Evolving Technology

Long-term effects in distal coronary anastomoses using different adhesives in a porcine off-pump model

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Objective: Adhesives are useful supplements to seal distal coronary anastomoses, particularly in patients who receive less-invasive coupling techniques. Information regarding long-term structural effects after application, however, is limited. The purpose of this large animal study was to examine the effects of 3 different commercially available surgical adhesives.

Methods: Twelve end-to-side anastomoses were created between the left internal thoracic artery and the left anterior descending coronary artery in a porcine beating heart model. Three different adhesives were applied externally and circumferentially to the anastomosis site. In group I (n = 4) gelatin-resorcinol-formaldehyde glue (Cardial, Technopole, Sainte-Etienne, France), in group II (n = 4) *n*-butyl-2-cyanoacrylate glue, and in group III (n = 4) albumin-glutaraldehyde glue were used. All anastomoses were examined intraoperatively by flow measurement. After 3 months the anastomoses were reassessed for patency and the vessels were evaluated histologically.

Results: By means of 4 stay sutures and subsequent glue application, anastomoses could be created successfully on the first attempt in all animals. Perioperative flow through the left internal thoracic artery was similar in all groups. In 4 animals an additional suture was placed to control bleeding. After 3 months, the patency rate was 83.3% (10/12). In group I all anastomoses were patent whereas in both groups II and III one anastomosis was occluded. None of the adhesives caused impaired vessel wall healing but they did demonstrate moderate-to-dense adhesions to the surrounding tissue. On histologic examination, gelantin-resorcinol-formaldehyde glue exhibited minimal tissue reaction (foreign-body granuloma) whereas *n*-butyl-2-cyanoacrylate glue showed moderate reaction. In contrast, albumin-glutaraldehyde glue caused severe inflammatory reaction with extensive fibroblastic proliferation.

Conclusion: Construction of an end-to-side internal thoracic artery–coronary artery sleeve anastomosis using adhesives was feasible in the pig. Among the tissue adhesives used in this study, gelantin-resorcinol-formaldehyde glue appeared to be superior to cyanoacrylate and albumin-glutaraldehyde glue. The latter one, however, caused severe adverse histologic effects and thus cannot be recommended for bonding coronary anastomoses.

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Truly minimally invasive access to the beating heart for coronary bypass surgery is a worthwhile goal. Various initiatives have already resulted in less-invasive incisions, such as mimimally invasive direct coronary bypass or even endoscopic or port-access approaches with or without remotely controlled

Abbreviations and Acronyms
AG = albumin-glutaraldehyde
CYAC = *n*-butyl-2-cyanoacrylate
GRF = gelatin-resorcinol-formaldehyde
ITA = internal thoracic artery
LAD = left anterior descending coronary artery
LITA = left internal thoracic artery

telemanipulators. The clinical success, however, varied. The necessity to perform a conventionally sewn coronary anastomosis under such constricted conditions has emerged as the major obstacle in using those very small apertures. Thus, a renewed interest in a simplified, timesaving, and reliable coronary artery anastomosis technique has emerged. To date, several strategies facilitating bypass construction have been described: stapling or mechanical coupling,[1] adhesive bonding,[2] and laser-assisted tissue welding.[3] Anastomosis construction by adhesives has the theoretical advantage of a fast, less complex method of facilitating vessels to bond accompanied by relatively simple delivery through small incisions. The use of biologic sealants has been promoted primarily on the basis of their ability to enhance coagulation in addition to their capacity to create a mechanical barrier at the site of bleeding. Synthetic glues have already become an attractive alternative to placement of additional sutures for controlling oozing from fragile and calcified vessels. Since 1964 these glues have been modified for clinical purposes and reported by Bachet and associates[4] to be effective in the surgical treatment of acute aortic dissection. Their adhesive properties also were confirmed experimentally by Albes and colleagues.[5] In this study, we compared 3 synthetic adhesives with regard to feasibility in constructing and sealing distal coronary anastomoses as well as proper healing and extent of tissue reaction in a long-term animal model: (1) gelatin-resorcinol-formaldehyde (GRF) glue, (2) albumin-glutaraldehyde (AG) glue, and (3) *n*-butyl-2-cyanoacrylate (CYAC) glue.

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Materials and Methods

Study

All experiments were performed with the use of juvenile white domestic pigs (38 ± 2 kg). The study was approved by the Animal Care and Use Committee of the Friedrich-Schiller University Jena. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" as revised by the National Institutes of Health in 1985. Twelve pigs were randomly assigned to 1 of 3 groups undergoing end-to-side sleeve anastomoses of the left internal thoracic artery (LITA) to the left artery descending coronary artery (LAD) in an off-pump coronary artery bypass model. In group I (n = 4) the anastomotic site was circumferentially covered with 2 mL of GRF glue (BARD, St Etienne, France), in group II (n = 4) 2 mL of AG sealant (BioGlue, Cryolife, Atlanta, Ga) was used, whereas group III was treated with 2 mL of CYAC glue (Glubran 2, Dahlhausen, Halberstadt, Germany).

Components and application methods. The gelatin-resorcinol mixture (GRF glue) is supplied in a tube and requires warming to 45°C before application. The polymerizing blend of glutaraldehyde and formaldehyde is provided in a glass vial. The blend is mixed with the gelatin-resorcinol component (3 drops to 1 mL of gelatin-resorcinol mixture) and thoroughly mixed with an applicator. Polymerization requires 1 to 2 minutes, resulting in an opaque product. BioGlue (AG) surgical adhesive is a proprietary compound that combines glutaraldehyde and concentrated bovine albumin with distinct properties. The compound does not become active until the two agents are mixed within the applicator tip and requires instant application before polymerizing to 65% holding power after 20 seconds. Glubran 2 (CYAC) is a new synthetic tissue adhesive in a "ready to use" applicator. It has better properties than previously available cyanoacrylate adhesives regarding elasticity and polymerization temperature. On contact with live tissue in a moist environment, it polymerizes rapidly to create a thin but elastic film of high tensile resistance, which guarantees firm adherence of tissues. Polymerization occurs at a temperature of 45°C so that there is no thermal damage to underlying tissues.

TABLE 1. Long-term results with visual histopathologic observation and evaluation

	GRF				AG				CYAC			
	1	2	3	4	5	6	7	8	9	10	11	12
Patency	+	+	+	+	−	+	+	+	+	−	+	+
Additional suture required	+	−	+	−	+	−	−	−	−	−	+	−
Stenosis	−	−	20%*	−	100%†	−	−	−	−	100%†	20%*	−
Histology												
Adhesive detectable	+	+	+	+	+	+	+	+	+	+	+	+
Inflammatory cells	−	+	−	−	++	+	++	+	+	−	+	+
Foreign-body granuloma	−	−	−	−	+	+	+	+	+	−	+	+
Scar tissue	+	−	+	−	++	+	++	+	+	−	+	+

Histologic findings are graded as follows: −, characteristics not found; +, isolated existing; ++, regular existing; +++, always existing. Causes of stenosis: *glue-dependent narrowing; †thrombus.

TABLE 2. Measurement of the perioperatively LITA–LAD flow (mL/min)

	GRF	AG	CYAC
1	50	62	51
2	58	43	47
3	48	51	42
4	39	37	57
Mean±SD	48.8 ± 7.8*	48.3 ± 10.8*	49.3 ± 6.3*

*P = not significant.

Operative technique and measurements. The animals were anesthetized with intravenous injection of 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol (Disoprivan 2% Emulsion, AstraZeneca, Germany) and bolus injection of 2 to 5 μg/kg fentanyl (Fentanyl-Janssen, Janssen Cilag, Neuss, Germany). Ventilatory support was established by intubation and connection to a respirator (Evita II dura, Dräger, Lübeck, Germany). Oxygen was supplemented to maintain an arterial oxygen saturation of 97%. The animals were placed in a supine position. After preparation, a 19-gauge detaining needle was inserted into the right internal carotid artery for blood pressure monitoring and blood gas analysis. A 4F catheter was placed into the right external jugular vein for measurement of central venous pressure and volume replacement. Full median sternotomy was performed and the LITA was harvested in a pedicled fashion. Before the internal thoracic artery (ITA) was severed, 400 UI/kg heparin was given and the heart was exposed by incising the pericardium. Lidocaine (Xylocaine, 100 mg) was administered to prevent fibrillation of the heart during preparation and metroprolol (7.5 mg) was given to reduce the heart rate from 120 to 70 beats /min. The mean arterial pressure was 72 ± 3 mm Hg. The midportion of the LAD artery far distal to the first diagonal branch was dissected and prepared for anastomosis in all animals. The distal segment of the LAD was dissected, prepared for anastomosis, and immobilized by a CTS tissue stabilizer (CTS, Cupertino, Calif) in all animals. The LITA was cut at an angle of approximately 45° and the LAD was temporarily occluded with tourniquets (4-0 Prolene, Ethicon Inc, Somerville, NJ), 1 cm proximal and distal to the anastomotic site, while the sleeve anastomosis was performed. No temporary intraluminal shunt was inserted and preischemic conditioning was not used before coronary artery occlusion. A longitudinal arteriotomy with a length of half the ITA circumference was performed by a diamond knife. First, a modified mattress stitch using a polypropylene 7-0 (Prolene) suture was placed at the toe and heel of the LITA and the coronary artery, slightly sleeving the ITA into the LAD. Thereafter, 2 mattress stitches were placed at the lateral walls of the anastomosis. While traction was placed manually on 2 adjacent sutures to stretch the intervening anastomotic segment, a simple on-site assembled air blower provided good visualization and allowed gentle removal of any excessive moisture before application of adhesive. Next, 2 mL of the different sealants was applied over the anastomotic line between the 4 stay suture lines. After adhesive polymerization, LITA graft flow was restored by first releasing the bulldog clamp on the ITA followed by release of the tourniquets. If substantial bleeding was encountered, it indicated that the LITA was not properly placed far enough into the coronary artery, and the anastomosis had to be redone. All anastomoses were performed by

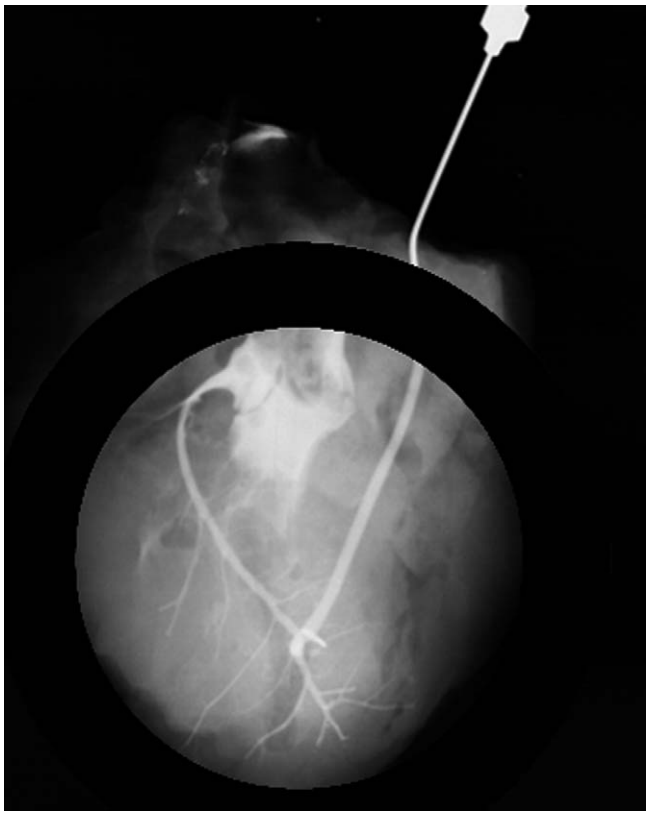

Figure 1. Three months after anastomosis, a representative angiogram shows a patent LITA-LAD anastomosis with no area of stenosis.

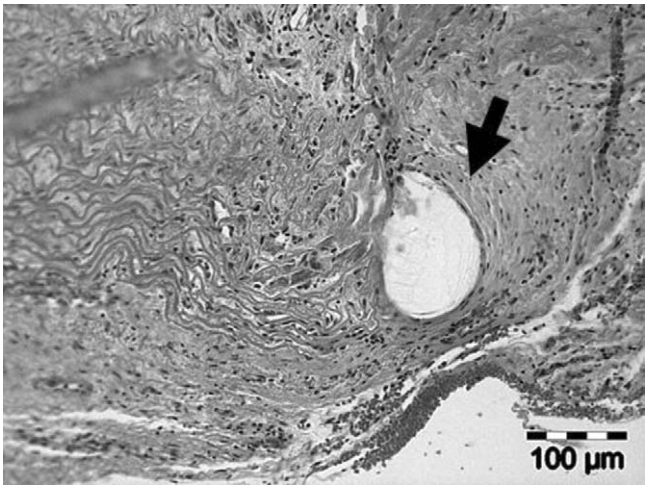

Figure 2. Microscopic section at the anastomotic site (hematoxylin-eosin stain). Erythrocytes are detectable at the luminal margin. Note the unexpected lack of inflammatory cells around the bubble *(arrow)* containing GRF glue.

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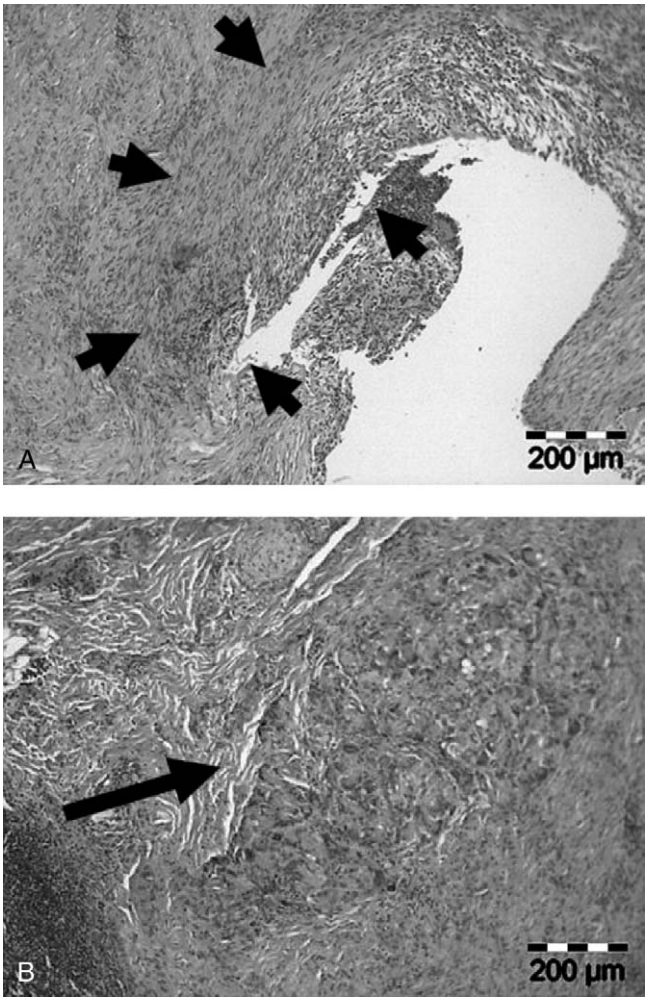

Figure 3. A, Photomicrograph of a paravascular abscess after AG application. A huge amount of leukocytes and giant foreign body cells are surrounding the cavity *(arrows)* as a result of a continuously ongoing inflammatory reaction. B, Histologic section showing a detailed magnification of a giant foreign-body cell *(arrow)* after AG application.

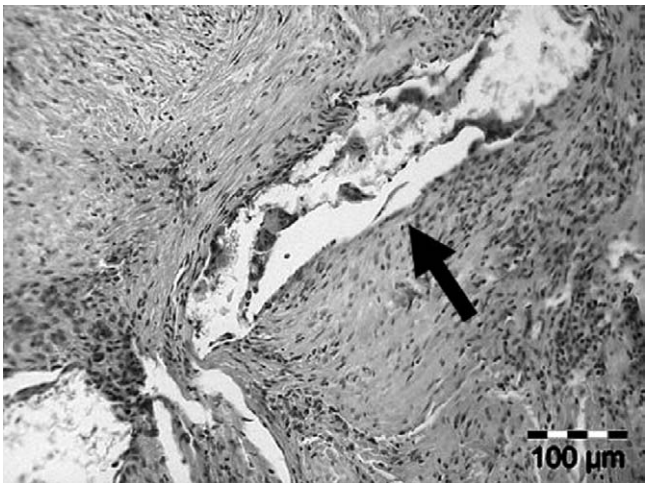

Figure 4. Photomicrograph showing a deposit of cyanoacrylate glue *(arrow)* with moderate inflammatory reaction, mainly caused by lymphocytes.

one investigator. After construction of the end-to-side anastomosis, protamine was given and patency was controlled by measurement of LITA flow (MediStim AS, Oslo, Norway) at a mean blood pressure of 70 mm Hg. After chest closure, all animals were allowed to grow for 3 months in a stable with free access to food and water and were then humanely killed by injection of pentobarbital (Narcoren, Merial, Germany).

Angiography. After the animal was killed, the heart was harvested and the anastomosis was visualized by ITA angiography. A 20-mL dose of iopromid (Ultravist, Schering, Berlin, Germany) was injected and cut film images were obtained, which were later graded by an independent radiologist.

Histology. After angiography, the heart was perfused for 30 seconds with a papaverine-saline solution (5 mg/mL) and perfusion-fixed for more than 30 minutes at 80 mm Hg with 4% formalin at a low perfusion rate. Subsequently, the anastomotic and reference segments (proximal LAD and ITAs) were excised, formalin-fixed overnight, embedded in paraffin, cut at 5-μm intervals, and inspected under the dissecting microscope to detect any intraluminal thrombus formation. The anastomosis and reference segments were sectioned in the transversal plane and were stained with hematoxylin-eosin. Light microscopy was used to identify intravascular glue formation, inflammatory foreign body reaction, or aneurysm formation. The analysis was performed by an independent pathologist in a blinded fashion, who graded the findings (Table 1): −, characteristics not found; +, isolated existing; ++, regular existing; +++, always existing.

Statistical analysis. Data were collected in a computerized database (Excel for Windows, Microsoft Inc, Redmond, Wash). Flow measurement data were expressed as mean ± SD. Differences between the groups were analyzed by a paired *t* test using SPSS for Windows statistical software package (SPSS, Inc, Chicago, Ill).

Results

All animals survived in each group throughout the experiment. LITA-LAD anastomoses were successfully constructed in 12 animals without the need for cardiopulmonary bypass. The mean time taken to perform the anastomoses was 8.8 minutes (range 5-17 minutes). Immediate hemostasis was obtained in 3 pigs (40%) in which CYAC adhesives were used. Five anastomoses showed minor oozing, which ceased within a few minutes after protamine. In 4 animals an additional 7-0 Prolene suture was placed (2 GRF; 1 AG; 1 CYAC) to control bleeding. All 12 anastomoses were patent after the release of the LITA bulldog clamp with good ITA flow in all groups (Table 2). The scheduled follow-up was completed by all animals, and their weight

increased to 65 ± 6 kg. Angiography at day 120 showed 10 anastomoses patent (Figure 1). One occluded vessel was found in both groups II and III. Aneurysmal dilatation was not observed in any animal. The histologic examination (Table 1) revealed in group I that GRF particles had not been absorbed but were entirely surrounded by a capsule-like formation (Figure 2). AG, in contrast, provoked a severe inflammatory reaction in all animals. Remaining glue was surrounded by a dense population of polymorphonuclear leukocytes or lymphocytes, which resulted in one instance in the development of a new pseudocystic cavity (Figure 3, *A* and *B*). Foreign-body giant cells were demonstrable in every animal and a great extent of scar tissue was also detectable. The inflammatory potency of CYAC was moderate, ranging between GRF and AG. Still present particles of adhesive were inducing an infiltration of lymphocytes and histiocytes, but foreign-body cells were rarely found (Figure 4). Fibroblastic ingrowth was less often present than in the AG group.[6-26]

Comment

The development of alternative means to construct graft-to-coronary anastomoses is characterized by a reduction of technical demand. Werker and Kon[6] reviewed different approaches to construct vascular anastomoses. Tissue approximation by stapling was introduced as early as 1908, when a stapling device for distal gastrectomy was presented. In the late 1940s, a group of Russian engineers and physicians developed a method of constructing end-to-end anastomoses for vascular surgery with a circular stapler. One has to distinguish 3 categories of approaches: anastomotic devices using micromechanical connectors, laser-assisted vascular anastomosis techniques, and adhesive bonding of donor and recipient vessel.

A clinical potential could already be demonstrated with 2 different proximal anastomotic devices.[7,8] Distal anastomotic devices, on the other hand, are only just about to emerge in clinical practice.[9] However, the results are inconsistent[10] and long-term results are not yet at hand with both approaches. Incorporation of artificial material into the anastomosis coming in contact with the bloodstream is an inherent necessity of many of these devices. On the other hand, automated "sewing" devices can only be used for end-to-side vein grafts because the graft must be mounted on the apparatus.[9] None of the mechanical coupling devices readily adapt to the varying individual anatomy of a respective coronary vessel.[10,11]

The idea of using tissue adhesives for vascular surgery is attractive and has therefore resulted in a considerable series of publications.[4,7,12-15] There is substantial evidence that biologic adhesives have a positive impact on the results of cardiovascular operations by shortening operation time, reducing perioperative bleeding, and providing more suitable tissue consistency for successful operative repair.[12,13] Some adhesives such as the polyethyleneglycol sealant Co-Seal (Cohesion Technologies, Palo Alto, Calif) were even evaluated to reduce postcardiotomy adhesions.[14] Obviously, the selection of a specific glue depends on several factors, including availability, hemostatic efficacy, mechanical properties, effects on wound healing, and finally inflammatory response.

Initial work with GRF glue, also called "French glue," was first performed in 1965. After extensive experimental work, the GRF glue was used for the first time in the clinical arena by Guilmet and colleagues[15] in 1979. Originally developed as a hemostatic agent in hepatic and renal operations, its most prevalent application has been in cardiovascular operations. Porcine gelatin as one of the components of the glue contains adhesive properties. Although some ambiguity remains as to its mechanism of action, it is postulated that hydrogen bonding between the cross-linked gelatin may be one of the factors responsible for its adhesive properties. Resorcinol as the second component of this adhesive improves moisture resistance of the final product because it rapidly forms a polymer with formaldehyde. While numerous authors have lauded the use of GRF glue in demanding cases, especially in acute aortic dissection,[4,16] some reports have noted late complications in the form of false aneurysm attributed to tissue toxicity and necrosis.[17,18] Interestingly, cellular toxicity as the underlying reason for these adverse effects could not be confirmed by our results. Although GRF was not used for aortic dissection in our experiment, tissue reaction of the bonded anastomoses was low after 3 months. Animal studies by Gundry, Black, and Izutani[2] looking at the effect of AG glue in coronary anastomosis in goats showed minimal inflammation at 3 months. However, we and others[19] noted considerable toxicity of the surrounding tissue in anastomoses bonded with AG. This was in fact an unexpected result as AG is considered to represent the next evolutionary step of aldehyde-based adhesives, showing identical bonding capacity while exhibiting enhanced stabilization of friable tissues accompanied by reduced local toxicity. At present, we do not have a sound explanation for this particular finding. The manufacturer merely suggests that caution should be used in applying AG in the vicinity of nerves as the glutaraldehyde component may cause toxic effects. In our opinion, the issue of late toxicity and scarring must always be taken into account, although our animal study showed an absence of tissue necrosis and very modest inflammatory response at 3 months with one of the investigated adhesives. Recent clinical articles[20,21] reported on patients after aortic surgery utilizing AG who had to undergo reoperation. Very much in contrast to preclinical histologic studies, dense fibrosis and significant acute inflammation with foreign-body giant cells were reported in

these cases. We hypothesize that the rather low antigenicity of polymerized gelatin[22] may serve as an explanation of why GRF glue appears to be superior to AG adhesive in terms of inflammatory response.

The application of cyanoacrylate adhesives to the medical field had already begun in the sixties. In the area of vascular surgery, it was primarily used for direct closure or repair of arterial incisions. Regarding applications to the anastomosis of blood vessels, all reports focused on the anastomosis of blood vessels in the living body. In addition, cyanaoacrylate adhesives were used as an auxiliary after placement of several stay sutures.[23] The resulting complications of cyanoacrylates were mainly bleeding in the early stages and aneurysmal dilatation in the later stages.[24] In our experiment, massive bleeding did not occur; on the contrary, immediate hemostasis was obtained in 3 of 4 animals in this group. Jacobson and coworkers,[25] who applied CYAC to the anastomotic line of blood vessels of mongrel adult dogs, initially reported necrosis rapidly involving the entire media of the vessel. After 3 months, the necrotic media had been completely replaced by fibrous tissue. Thermal injury was considered to cause these effects as cyanoacrylate polymerizes in an exothermic reaction.

Fibrinogen plays an important role during the healing process of injuries by forming fibrin nets, which have adhesive properties. Fibrin glue was therefore developed to mimic these reactions and to serve as a sealant. A large number of publications have already addressed the multiple benefits of fibrin glue in cardiovascular surgery. The bonding properties of fibrin glue, however, are weak, especially under wet conditions. Thus, after completion of a vascular anastomosis, it is mainly used in an auxiliary fashion to prevent oozing from suture line perforations. In a previous study,[5] we could already demonstrate the biophysical properties of 3 clinically used adhesives (cyanoacrylate, gelatin-resorcine-glutar/formaldehyde adhesive, and fibrin glue). While both cyanoacrylate adhesive and gelatin-resorcine-aldehyde glue demonstrated sufficient bonding power, fibrin glue failed to show any reasonable tensile strength. As a consequence, fibrin glue was not considered to serve as an adequate adjunct for the construction of a sutureless anastomosis in a high-pressure field such as the coronary system. The selected adhesives in this study included 2 biologic and 1 synthetic glue for bonding distal coronary anastomoses, which are currently used in clinical practice. Furthermore, our intention was to use the smallest possible number of sutures. Four stay sutures appeared to be sufficient to maintain the desired oval shape of the anastomosis. It is not entirely unlikely that a certain number of stay sutures or clips will become an appropriate measure in the clinical setting to optimize shape and positioning of the anastomosis before bonding and to simply serve as a safeguard.

We observed that an even application of not more than 2 mL of adhesive around the anastomotic line best served that purpose. In contrast, it was our impression that a surplus of adhesive simply resulted in an unyielding rigid ring around the coronary anastomoses, which failed to adapt and led to late stenosis. We observed this phenomenon in 2 cases, resulting in a narrowing of the ITA lumen (Table 1). Hemostasis was achieved within 2 to 3 minutes in all groups, and the hemostatic action tended to occur preferentially on a dry surface rather than on a wet or bloody surface; therefore, it was advisable to use an air blower to remove blood before applying the glue on the surfaces. The reabsorption rate of all adhesives was very slow. On re-exploration after 3 months, fragments of the glue were detected that promoted moderate adhesions in all animals. The observed occlusions were probably due to thrombosis most likely caused by adhesive leaking into the lumen. Subsequent microscopic examination revealed fibroblastic proliferation, especially when AG and CYAC were used. Our observation was confirmed by Braunwald, Gay, and Tatooles,[26] who reported residual glue with fibroblast infiltration even after 6 months. In our experiment, inflammatory reactions around the anastomotic line were also observed at the end of 3 months, but scar tissue was only isolated, detectable in the media layer. We believe the lower temperature during polymerization at 45°C by using Glubran 2 might be an explanation.

The principal findings of our study were as follows: First, the anastomosis technique was effective in producing stay suture–assisted coronary artery anastomoses capable of withstanding normal porcine blood pressure; second, GRF glue deserves interest for bonding anastomoses because it is much less histotoxic than AG adhesive. Moreover, our in vivo study suggests that bonded anastomoses can be patent more than 3 months after construction without showing aneurysmal formation indicating weak anastomotic areas.

Limitations of the Study

The current experiment was small in number and limited to a 3-month follow-up in the porcine model. The feasibility of this technique in the small-caliber human atherosclerotic coronary artery remains to be established. Further work is needed to delineate the patency rates and the histiologic reaction of the vessels and surrounding tissue beyond 120 days and to characterize the biomechanical properties, such as tensile strength and pliability in the vessels, before clinical application can commence.

At present, there are very few reports about long-term effects in bonded coronary anastomoses comparing sealants in a comprehensive fashion. In our study, however, we found a satisfactory patency rate of 83%. It therefore appears to be possible to perform sutureless coronary anasto-

moses with the use of adhesives. On the basis of the results of our study, we suggest that in terms of bonding power *and* biocompatibility GRF glue should be used to construct a sutureless coronary anastomosis. Further studies are warranted to verify the impact of tissue reaction regarding true long-term patency. A first step toward a truly minimally invasive sutureless distal coronary anastomosis, however, has been taken.

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