstruction in 1977.[1] The main reasons for using GRF glue were to reinforce the aorta which was rendered fragile by acute dissection and to strengthen the aortic anastomosis. Subsequently, GRF glue has been widely used in operations for acute type A aortic dissection, and good results have been obtained.[2–7] In 1995, we started to use GRF glue for the surgical repair of acute type A aortic dissection. Recently, however, late complications, possibly ascribed to toxic effects of GRF glue, have been reported.[8–12] To decide whether the use of GRF glue should be continued, we analyzed the

From Department of Cardiovascular Surgery, Yokohama City University School of Medicine, Cardiovascular Center, Yokohama, Japan

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Address reprint requests to Shinichi Suzuki, MD: Department of Cardiovascular Surgery, Yokohama City University School of Medicine, Cardiovascular Center, 4–57 Urafune-cho, Minami-ku, Yokohama, Kanagawa 232–0024 Japan.

Table 1. Patient demographics

	Non-GRF group (n=47)		GRF group (n=222)		Total (n=269)	
	No.	%	No.	%	No.	%
History						
Hypertension	34	72.3	153	68.9	187	69.5
IHD	5	10.6	22	9.9	27	10.0
CVD	5	10.6	17	7.7	22	8.2
Marfan syndrome	3	6.4	1	0.5	4	1.5
AVR	0	0.0	1	0.5	1	0.4
Preoperative state						
Cardiac tamponade	8	17.0	60	27.0	68	25.3
Shock	8	17.0	44	19.8	52	19.3
CPA	5	10.6	13	5.9	18	6.7
Syncope	6	12.8	25	11.3	31	11.5
Hemiplegia	1	2.1	5	2.3	6	2.2
Paraplegia	0	0.0	4	1.8	4	1.5
Leg ischemia	4	8.5	28	12.6	32	11.9

IHD, ischemic heart disease; CVD, cerebrovascular disease; AVR, aortic valve replacement; CPA, cardioplumonary arrest; GRF, gelatin-resorcinol-formaldehyde.

pros and cons of using GRF glue in patients undergoing surgery for acute type A aortic dissection.

Patients and Methods

Between January 1990 and August 2003, 269 consecutive patients underwent emergency operations for acute type A aortic dissection. There were 153 men and 116 women 33–86 years of age (mean, 61.2±11.2 years). This study was approved by the ethics committee of our institution.

The ascending aorta was involved in all the dissections. Chronic arterial hypertension was present before operation in 187 patients (69.5%). Twenty-seven patients (10.0%) had a history of ischemic heart disease, including 3 who had received percutaneous coronary intervention. Twenty-two patients (8.2%) had a history of cerebrovascular disease. Four patients (1.5%) had Marfan syndrome. One patient (0.4%) had undergone previous cardiac surgery (aortic valve replacement).

Preoperative risk factors included shock in 52 patients (19.3%), cardiopulmonary arrest in 18 (6.7%), syncope (transient cerebrovascular accidents) in 31 (11.5%), hemiplegia in 6 (2.2%), paraplegia in 4 (1.5%), and leg ischemia in 32 (11.9%)(Table 1).

The operation was performed within 24 hours after the onset of symptoms in 222 patients (82.5%), and within 48 hours after the onset of symptoms in 237 (88.1%). The mean period between the onset of symptoms and operation was 30.5±70.0 hours. Operations were started as soon as possible after admission. A total of 239 patients (88.8%) were operated on within 4 hours after admission.

GRF glue was not used in 47 patients who had received operation from January 1990 through May 1995 (non-GRF group).

We started to use GRF glue in June 1995. GRF glue was used in all but 1 of 222 patients who received surgery of acute type A aortic dissection (GRF group). The patient in whom GRF glue was not used had Marfan syndrome and underwent root replacement.

Operative Technique

All patients underwent emergency operation on confirmation of the diagnosis. The surgery entailed resection of the aorta with the primary intimal tear, whenever feasible. Ascending aortic replacement or hemiarch replacement was performed during hypothermic circulatory arrest with or without retrograde cerebral perfusion. Total arch replacement was performed with the use of antegrade selective cerebral perfusion.

Proximal aortic reconstruction

The ascending aorta was transected about 5 mm above the aortic commissure.

Table 2. Prosthetic grafts

	Non-GRF group (n=47)		GRF group (n=222)		Total (n=269)	
	No.	%	No.	%	No.	%
UB	9	19.1	166	74.8	175	65.1
TORAY	31	66.0	28	12.6	59	21.9
Hemashield	2	4.3	28	12.6	30	11.1
Gelseal	5	10.6	0	0	5	1.9

UB (Ube Industries, Ltd., Ube, Japan); TORAY (Toray Medical Co., Ltd., Tokyo, Japan); Hemashield (Boston Scientific Corp., Natick, MA, USA); Gelseal (Vascutek Ltd., Glasgow, Scotland, UK).
GRF, gelatin-resorcinol-formaldehyde.

In the non-GRF group, root replacement was done in 10 patients (21.3%) with proximal dissection deeply extending to the right or left coronary cusps. In the other 37 patients, Teflon felt strips were placed on both the inner and outer surfaces of the aorta for reinforcement, using 3–0 polypropylene sutures. Aortic valve resuspension was done in 11 patients (23.4%).

In the GRF group, GRF glue was infused into the proximal false lumen after removing blood and clots to dry the lumen. The layers of the aortic wall were then compressed with clamps for 3 minutes. No Teflon felt strips were used for reinforcement. Aortic valve replacement was performed in one patient (0.5%) with aortic regurgitation caused by previous valvular disease. Aortic valve resuspension was not done in the other patients.

Distal aortic reconstruction

In patients undergoing ascending aortic or hemiarch replacement, Teflon felt strips were placed on both the inner and outer surfaces of the aorta for reinforcement, using 2–0 polyester sutures.

In patients who received total arch replacement, the elephant technique was used. A graft was inserted into the descending aorta, and a Teflon felt strip was placed on the outer surface for reinforcement, using 2–0 polyester sutures.

In the GRF group, GRF glue was used to reinforce the dissected aortic layers at the site of distal anastomosis in 119 patients (53.6%).

Graft replacement

A graft (Table 2) was anastomosed to the distal aortic stump with 4–0 polypropylene running sutures, and the proximal side of the graft was anastomosed to the proximal aortic stump with 4–0 polypropylene running sutures.

Indications for total arch replacement were intimal tears very close to the ostia of the neck arteries (brachiocephalic artery, left carotid artery, and left subclavian artery), intimal tears in the proximal part of the descending aorta, and young age. Concomitant procedures included coronary artery bypass grafting (CABG) in 20 patients (7.4%), atrial septal defect patch closure in 1 (0.4%), and abdominal aortic fenestration in 1 (0.4%).

Follow-up

The patients were followed up until July 2004 at the outpatient clinic or were contacted by phone. No patient was lost to follow-up. The mean duration of follow-up was 97.2±47.7 months in the non-GRF group and 53.8±30.3 months in the GRF group.

Statistical Analysis

The data were evaluated with Dr. SPSS II for Windows. Continuous data are expressed as means ± standard deviation. Actuarial survival and freedom from reoperation were estimated by the Kaplan-Meier method.

Results

Early results

The entry site was located in the ascending aorta in 124 patients (46.1%), in the transverse arch in 62 (23.0%), and in the descending aorta (retrograde dissection) in 83 (30.9%).

Root replacement was performed in 10 patients (21.3%) in the non-GRF group and in 1 (0.5%) in the GRF group ($p<0.0001$). Ascending aortic or hemiarch replacement was done in 24 patients (51.1%) in the non-GRF group and in 185 (83.3%) in the GRF group. Total arch replacement was performed in 13 patients (27.7%) in

Table 3. Causes of mortality

	Non-GRF group (n=47)		GRF group (n=222)	
	No.	%	No.	%
Operative mortality	**15**	**31.9**	**28**	**12.6**
LOS	8	17.0	8	3.6
Stroke	3	6.4	5	2.3
Hemorrhage	1	2.1	5	2.3
MOF	1	2.1	7	3.2
Necrosis of abdominal organs	2	4.3	3	1.4
Late mortality	**10**		**18**	
Reoperation	2		5	
Rupture of chronic dissection	1		3	
Rupture of aortic root necrosis	0		4	
Stroke	3		3	
IHD	0		1	
Pneumonia	2		0	
Cancer	1		1	
PVE	0		1	
Suicide	1		0	

LOS, low output syndrome; MOF, multiorgan failure; IHD, ischemic heart disease; PVE, prosthetic valve endocarditis; GRF, gelatin-resorcinol-formaldehyde.

the non-GRF group and in 36 (16.2%) in the GRF group.

Hypothermic circulatory arrest with or without retrograde cerebral perfusion was used in 34 patients (72.3%) in the non-GRF group and in 184 (82.9%) in the GRF group. Antegrade selective cerebral perfusion was done in 13 patients (27.7%) in the non-GRF group and in 38 (17.1%) in the GRF group.

The mean duration of operation was significantly longer in the non-GRF group (578±173 minutes) than in the GRF group (467±206 minutes, $p<0.01$). The mean duration of cardiopulmonary bypass was significantly longer in the non-GRF group (282±132 minutes) than in the GRF group (202±88 minutes, $p<0.01$). The mean duration of aortic cross-clamping was significantly longer in the non-GRF group (159±69 minutes) than in the GRF group (141±53 minutes, $p<0.05$).

The overall in-hospital mortality was significantly higher in the non-GRF group (15/47 patients, 31.9%) than in the GRF group (28/222 patients, 12.6%; $p<0.0001$).

The causes of in-hospital mortality are summarized in Table 3. The rate of mortality from low output syndrome was significantly higher in the non-GRF group (8/47 patients, 17.0%) than in the GRF group (8/222 patients, 3.6% $p<0.01$).

Late results

a. Late survival

Thirty-two patients in the non-GRF group and 194 in the GRF group survived and were followed up as outpatients. Ten patients in the non-GRF group and 18 in the GRF group died during follow-up. The causes of late mortality are summarized in Table 3. Survival rates for all patients 1, 3, 5 and 7 years after operation, including in-hospital mortality, were respectively 59.6±7.2%, 57.5±7.2%, 51.1±7.3% and 48.9±7.3% in the non-GRF

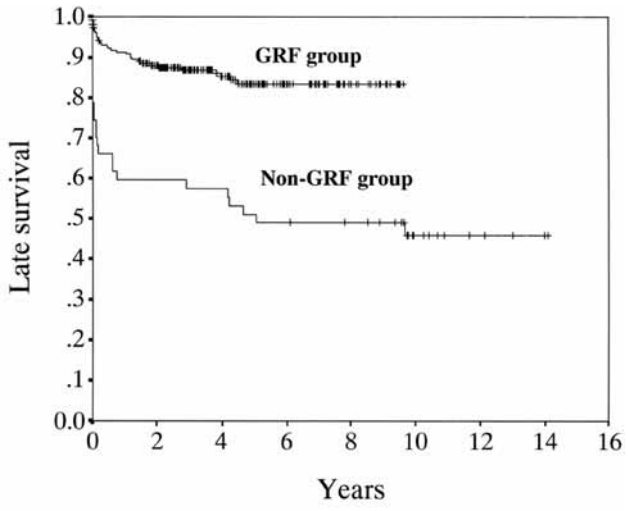


Fig. 1. Actuarial (Kaplan-Meier) survival rate (including hospital mortality) of patients operated on for acute type A aortic dissection.
GRF, gelatin-resorcinol-formaldehyde.

Table 4. Reasons for reoperations

	Non-GRF group (32 survivors)	GRF group (194 survivors)
	No.	No.
Aortic valve regurgitation	3	1
Aortic root necrosis	0	24
Chronic dissection		
Arch	5	8
Descending	2	13
Thoracoabdominal	2	1
Abdominal	3	1
Leg ischemia	0	1
Total	15	49

GRF, gelatin-resorcinol-formaldehyde.

group, as compared with 84.7±2.4%, 80.4±2.7%, 78.2±2.9% and 78.2±2.9% in the GRF group ($p< 0.01$)(Fig. 1).

b. Reoperation

During follow-up, 10 patients (31.3%) required a total of 15 reoperations in the non-GRF group, and 42 patients (21.6%) required a total of 49 reoperations in the GRF group. The reasons for reoperation are summarized in Table 4.

Actuarial freedom from reoperation at 1, 3, and 5 years was respectively 96.6±3.4%, 85.7±6.6%, and 74.5±8.3% in the non-GRF group, and 92.3±1.9%, 79.4±3.2%, and 70.5±4.2% in the GRF group (no significant difference).

The in-hospital mortality rate of the reoperations was 13.3% (2/15 reoperations) in the non-GRF group and 10.2% (5/49 reoperations) in the GRF group.

c. Aortic necrosis

In the non-GRF group, 2 patients (6.3% of survivors) received aortic valve replacement because of severe aortic regurgitation without aortic necrosis.

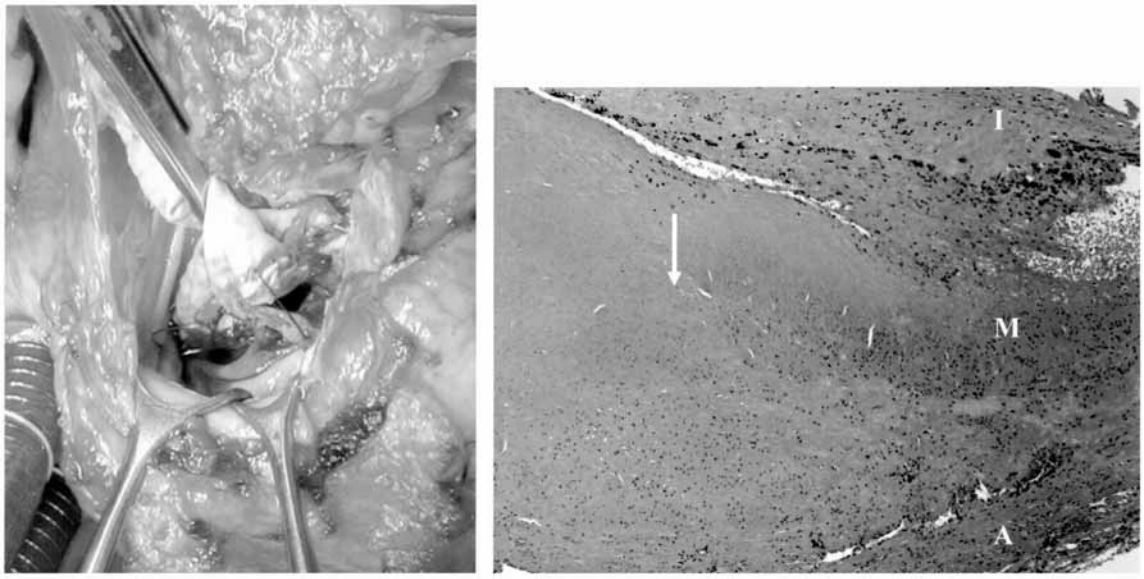
In the GRF group, false aneurysms at the aortic root, where GRF glue had been applied, were found in 31 patients (16.0% of survivors) 1–65 (mean 30±18) months after initial operation. In 8 of these patients, shock was the initial symptom of ruptured false aneurysms. Four patients did not have chances to undergo reoperations because of the state of cardiopulmonary arrest. Two patients refused reoperation, and one patient died due to stroke before reoperation. Reoperations were performed in 24 patients. Actuarial reoperation event-free rates for proximal aortic lesions in the GRF group were respectively 97.9±1.0%, 90.3±2.4%, and 78.9±4.0% 1, 3, and 5 years after initial operation.

Degeneration of the site in which GRF glue was applied at initial operation was found at reoperation. The anastomosis between the aortic root and prosthesis had opened widely, creating a false aneurysm and resulting in aortic regurgitation with prolapse of the coronary cusps (Fig. 2A). Macroscopically, the tissue to which GRF glue was applied had apparently undergone necrosis. Microscopic examination revealed medial degeneration and disappearance of the nuclei of medial smooth muscle cells, which were findings of necrosis (Fig. 2B).

Aneurysmectomy with reanastomosis was performed in 15 patients, and aneurysmectomy with aortic valve replacement (21- or 23-mm CarboMedics valve prostheses, CarboMedics Inc., Austin, TX, USA) was carried out in 3 patients. Six patients underwent aortic root replacement using composite graft prostheses made of 22- or 24-mm Hemashield grafts (Boston Scientific Corp., Natick, MA, USA) and 19- or 21-mm SJM hemodynamic plus (HP) valve prostheses (St. Jude Medical Inc., St. Paul, MN, USA) or 21- or 23-mm CarboMedics valve prostheses. Concomitant procedures included total arch replacement in 6 patients (25%) and CABG in 2 (8%). The mortality rate of reoperation was 4.2% (1/24). One patient went into shock due to a ruptured false aneurysm and died of low output syndrome.

Discussion

The surgical technique of choice for aortic root reconstruction in acute type A aortic dissection remains controversial. Aortic valve regurgitation caused by leaflet prolapse is a major complication of aortic dissection as-



A B

Fig. 2. Findings of aortic root necrosis.
A: Operative findings; The anastomosis between the aortic root and prosthesis had opened. Necrosis of the right and non-coronary cusps where GRF glue was used.
B: Microscopic findings; Nuclei of the medial smooth muscle cells have almost disappeared (arrow). (HE stain: ×40)
I, tunica intima; M, tunica media; A, tunica adventitia.

sociated with increased morbidity and mortality.[13,14] Root replacement with a composite graft may prevent the need for reoperation.[15,16] However, root replacement has additional risks associated with use of an aortic valve prosthesis and can lead to problems in patients with dissection involving the coronary ostia.

The Stanford group and others have advocated preservation of the aortic valve by resuspension, whenever possible.[13,17–22] However, operative mortality remains high, ranging from 20% to 30%.[19–21] Most operative mortality involves intraoperative hemorrhage and left ventricular pump failure.[19] This latter complication may be caused by residual blood flow in the false lumen of the aortic root.

In 1977, Guilmet's group first used GRF glue for aortic root reconstruction.[1] Since then, GRF glue has been used to repair all acute type A aortic dissections at their hospital. The use of GRF glue simplifies the operative procedure at the aortic root. GRF glue has therefore been widely used for the surgical repair of acute type A aortic dissection. Bachet et al. and others have assessed the benefits of using GRF glue.[3–7]

In our series, the rate of in-hospital mortality with GRF glue was 12.6%, significantly lower than the rate of 31.9% without GRF glue ($p<0.0001$). There might have been several reasons for decreasing mortality. First, and foremost, mortality from low output syndrome was only 3.6% in the GRF group, as compared with 17.0% in the non-GRF group. This lower mortality is ascribed to the fact that the use of GRF glue has simplified repair of the aortic root. The use of GRF glue might have been the primary reason. Secondly, we stopped performing aortogram prior to surgery in 1995, and we started operation as soon as possible after patients were admitted to our hospital. Thirdly is the method of cardiopulmonary bypass. Since 1995, in some patients we placed the arterial return at the axillary artery beside the femoral artery to avoid mulperfusion to the brain, abdominal organs or others. Fourthly, in 2000 we started to use sealed branched grafts for total arch replacement, which decreases the risk of bleeding more than previous grafts.

On the other hand, late complications possibly caused by toxic effects of GRF glue have been reported.[8–12] In 2001, Kazui et al.[10] reported that redissection of the aortic root developed in 4 (7%) of 57 patients who had undergone root reconstruction using biologic glue. Reoperation revealed dehiscence of the proximal suture line, the site

in which GRF glue was applied.

In our series, GRF glue was used in 221 patients. False aneurysms were found in 31 of 193 survivors (16.0%) 1–65 (mean, 30±18) months after surgery for acute type A aortic dissection. Redissection, dehiscence of the proximal suture line, and aneurysm formation may have been caused by toxic effects of GRF glue, because these complications and operative findings never occurred in aortic operations without GRF glue. Our findings suggest that the use of GRF glue is associated with an increased risk of potentially lethal complications. Such complications have been ascribed primarily to the use of excess formaldehyde. Only 2–3 droplets of formaldehyde, or even less, is considered sufficient to polymerize 1 ml of gelatin-resorcinol mixture.[23,24] We used a small syringe (Kanda Rubber Corp., Tokyo, Japan) to apply formaldehyde because too much formaldehyde might be toxic to the aortic wall. The syringe could add a small volume of formaldehyde to gelatin-resorcinol. One drop from the syringe was equivalent to about 0.04 ml. We added 3–5 drops (0.12–0.20 ml) of formaldehyde to 3–5 ml of gelatin-resorcinol. However, this small volume of formaldehyde might have had toxic effects on the aortic wall.

The reoperation rate of aortic necrosis in our series was higher than that reported by Kazui et al.[10] and Suehiro et al.[11] Several factors may underlie this discrepancy. First, the volume of formaldehyde used in our study might have been much greater than the other studies. Second, mean follow-up was longer in our study (53.8±30.3 months) than in Kazui's[10] (36.3±24.1 months) or Suehiro's[11] (34 months). Third, different types of grafts were used for operation: we used UB grafts (woven Dacron graft, porosity 50 ml/min/cm^2) in 74.8% of the patients in the GRF group (Table 2), whereas Kazui et al. used Hemashield grafts. (Suehiro et al. did not specify the type of graft used.) The mean period between initial operation and aneurysmal formation was 30 (1–67) months in our study, comparable to that of the other studies. During this period, the grafts are covered by surrounding connective tissue. The adhesive strength between the graft and the surrounding connective tissue may depend on the type of graft used. Such graft-tissue adhesion might be weaker with UB grafts than with Hemashield grafts. UB grafts may thus have a higher risk of false aneurysm formation after the onset of necrotic changes and dehiscence. In fact, we found that UB grafts were easily separated from the surrounding connective tissue on reoperation. In our series, the rate of reoperation for aortic necrosis was 21.1% (30/142 survivors) in UB grafts, as compared 0% (0/27 survivors) in those with Hemashield grafts and 4.0% (1/25 survivors) in those with TORAY grafts (woven Dacron graft, porosity 100 ml/min/cm^2). But, UB grafts must not have been the cause of aortic root necrosis. We have used UB grafts for 146 operations of degenerative or chronic dissectiong thoracic aneurysm without GRF glue and there was no patient who has undergone reoperation because of aortic wall necrosis or false aneurysm.

However, necrosis of sites in which GRF glue was applied might have occurred in all patients in whom GRF glue was used. The incidence of reoperation due to aortic necrosis in our series was so high that we discontinued using GRF glue and UB grafts in September 2003. Since October 2003, we have been using fibrin glue. We infuse fibrin glue into the proximal false lumen and place Teflon felt strips on both the inner and outer surfaces of the aorta for reinforcement, using 3–0 polyester interrupted mattress sutures. To date, we have used this method in 51 patients with acute type A dissection, with an in-hospital mortality rate of 11.3% (6/53 patients).

In 1994, Séguin et al.[25] reported on aortic valve repair with fibrin glue for acute type A aortic dissection. There was one non-valve-related early death (6.7%) and no late mortality. However, Casselman et al.[26] reported in 2000 that the use of fibrinous glue for root reconstruction may compromise the long-term durability of repair as compared with Teflon felt and GRF glue. Early results with fibrin glue have been satisfactory; however, long-term follow-up is necessary.

In 1992, David and Feindel[27] proposed a new strategy for aortic root repair in acute type A dissection, which avoided the use of a prosthesis (valve-sparing aortic root replacement). David et al.[28] and others[29,30] reported the results of valve-sparing aortic root replacement in acute type A aortic dissection. The in-hospital mortality rates were 10% (2/20 patients) and 9.1% (2/22 patients).[29,30] Valve-sparing aortic root replacement thus appears to have the potential to improve the outcome of surgery for acute type A aortic dissection. However, long-term observations are necessary to confirm initial findings.

In conclusion, the use of GRF glue improved the short-term outcome of surgery for acute type A aortic dissection, but was associated with a high incidence of false aneurysm formation at the site of proximal anastomosis, where GRF glue had been applied. Patients in whom GRF glue has been used should be carefully followed up after surgery.

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