Stapled coronary anastomosis with minimal intraluminal artifact: The S² Anastomotic System in the off-pump porcine model

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Objective: A reliable, easy-to-use, 1-shot anastomotic device will significantly push the barrier for less invasive coronary bypass surgery. The current study was designed to test the safety, efficacy, and early patency of a novel distal anastomotic device.

Methods: The S² Anastomotic System (iiTech BV, Amsterdam, The Netherlands) was used in 10 consecutive pigs (73 kg) on a mild antiplatelet regimen. In each animal, the device was used to create an internal thoracic artery to left anterior descending bypass on the beating heart. The anastomoses were evaluated intraoperatively (n = 10), at 2 days (n = 2), and at 5 weeks (n = 8) by functional flow measurements, postmortem angiography, and histomorphologic examination.

Results: In all pigs, the S² Anastomotic System rapidly created successful anastomoses at the first attempt (graft loading and coronary ischemia time: 1.2 ± 0.3 minutes and 3.0 ± 0.6 minutes) on target vessels of 1.6 to 2 mm inner diameter. There were no technical failures or anastomotic leaks requiring additional sutures. Both intraoperatively and at the time of death, ischemically induced peak hyperemic flow responses demonstrated widely patent bypasses, which were confirmed by postmortem angiography (FitzGibbon grade A, n = 10) and macroscopic evaluation (anastomotic orifice: 2 mm). Histomorphologic evaluation showed a normal healing response with negligible neointima covering the connector and limited streamlining repair tissue formation between the staple-like elements of the connector.

Conclusions: The S² Anastomotic System consistently created automated, fast, and reliable internal thoracic to coronary artery anastomoses on the porcine beating heart with excellent graft patency and healing characteristics at the 5-week follow-up.

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The current interest in achieving coronary artery bypass surgery through ever-shrinking incisions has prompted us to reconsider previously established techniques for creating vascular anastomoses. For example, manual suturing of the anastomosis in video-assisted port access surgery on the beating heart, even with the aid of a master-slave robotic surgery system, has proved to be prohibitively difficult.^{1,2} To facilitate minimal access coronary surgery, therefore, new techniques to replace the current “gold standard” of manual suturing have to be developed.

One way to achieve both facilitated and predictable tissue bonding is the use of stapling techniques.³ Although many types of devices based on a broad range of principles have been proposed, only a few are beginning to become available to the

Figure 1. S² Anastomotic system preloaded with graft.

market today.⁴⁻⁷ The reason is that the small vessel sizes encountered in coronary surgery (1.3-3.5 mm inner diameter [ID]) have proved to pose enormous technical difficulties.

With a strong emphasis on the preservation of basic surgical principles (eg, minimizing vessel wall trauma, foreign material, and non-endothelialized surfaces exposed to the blood), a novel mechanical vessel coupling system capable of handling small vessel sizes was developed: the S² Anastomotic System (S²AS; iiTech BV, Amsterdam, The Netherlands). This study evaluates the consistency and reliability of the system during internal thoracic to anterior descending bypass grafting on the porcine beating heart and assesses the early patency and 5-week healing response of the constructed anastomoses.

Material and Methods

Design of the Connector and Delivery System

The S²AS is a micro-stapler designed to create a side-to-side anastomosis. It consists of a stainless steel 1-piece microconnector and an applicator (Figure 1). The connector consists of a thin, expandable meandering ring (thickness 0.07 mm) and 8 marginally broader, initially straight staples. The surface of the connector has not been treated. After expansion, the connector creates a rounded octagonal anastomotic orifice of slightly more than 2 mm diameter. The staples are deformed to a circular shape of 0.5 mm diameter. The connector is suitable for target coronary arteries of 1.6 to 2.1 mm ID, with a graft size of at least 2 mm ID. The applicator securely covers all staple points until firing-off the device, allowing safe intravascular manipulation, positioning, and removal without firing-off, if necessary. The key feature of the applicator is the sequence of actions that control device deployment. The first is radial expansion of the “meandering ring” followed by closure of all staples. This sequence provides an unhindered introduction of the device into the vessels and helps to reliably position the vessel walls between the anvils before stapling. Smooth introduction into

Figure 2. Completed anastomosis.

the target vessel is supported by a shoe-like structure at the tip of the device. Preloading consists of passing the device through the free distal end of the graft and out through an arteriotomy (Figure 1). Subsequently, the device is introduced into the arteriotomy of the targeted coronary artery in a position perpendicular to the epicardium by first inserting the toe of the shoe in a way comparable to the introduction of an aortic punch. As a result, any contact between the back wall of the coronary artery and the staples is avoided. The applicator is activated by remote control using a hydraulic pressure unit connected to the applicator with flexible tubing to avoid transmitting any undue forces to the vessel tissue. When the pressure is released, the device returns to the unexpanded state for controlled withdrawal from the anastomosis site and the distal stump of the internal thoracic artery (ITA) graft. The anastomosis is completed with a clip closing the distal free end of the left ITA (LITA) (Figure 2).

Animals

Ten female Dutch Landrace pigs (60-80 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). The protocol was approved by the animal experimentation committee of the Utrecht University. All animals received 560 mg of acetylsalicylic acid orally 1 day before the operation. This was continued at a dose of 160 mg/day until the time of death.

Anesthesia and Euthanasia

Anesthesia was induced with ketamine (10 mg/kg) intramuscularly. Each animal received thiopental sodium (4 mg/kg), atropine (1 mg), and antibiotic prophylaxis (500 mg of amoxicillin) through an intravenous line. The animals were intubated and ventilated. Anesthesia was maintained by a continuous intravenous infusion of midazolam ($0.7 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Analgesia was obtained with an infusion of sufentanil citrate ($2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and muscle relaxation with pancuronium ($0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). 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. Postoperatively, 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 pentobarbital sodium (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

After a partial median sternotomy, the LITA was harvested in a skeletonized fashion. After intravenous heparinization to obtain an ACT (determined at 10 and 60 minutes after injection and every 30 minutes afterward until the end of procedure) of twice the control value, the distal LITA was transected. Next, the LITA was sprayed with a papaverine-saline solution (5 mg/mL) to prevent spasm, after which the nonpressurized vessel's half circumference was measured with a caliper. Then, the distal segment of the left anterior descending artery (LAD) (2.0-2.5 mm outer diameter) was immobilized by the Octopus 3 Tissue Stabilizer (Medtronic, Inc, Minneapolis, Minn) and measured with a caliper in a perfused state.⁸ At the end of the anastomotic procedure, protamine hydrochloride (5000 IU/5 mL) was given intravenously.

Anastomotic Procedure

The distal end of the LITA (cut at an angle of 90 degrees) and LAD were cleared of loose periadventitial tissue. No myocardial preischemic conditioning was used before construction of the anastomoses. Coronary artery occlusion was achieved with a single, upstream polypropylene 4-0 tourniquet (Ethicon, Inc, Somerville, NJ).

A small arteriotomy of approximately 1 mm was made in the LITA using a 15° microsurgical knife (SharpPoint; Surgical Specialties Corporation, Reading, Pa), followed by insertion of a conical tool to produce a standardized opening of approximately 2 mm in diameter. Next, the LITA was mounted onto the distal end of the S²AS applicator between the anvils of the staple-like connector. After coronary occlusion, the LAD arteriotomy was performed in a stepwise fashion. First, a small 1-mm incision was made with the 15° microsurgical knife, which was extended to approximately 2 mm using standard microscissors. A conical tool was used in an upstream direction to check the size of the arteriotomy and slightly dilate it, if necessary, to ensure subsequent smooth insertion of the device. Next, the mounted S²AS was inserted into the LAD, and after scrutinizing for proper positioning, the applicator was activated, resulting in expansion followed by closure of the staples of the vessel connector. Subsequently, the applicator was withdrawn from the distal end of the LITA. After clip placement (medium Atraumaclip; Pilling, Inc, Fort Washington, Pa) on the distal graft to convert the side-to-side anastomosis into an end-to-side configuration, perfusion through the graft was initiated, and the LAD was ligated proximal to the anastomosis.

The animals were evaluated intraoperatively (10 animals), at 2 days (2 animals), and at 5 weeks (8 animals).

Intraoperative and Postoperative Measurements

Both intraoperatively and at the time of death, LITA flow and coronary peak hyperemic response (after 30-second graft occlusion; ratio of peak mean graft flow after reestablishment of perfu-

TABLE 1. Operative data

Time to deploy (min)	
LITA mounting time	1.2 ± 0.3
Anastomosis construction time	2.7 ± 0.5
Coronary occlusion time	3.0 ± 0.6
Vessel sizes (mm)	
LITA outer diameter (nonperfused)	2.4 ± 0.2
LAD outer diameter (perfused)	2.4 ± 0.2
LITA inner diameter (estimated*†)	2.2 ± 0.2
LAD inner diameter (estimated*)	1.8 ± 0.2

Data are presented as mean ± SD; n = 10 anastomoses (10 animals).

LITA, Left internal thoracic artery; LAD, left anterior descending.

*Estimation based on 1/9 wall thickness to outer diameter ratio.

†Estimation based on 15% increase when pressurized.

sion divided by baseline flow) were measured and recorded with a calibrated transit time flow probe (size 3S) connected to a flow meter (model T208, Transonic Systems, Inc, Ithaca, NY) at a mean blood pressure of 70 mm Hg as previously described.⁸

Angiography

After the animals were killed, the anastomoses were visualized by ITA angiography (C-arm BV27; Philips, Eindhoven, The Netherlands) and graded by an independent observer according to FitzGibbon and colleagues.⁹

Histology

After angiography, the anastomoses were perfused for 120 minutes with 4% formalin at 80 mm Hg at a low perfusion rate. After overnight fixation, the anastomotic segments were excised and longitudinally cut open (2-day follow-up) for inspection under the dissecting microscope at 10 to 20× magnification to detect any mural or intraluminal thrombus formation. The segments were subsequently embedded in methyl methacrylate and sectioned in the transversal plane at ±350-μm intervals. The sections were stained with methylenblue-basic fuchsin. The dimension of thrombus formation (2-day follow-up) and resulting anastomotic narrowing as the percentage of total anastomotic orifice were assessed with the use of the software package AnalySiS (Soft-Imaging Software GmbH, Münster, Germany). Vessel wall apposition (eg, adventitia-to-adventitia and media-to-adventitia) and the process of hyaline degeneration, fibrosis, and media necrosis (ie, complete absence or pyknosis of smooth muscle cell nuclei) were recorded. Vessel wall inflammation (presence of acute [polymorphonuclear cells and macrophages] and chronic [foreign body giant cells] inflammatory reaction¹⁰) and intimal hyperplasia (as height [millimeters] enclosed by luminal border and internal elastic laminae) were assessed with AnalySiS.

Statistical Analysis

Data are presented as mean ± SD, median and range, or 15th through 85th percentiles.

Results

Surgery

All anastomoses were performed by 1 investigator (M. P. B.). The operative data are given in Table 1. Mount-

Figure 3. Gross view from the bottom of the LAD (cut open longitudinally) into the S²AS anastomosis (diameter 2.0 mm) after excision at 5 weeks.

ing of the LITA onto the S²AS lasted 1.2 ± 0.3 minutes, including making the arteriotomy but excluding complete skeletonization of the vessel wall. Construction of the anastomosis took 2.7 ± 0.5 minutes, including making the arteriotomy and clipping the distal end of the ITA graft but excluding epicardial incision.

Immediate full hemostasis was obtained in 8 of 10 anastomoses. Two anastomoses showed some oozing, which stopped spontaneously within a few minutes before administration of protamine.

The ACT was 90 ± 12 seconds before heparin administration and 235 ± 36 seconds during the anastomotic procedure.

Follow-Up

The scheduled follow-up was completed for all 10 animals. Their weights had increased from 73 ± 7 kg to 78 ± 6 kg. Before the time of death, no myocardial infarctions or wall motion disturbances were noted. All anastomoses were patent at 2 days and 5 weeks. Macroscopically, the anastomoses showed a smooth round to slightly oval orifice of approximately 2 mm ID (Figure 3).

Intraoperative and Postoperative Measurements

ITA flow measurements are given in Table 2. The median flow at unstressed resting condition over the bypasses was 15 mL/min or less and consequently classified as “low-flow bypass condition” (Table 2).⁸ Flow capacity was demonstrated by the mean hyperemic flow response at the time of death (5.3 and 5.6 times baseline flow at 2 days and 5 weeks [133 mL/min and 73 mL/min, respectively]), which was comparable to the intraoperative response (mean 5.9 times baseline flow [77 mL/min]), indicating hemodynamically fully patent anastomoses over time.

TABLE 2. Intraoperative and postoperative measurements

	Intraoperative	2 d	5 wk
ITA graft flow (mL/min)			
<i>n</i> = 2	11 (range 10-11)	25 (range 24-25)	–
<i>n</i> = 8	11 (9-18)*	–	13 (12-17)*
Coronary peak hyperemic response (peak/baseline flow)			
<i>n</i> = 2	8.1 (range 6.8-9.3)	5.3 (range 5.1-5.4)	–
<i>n</i> = 8	5.3 $\pm$ 0.8	–	5.6 $\pm$ 0.9

Data are presented as median and range, 15th through 85th percentiles, or mean $\pm$ SD. Flows were measured at MAP of approximately 70 mm Hg. *Coronary peak hyperemic response* as mean of duplicate measurements; intraoperative = after stabilization of flow after completion of anastomosis. ITA, Internal thoracic artery; MAP, mean arterial pressure.

Angiography

At the time of death, all postmortem angiograms revealed FitzGibbon grade A anastomoses with rapid distal run-off (Figure 4). No anastomotic aneurysm formations were observed.

Histology

Vessel Wall Apposition. In all anastomoses, the adventitia of the graft was apposed to the adventitia of the LAD along its full circumference (Figure 5). Thus, the medial layers of both the coronary and thoracic artery were initially exposed to blood. In 4 anastomoses, a small part of the adventitia of the LAD at the lateral walls of the connector anastomoses had been intraluminally exposed. In all anastomoses, major parts of the connector (ie, staples and inter-connecting elements) were exposed. Fibroblastic tissue was observed between vessel walls and surrounding the connector frame. No dehiscence or aneurysm formation was observed.

Mural Thrombus. After 2 days, the anastomotic orifices inspected under the dissecting microscope did not show intraluminal thrombus formation. The clipped distal end of the thoracic artery, forming a cul-de-sac, was filled with thrombus. A continuous thin layer of thrombus less than 30 μ m thick was found on the intraluminally exposed media of both graft and coronary artery. On the intraluminally exposed connector frame, small platelet depositions were found. At 5 weeks, no fresh or organized thrombus was detected.

Intimal Hyperplasia. At 5 weeks, both the intraluminally exposed medias and the connector were covered by thin neointimal repair tissue formation. Thickness of this layer ranged from 30 to 100 μ m on the metal parts to 300 μ m in places where anastomotic recesses, resulting from the anastomotic configuration, had been covered. No excessive, lumen-narrowing intimal hyperplasia was found in any of the anastomoses ($0.14 \text{ mm} \pm 0.04 \text{ mm}$ [mean $\pm$ SD]) (Figure 5). Toward the toe of the anastomosis (ie, the clipped distal end of the conduit), neointimal repair tissue reorganized the lumen of the thoracic artery.

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Figure 4. Representative angiogram at 5 weeks postoperatively, demonstrating patent LITA-to-LAD anastomosis (arrow).

Figure 5. Representative histologic transverse cross-section of a LITA-to-LAD anastomosis at 5 weeks postoperatively. Note the internal connector covered by small layer of neointimal tissue (methyleneblue-basic fuchsin stain). ITA, Internal thoracic artery; LAD, left anterior descending artery.

Medial necrosis. Full-thickness medial necrosis was recorded near the penetrating staple elements of the ring frame. No medial necrosis or thinning of either the coronary or the thoracic artery was observed in between the staple elements.

Inflammation. At 2 days, the frame was surrounded by a focal, acute inflammatory cell reaction (polymorphonuclear cells and macrophages <100 inflammatory cells/field; magnification $\times 1000$). At 5 weeks, the connector was surrounded by an acute (<100 cells/field) and limited chronic inflammatory cell reaction (foreign body giant cells, occasionally seen in 5 anastomoses). No extensive or full-thickness media inflammation was seen in any of the anastomoses.

Discussion

The principal findings of this study are the following: (1) Using arterial grafts exclusively, we determined that the S²AS device performed as intended in all 10 pigs. Ease-of-use, expedience, and consistency were illustrated by the creation of 10 consecutive, surgically hemostatic anastomoses within 3.0 ± 0.6 minutes coronary occlusion time. (2) At 5 weeks, all S²AS anastomoses were both angiographically and hemodynamically fully patent (FitzGibbon grade A with rapid distal run-off, peak hyperemic flow response: 5.6 ± 0.9). This was achieved in deliberately chosen small-caliber peripheral target vessels under prothrombotic low base flow conditions (≤ 15 mL/min) using a low-dose Aspirin regimen. (3) The anastomoses showed a normal healing response with thin neointimal coverage (≤ 100 μ m) of the internal connector and minimal inflammatory reaction.

Key Features of the S²AS

Compared with other coronary anastomotic connectors^{4,5} (particularly the SJM distal connector,⁶ which has some features in common with the present device), the S²AS incorporates 4 specific features that are presumed to be useful. (1) By radial expansion of the applicator, reliable tissue positioning between the anvils was obtained before stapling took place. (2) The anvils allowed the exertion of force directly on the staples. (3) The foreign body area exposed to blood was limited to a 0.07-mm (<0.003 inch) meandering ring to avoid the necessity of aggressive anticoagulation or antiplatelet therapy. This small area approaches the standard suture material area. (4) With the staple ends covered completely by the anvils, perpendicular introduction of the S²AS applicator could be performed easily and without the risk of capturing the back wall of the coronary artery.⁶

Anastomotic Geometry and Wall Apposition

For long-term reliability, it seems safe to adhere as much as possible to the basic principles of the “gold standard”: the hand-sewn anastomosis. The overall geometry and wall apposition of the S²AS anastomosis was inspired by the diamond-shaped (90-degree), side-to-side, hand-sewn anastomosis, which is commonly used for sequential grafts. One of its main features is the necessity to limit the arteriotomy

in the target vessel to avoid an awkward indentation resulting from transversely overstretching the graft at the anastomotic site (the “sea-gulling” effect). Despite the small arteriotomy, diamond-shaped anastomoses reveal excellent patency and functionality.¹¹ Finishing the side-to-side anastomosis by closing the free end of the graft resulted in a smooth end-to-side configuration, as experienced by other investigators.^{5,6} An important additional advantage of the side-to-side approach is the favorable take-off angle and complete directional freedom of the graft that prevents kinking.

Advantages Over Conventional Suturing

The predictable result of a standardized anastomosis, paired to speed and a reduced dexterity requirement, even in difficult to reach locations, offers an attractive alternative to suturing. In open chest procedures, therefore, these devices may stimulate surgeons to opt more often for off-pump techniques. These connectors may represent important enabling technology for more limited access procedures and, ultimately, totally endoscopic coronary artery bypass grafting in the future.

Limitations of the Study

The current experiment was limited to a 5-week follow-up in the porcine model, which correlates with a 15- to 30-week healing response in the human coronary artery.¹² Nevertheless, the currently presented initial results need to be further substantiated with longer term survival studies. In addition, the feasibility of the system in small-caliber, human, atherosclerotic coronary arteries remains to be established.

Conclusions

In the healthy pig, the S²AS consistently created automated, fast (<3 minutes), and surgically hemostatic LITA-to-LAD anastomoses of 2 mm orifice diameter in target vessels of 1.6 to 2 mm ID on the beating heart with excellent graft patency and healing characteristics with a mild antiplatelet regimen. This device may help to expand the scope of

full-access off-pump coronary artery bypass grafting and encourage limited access procedures, ultimately enabling totally endoscopic multivessel myocardial revascularization.

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