Unconventional vessel wall apposition in off-pump porcine coronary artery bypass grafting: Low versus high graft flow

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Objective: Facilitated coronary anastomosis techniques may involve unconventional vessel wall apposition in contrast to standard intima-intima apposition. We assessed the patency, anastomotic thrombus formation, and intimal hyperplasia of unconventional intima-adventitia apposition versus conventional suturing techniques in beating heart coronary bypass grafting under low versus high graft flow conditions.

Methods: The intima-adventitia (n = 28) and conventional anastomoses (n = 28) were evaluated intraoperatively (n = 56), at 4 hours (n = 20), and at 5 weeks (n = 36) in a new off-pump low-flow (n = 28) and high-flow (n = 28) porcine bypass model (≤ 15 mL/min and about 60 mL/min, respectively). The anastomoses were assigned to the animals by means of randomized stratification and examined by means of flow measurements, angiography, and histology.

Results: Mean graft flows in intima-adventitia and in conventional anastomoses were similar ($P = .709$). All but 1 of 56 anastomoses (low flow conventional) were fully patent at the time of death. At 4 hours, only small platelet depositions were found at the exposed media and adventitia in the unconventional anastomoses. At 5 weeks, little streamlining intimal hyperplasia was found, which was comparable between the anastomoses ($P = .600$).

Conclusions: In low-flow conditions (≤ 15 mL/min) unconventional intima-adventitia apposition was not detrimental to the internal thoracic–coronary artery anastomosis in the pig. This finding may expand design strategies of facilitated coronary artery bypass anastomosis techniques.

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In off-pump and endoscopic coronary bypass surgery, there is a need for a simple, timesaving, and reliable facilitated distal anastomosis procedure to replace the technically demanding manual suturing process.^{1,2}

Facilitated coronary anastomosis techniques may involve unconventional vessel wall apposition in contrast to the current surgical practice of intima-intima (I-I) apposition in conventional suturing. Despite media exposure, adventitia exposure, or both, to blood in some microvascular anastomotic techniques, their patency rates and healing responses were comparable with the conventional technique.³⁻⁵ Alternative wall apposition, however, has been evaluated both clinically⁴ and experimentally^{3,5} under high or normal anastomotic flow (ie, shear-stress conditions). We hypothesized that the patency rate of unconventional apposition techniques in coronary bypass surgery will be reduced when the bypass graft flow is lowered.

Therefore, we have developed a porcine model in which relatively low and high internal thoracic coronary artery bypass graft flow conditions can be simultaneously established. Our objective was to assess the patency, anastomotic thrombus formation,

Figure 1. Schematic drawing of the beating porcine heart low and high bypass graft-flow model. 1, The midsegment of the LAD was ligated with 2 medium Atraumacclips to create the distal low-flow bypass. 2, The main stem of the LAD was occluded with an aneurysm clip to include the circumflex territory (CX) in the high-flow bypass.

and intimal hyperplasia of unconventional intima-adventitia (I-A) apposition versus conventional suturing techniques in beating heart coronary bypass grafting under low- versus high-flow conditions in the internal thoracic artery (ITA) graft.

Materials and Methods

Animals

Thirty-two Dutch female Landrace pigs (weighing 70-80 kg) were used. The animals were fed a normal diet and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press (revised 1996) and were approved by the Animal Experimentation Committee of the Utrecht University. All animals received 560 mg of acetylsalicylic acid orally 1 day before surgical intervention.⁵ This was continued in a dose of 160 mg per day until death.

Anesthesia

Anesthesia was induced with ketamine (10 mg/kg) intramuscularly. Each animal received thiopentalnatrium (4 mg/kg), atropine (1 mg), and antibiotic prophylaxis (500 mg of amoxicillin [INN: amoxicilline]) through an intravenous line. The animals were intubated and ventilated. Anesthesia was maintained by supplying a mixture of oxygen and air (1:1 vol/vol) with 0.5% to 1% halothane added and by a continuous intravenous infusion of midazolam (0.3

mg · kg⁻¹ · h⁻¹). Analgesia was obtained with an infusion of sufentanilcitrate (1 μg · kg⁻¹ · h⁻¹) and muscle relaxation with pancuronium (0.1 mg · kg⁻¹ · h⁻¹). During the operation, each animal received a continuous infusion of saline solution (300 mL/h). Propranolol was administered intravenously (range, 10-25 mg) to reduce the mechanical irritability of the heart until a heart rate of less than 70 beats/min was obtained.

Postoperatively, antibiotic amoxicillin trihydrate (15 mg/kg) was administered, and analgesia was obtained with buprenorphine (0.6 mg) intramuscularly for 3 days.

Animals were put to death with pentobarbitalnatrium (200 mg/kg) intravenously after having been heparinized to obtain an activated clotting time (ACT; Hemotec, Inc, Englewood, Colo) of at least 4 times the control value.

Surgery and Experimental Model

After a partial median sternotomy, both the left and right ITA were harvested in a skeletonized fashion until sufficient length had been obtained. The animal was heparinized intravenously (150 IU/kg) to obtain an ACT of twice the control value. The ACT was determined at 0, 5, 60, 90, and 120 minutes after injection until the end of the procedure. The heparin was not counteracted at the end of the procedure. Both distal ITAs were dissected and sprayed with a papaverine-saline solution (5 mg/mL) to prevent spasm, and the vessel half circumference was measured with a caliper. The pericardium was opened, and its edges were suspended.

The distal segment of the left anterior descending artery (LAD) was immobilized with the Octopus 2 Tissue Stabilizer (Medtronic, Inc, Minneapolis, Minn)⁶ and dissected free. Loose periadventitial tissue at the anastomotic site was carefully removed, and the outer vessel diameter was measured. Under the microscope (magnification 12.5×; Wild M680; Leica AG, Heerburg, Switzerland), the distal end of the right ITA was cleared of loose periadventitial tissue and cut at an angle of about 45°. Preconditioning was achieved by means of 5 minutes of stop-flow ischemia with a microvascular Acland clamp (B-3V; S&T Marketing Ltd, Neuhausen, Switzerland) and reperfusion for 5 minutes. After reclamping, a standardized longitudinal slit arteriotomy of about 3.5-mm length was performed with a diamond knife, and the right ITA-LAD anastomosis (distal bypass) was constructed. After restoration of graft flow, the proximal anastomotic procedure (left ITA-LAD) was performed in the same way, but the anastomotic toe was positioned toward the proximal end (Figure 1).

All end-to-side anastomoses were constructed under 12.5× magnification with a running polypropylene 8-0 suture (Ethicon, Inc, Somerville, NJ). In the I-A anastomoses the stitches were placed through the ITA graft and intramurally through the adventitia and media of the LAD, leaving a vessel wall rim (coronary adventitia and media) of approximately 0.2 mm inside the anastomotic orifice (Figure 2). In the I-I anastomoses the stitches were placed conventionally.

After construction of the 2 anastomoses (midsegment of the LAD between the proximal and distal anastomoses occluded with an Acland clamp), the main stem of the LAD was permanently occluded with an aneurysm clip (Yasargil-type, curved, 9 mm; Scanlan International, Inc, Saint Paul, Minn). By this means, the circumflex territory was included in the proximal anastomosis (high-flow bypass). Next, the midsegment of the LAD was ligated

with 2 medium Atraumacclips (Pilling, Inc, Fort Washington, Pa). The clips were positioned sufficiently distally to create a distal bypass graft flow of maximally 15 mL/min at a mean blood pressure of 90 mm Hg (low-flow bypass), thereby determining also the flow over the high-flow bypass (Figure 1).

Each animal was randomly assigned to one of the following combinations of anastomoses: (1) low-flow I-A plus high-flow I-A; (2) low-flow I-A plus high-flow I-I; (3) low-flow I-I plus high-flow I-A; and (4) low-flow I-I plus high-flow I-I. The experiment was completed in 28 animals. The animals were evaluated intraoperatively ($n = 28$ animals; 28 I-A and 28 I-I anastomoses; 14 low-flow and 14 high-flow anastomoses), at 4 hours ($n = 10$ animals), and at 5 weeks ($n = 18$ animals).

Intraoperative and Postoperative Measurements

After completion of the anastomoses and stabilization of flow, mean ITA flow was measured with a calibrated transit time flow probe (3S) connected to a flowmeter (model T208; Transonic Systems, Inc, Ithaca, NY) and recorded at a mean blood pressure of 90 mm Hg. After clamping of the ITA for 30 seconds, the coronary peak hyperemic response was determined as the ratio of the peak mean graft flow divided by the mean baseline flow. The hyperemic response was measured at a mean blood pressure of 90 mm Hg in duplicate at an interval of at least 10 minutes, both after anastomosis construction and at follow-up (5 weeks). Preceding closure, ITA flows were monitored continuously for up to 4 hours to observe any cyclic flow reductions caused by repetitive thrombus formation and distal embolization.^{5,7}

Angiography

After death, the anastomoses were visualized in all animals by means of ITA angiography ex vivo (C-arm BV27; Philips, Eindhoven, The Netherlands) and graded by an independent observer according to the method of Fitzgibbon and colleagues.⁸

Histology

All arteries were perfused at a low perfusion rate (15 mL/min) with agarose 2% (SeaPlaque; FMC BioProducts, Rockland, Me) to preserve anastomotic geometry. After overnight fixation in formalin 4%, the anastomotic segments were excised and longitudinally cut open (4 hours group) and inspected under the dissecting microscope to detect any intraluminal thrombus formation. The segments were subsequently embedded in paraffin and sectioned in the longitudinal plane (3 adjacent midline longitudinal sections at $\pm 100\text{-}\mu\text{m}$ intervals). The sections were stained with hematoxylin-and-eosin and van Gieson elastin stain.

In van Gieson elastin-stained sections at 4 hours, the presence of an intraluminal thrombus, mural thrombus, or both, at the anastomotic orifice was recorded, the accuracy of the vessel wall appositions were described, and the outline of the intraluminal vessel wall rim (in millimeters) was assessed with use of the software package AnalySiS (Soft-Imaging Software GmbH, Münster, Germany). At 5 weeks, mean values of intimal hyperplasia (in square millimeters) at the toe or heel were calculated in the van Gieson-stained sections by using the software package AnalySiS. The area enclosed by the luminal border and the internal elastic lamina adjacent to the suture line in the thoracic grafts, and LAD was defined as intimal hyperplasia.

Figure 2. A, Schematic drawing of the unconventional I-A suturing technique. B, Schematic drawing of longitudinal section of the I-A anastomosis, demonstrating the vessel wall rim (coronary adventitia and media) of approximately 0.2 mm inside the anastomotic orifice.

Statistical Analysis

Data are presented as means $\pm$ SD or as medians and 15th to 85th percentiles. Because of dependency in the data caused by the fact that each animal received a low- and high-flow anastomosis, the Linear Mixed-Effects Model⁹ was used to compare means with use of software package S-PLUS (Insightful, Inc, Seattle, Wash). In case of interaction, main effect and interaction effects are reported. When no dependencies were present, analysis of variance was used.

Results Surgery

All anastomoses were performed by one investigator (M.P.B.). The anastomosis groups (eg, low-flow I-A and low-flow I-I) and operative data are given in Table 1. The

TABLE 1. Operative data

	Anastomotic surgery time (min)	Coronary occlusion time (min)	Length of arteriotomy (mm)	No. of suture bites	ITA outer diameter (mm)	LAD outer diameter (mm)
Low flow I-A	11.4 ± 1.5	12.8 ± 2.0	3.5 ± 0.1	11.3 ± 0.9	2.2 ± 0.3	2.8 ± 0.5
	$P = .0002$	$P = .0006$		$P = .002$		
I-I	8.9 ± 1.5	10.0 ± 1.7	3.5 ± 0.0	12.6 ± 1.2	2.1 ± 0.2	2.8 ± 0.4
					$P = .033$	$P = .002$
High flow I-A	10.9 ± 1.5	11.7 ± 1.7	3.6 ± 0.2	11.6 ± 0.8	2.3 ± 0.3	3.3 ± 0.5
	$P = .0002$	$P = .0006$		$P = .002$		
I-I	9.3 ± 1.7	10.4 ± 2.1	3.6 ± 0.2	12.5 ± 1.0	2.4 ± 0.4	3.3 ± 0.5

Data are presented as means ± SD (n = 56 anastomoses [28 animals]).

TABLE 2. Intraoperative and postoperative measurements and angiography

		ITA graft flow (mL/min)					Coronary peak hyperemic response		Patency	
		n = 10*		n = 18*			n = 28*		n = 18*	
		Intraoperative	4 h	Intraoperative	2 h	5 wk	Intraoperative	5 wk	4 h	5 wk
— $P < .0001$ § —										
Low flow	I-A	9 ± 3	13 ± 8	9 ± 3	10 ± 4	12 ± 6	6.4 (5.4-8.0)	2.4 (1.8-6.7)	5/5	9/9
	I-I	10 ± 2	13 ± 5	10 ± 3	12 ± 4	14 ± 8	6.2 (4.8-6.8)	3.4 (2.1-6.7)	5/5	8/9
$P < .0001$ †										
High flow	I-A	70 ± 15	75 ± 28	75 ± 13	81 ± 19	59 ± 12	2.6 (2.3-3.4)	4.8 (2.6-6.8)	5/5	9/9
	I-I	52 ± 4	85 ± 52	57 ± 8	74 ± 19	57 ± 10	3.2 (2.9-3.4)	4.4 (3.0-5.0)	5/5	9/9

Coronary peak hyperemic response as mean of duplicate measurements is presented as median (15th-85th percentile). Patency is graded according to the method of Fitzgibbon and coworkers (grade A). Occluded low-flow I-I anastomosis was excluded from analysis at 5 weeks. Because of imperfect occlusion of midsegment LAD, one animal (low-flow I-I and high-flow I-A) was excluded from hyperemic response analysis. *Intraoperative*, After stabilization of flow after completion of anastomosis.

*Number of animals.

†Intraoperative and at 4 hours.

‡Intraoperative, at 2 hours, and at 5 weeks. Interaction flow/anastomosis and flow/follow-up ($P = .020$ and $P = .022$, respectively).

§Interaction flow/follow-up ($P < .0001$).

operative data were comparable between groups apart from the ITA and LAD outer diameter (which was less in the more distally positioned low-flow compared with the high-flow anastomoses, Figure 1) and specific I-A/I-I procedure-related parameters (Table 1).

In 17 animals no ventricular arrhythmias other than occasional premature ventricular beats were observed during the operative procedure. In 7 animals ventricular fibrillation occurred during coronary preconditioning or the anastomotic procedure, and in 8 animals ventricular fibrillation occurred on reperfusion or during main stem occlusion. All 15 animals were successfully managed by means of electrical defibrillation.

Two animals died during the operative procedure because of iatrogenic rupture of the main stem during ligation.

The ACT at 0 minutes, during the anastomotic procedure and at 240 minutes after administration of heparin was 96 ± 10 , 221 ± 38 , and 116 ± 21 seconds, respectively. During

the anastomotic procedure, the ACT was slightly different but, at 240 minutes, was comparable between the anastomosis groups ($P = .085$ and $P = .327$, respectively).

Follow-up

The scheduled 5-week follow-up was completed by 28 animals. One animal (low-flow I-I plus high-flow I-A) suddenly died on postoperative day 1 of an unknown cause. One other animal (low-flow I-A plus high-flow I-I) died of mediastinitis on day 13. In both animals the anastomoses, examined by means of angiography and histology, were fully patent.

All anastomoses were patent at 4 hours and 5 weeks, except one low-flow conventional anastomosis that was occluded at 5 weeks. Because of a technical error during its construction, loose periadventitial tissue of the LAD had not been removed.

Before death, no myocardial infarctions or wall motion disturbances were noted.

At 5 weeks, the weight of the animals had increased from 72 ± 5 to 78 ± 7 kg. The increase was slightly different between the anastomosis groups ($P = .092$).

Intraoperative and Postoperative Measurements

As intended, the intraoperative mean ITA flow was 10 ± 3 mL/min in the low-flow anastomoses compared with 64 ± 14 mL/min in the high-flow anastomoses. The intraoperative hyperemic response was 6.3 (15th-85th percentile, 5.1-7.3) in the low-flow group compared with 3.0 (15th-85th percentile, 2.4-3.4) in the high-flow group ($P < .0001$).

Compared with the intraoperative situation, ITA flows were only slightly different at 4 hours ($P = .086$) and were comparable at 5 weeks ($P = .329$, Table 2). At death, the hyperemic response was 2.6 (15th-85th percentile, 1.8-6.8) in the low-flow anastomoses and 4.5 (15th-85th percentile, 2.7-5.1) in the high-flow anastomoses.

Only small differences in flow (4 ± 4 mL/min in the low-flow group and 17 ± 15 mL/min in the high-flow group) were noted between the I-A and I-I anastomoses ($P = .709$, interaction flow/anastomosis; $P = .020$; ie, the flow difference between the low-flow I-A and low-flow I-I anastomoses [4 ± 4 mL/min] differed from that in the high-flow group [17 ± 15 mL/min]; interaction flow/follow-up; $P = .022$; ie, the flow difference between the low-flow anastomoses intraoperatively and the low-flow anastomoses at follow-up differed from that in the high-flow group; Table 2). The hyperemic response was similar in I-A anastomoses (4.1 [15th-85th percentile, 2.4-7.1]) and in I-I anastomoses (4.0 [15th-85th percentile, 3.0-6.6]).

No cyclic flow reductions were observed during flow monitoring after anastomosis construction.

Angiography

At death, 55 of 56 anastomoses were fully patent (grade A, Figure 3); one low-flow I-I anastomosis was occluded (Table 2).

In 1 animal angiographic evidence of imperfect occlusion of the aneurysm clip at the main stem was found. In 2 animals the Atraumaclip on the midsegment of the LAD was not totally occlusive. The competitive flow, however, had not affected the patency of the anastomoses.

Histology

After conventional suturing, the medial layer of the coronary or thoracic artery was occasionally exposed to blood, but the adventitia was never exposed intraluminally. After I-A apposition, the adventitia and media protruded 0.23 mm (0.15–0.30 mm) into the lumen (22% [16%–27%] of total anastomotic orifice area).

Mural thrombus. After 4 hours, the anastomotic orifices inspected under the dissecting microscope did not show any intraluminal thrombus formation.

Figure 3. Representative angiogram at 5 weeks postoperatively, demonstrating a patent low-flow I-A anastomosis (graft flow at 5 weeks postoperatively, 9 mL/min).

In the histologic sections of the I-A anastomoses, the intraluminally exposed adventitia was only covered with a continuous less-than-20- μ m-thin layer of thrombus. The exposed media and the subendothelial layer of either the coronary artery or the ITA graft were variably covered with platelet aggregates. On the intraluminally exposed sutures, small platelet depositions, but no mural thrombus, were found in the conventionally sutured anastomoses. At 5 weeks, no fresh thrombus was detected.

Intimal hyperplasia In both low- and high-flow conditions, little, but variable, streamlining intimal hyperplasia coverage of the exposed adventitia and media was observed at 5 weeks (Table 3 and Figure 4, A). No excessive lumen-narrowing intimal hyperplasia was found in any of the unconventional anastomoses. Intimal hyperplasia was comparable between the I-A and I-I anastomoses (0.04 mm² [15th-85th percentile, 0.02–0.12 mm²] in unconventional and 0.04 mm² [15th-85th percentile, 0.01–0.07 mm²] in conventional anastomoses; $P = .600$).

Discussion

The principal result of this study was the surprising observation that in the low-flow condition (ITA flow ≤ 15 mL/min) all unconventional I-A anastomoses remained fully patent and showed a normal healing response.

Experimental Model

A new reproducible beating porcine heart model has been developed in which one can vary arterial blood flow (in milliliters per minute) in 2 ITA-LAD grafts to assess the

Figure 4. Representative histologic longitudinal sections of the heels of low-flow (A) I-A and (B) I-I anastomoses at 5 weeks post-operatively. *IH*, Intimal hyperplasia. (Elastin van Gieson stain; bar = 250 μ m.)

patency of unconventional coronary anastomoses under reduced graft flow by varying the anastomosis locations, as well as the position of an LAD clip in between the 2 anastomoses (Figure 1). This model may be useful in future testing of the feasibility of applying facilitated anastomosis techniques to the beating heart under (simultaneous) low and high graft flow conditions.

TABLE 3. Intimal hyperplasia area in longitudinal section through heel and toe of the anastomosis

		Intimal hyperplasia (mm ²)		
		n	Heel	Toe
Low flow	I-A	5	0.07 (0.04-0.24)	0.03 (0.03-0.13)
	I-I	7	0.04 (0.04-0.06)	0.01 (0.01-0.04)
High flow	I-A	8	0.04 (0.01-0.11)	0.02 (0.02-0.06)
	I-I	7	0.05 (0.03-0.07)	0.04 (0.02-0.06)

Data are presented as median (15th-85th percentile). I-A versus I-I, $P = .600$; Heel versus toe, $P = .005$. *n*, No. of anastomoses.

I-A Apposition

In contrast to current surgical practice, which dictates careful approximation of both intimas,^{10,11} in facilitated anastomosis techniques the media and even the thrombogenic adventitia¹² may be exposed to the bloodstream. An example is the sleeve end-to-end technique¹³ that has patency results that are comparable with those of the conventional end-to-end technique.^{3,14,15} Tulleken and coworkers⁴ have been introducing an exceptionally unconventional vessel wall apposition in arterial end-to-side anastomosis by using a nonocclusive technique. In their approach the intima of the graft is apposed to the adventitia of the recipient artery. Experimental and clinical experience demonstrated that in high-flow anastomoses exposure of the highly thrombogenic adventitia to blood did not provoke massive mural thrombus formation and subsequent anastomosis closure. Using saphenous vein conduits in neurosurgical patients, Tulleken and colleagues⁴ reported a patency rate of 92%. Testing the applicability of this alternative apposition technique in a porcine carotid artery bypass model, Heijmen and colleagues⁵ reported that all anastomoses remained fully patent, whereas thrombotic cyclic flow phenomena were observed in the first 2 hours after anastomosis construction.

The results of those studies cannot be extrapolated to reduced bypass graft flow conditions in coronary bypass surgery. Previous studies have stressed the importance of both rate and hemodynamic nature of blood flow in avoiding anastomotic thrombosis and thrombotic occlusion, especially in cases of suboptimal surgical anastomosis techniques.^{16,17}

Histology and Intraoperative and Postoperative Measurements

Under this study's conditions, it was found that even in low-flow conditions, intentional exposure of highly thrombogenic adventitia and media in the distal anastomosis did not adversely affect anastomosis healing.

In contrast to earlier observations in the porcine carotid artery by Heijmen and colleagues,⁵ this time we did not observe thrombotic cyclic flow phenomena. The present findings support observations by Tulleken and coworkers.⁴

The persistent rim in the anastomosis (Figure 2, B) was similar to the one in our preceding carotid artery study (diameter reduction of about 20%).⁵ Whether the absence of cyclic flow in our study has to be attributed to the different preoperative anticoagulation protocol (560 mg of acetylsalicylic acid 1 day preoperatively vs 80 mg per day for the last week before the operation), different adventitial collagen type I expression in the coronary artery than carotid artery or easier removal of loose periadventitial fibrofatty tissue in the coronaries remains unclear.⁵

It is conceivable that, for a given anticoagulation, the risk of anastomosis closure is proportional to the sum of potential surgical flaws, with the relative contribution of each flaw remaining unknown. Provided loose periadventitial tissue is absent and intramural stitches are used (no intima disruption and no intraluminal foreign-body exposure), adventitia exposure amounting to 20% of orifice area appeared not to endanger the quality of the bypass in the low-flow end-to-side anastomosis. This strongly supports the safety of using less thrombogenic unconventional wall appositions¹² in current clinical¹⁸ or future design strategies of facilitated coronary artery bypass anastomosis techniques. We assume, however, that with adventitia exposure, the tolerance to additional technical errors becomes small.^{4,19} The feasibility of unconventional wall apposition in human atherosclerotic coronary arteries that promote enhanced platelet deposition¹² remains to be established.

Conclusions

In low-flow conditions (≤ 15 mL/min) unconventional I-A apposition was not detrimental to the internal thoracic to coronary artery anastomosis in the pig. This finding may expand the design strategies of facilitated coronary artery bypass anastomosis techniques.

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