S2 Connector Versus Suture: Distal Coronary Anastomosis Remodeling, Patency, and Function in the Pig

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Background—Anastomotic connectors could be the key to less invasive bypass surgery, including endoscopic procedures, but equivalence to conventional suturing needs to be established. A novel distal coronary connector was tested pre-clinically for safety and efficacy in comparison to conventional suturing.

Methods and Results—Left internal thoracic to left anterior descending coronary artery bypasses were constructed off-pump in 35 pigs (73±8 kg). An intraluminal metal connector (S2AS) was used in 21 and conventional suturing in 14 animals. S2AS anastomosis construction was easier achieved in one-fourth of the conventional construction time (3.7±0.7 versus 16.5±2.6 minutes; \( P<0.001 \)). Acute patency tended to be better (\( P=0.15 \)). All anastomoses were evaluated intraoperatively, and subgroups at 90 and at 180 days. Patency was 100%. An effective remodeling response was observed in all groups, resulting in unobstructed anastomoses with excellent hemodynamic performance (fractional flow reserve \( \geq 0.93 \) at 180 days). At 6 months, the noncompliant connector was covered with stabilized neointima that was thinner than found on the suture line (0.10±0.04 versus 0.31±0.13 mm; \( P=0.01 \)). The connector induced less lumen loss (−0.6±6.5 versus 21.6±19%; \( P=0.03 \)). The initial side-to-side configuration had remodeled to an end-to-side shape as intended.

Conclusions—In the porcine model, the connector rapidly and consistently produced high-quality anastomoses that fully met current standards on patency and function. Unconventional aspects like a noncompliant intraluminal ring and a side-to-side to end-to-side converted configuration did not interfere with favorable anastomosis remodeling. These findings shed a new light on the anatomical prerequisites for anastomosis patency. (Circulation. 2006; 114[suppl I]:I-390–I-395.)

Key Words: anastomosis ■ bypass ■ connector ■ hemodynamic ■ remodeling ■ surgery

To facilitate, standardize, and accelerate distal coronary anastomosis construction, several mechanical “one-shot” connectors have been developed.1–5 By substantially simplifying the procedure, these devices may boost off-pump procedures and may enable less invasive and ultimately port access strategies. However, clinical experience with first-generation anastomotic devices has revealed difficulties in achieving equivalence to the conventionally sutured standard.3 Acquisition of detailed data on tissue response and hemodynamic performance is necessary to identify design and delivery essentials.

We previously described the design principles, application reliability and early patency of the S2 Anastomotic System (S2AS), a novel “one-shot” distal coronary connector.5 In the current preclinical validation study of this connector, we acquired data on anastomosis remodeling and function at 3 and 6 months in the off-pump porcine model. Patency, anastomosis dimensions, and hemodynamic function were compared with conventionally sutured anastomoses using epicardial ultrasound (ECUS), angiography, intravascular ultrasound (IVUS), fractional flow reserve (FFR) and coronary flow reserve (CFR) determinations, luminal casts, and wall histology.

Methods

Study Design

In 35 Dalland race female pigs (van Beek VOF; Putten, The Netherlands), 21 received a connector constructed and 14 received a
conventionally sutured left internal thoracic artery (LITA) to left anterior descending (LAD) anastomosis. Subgroups were terminally evaluated at 3 and 6 months (Table 1). Interim evaluation in the 6-month subgroups included neither IVUS, to reduce potentially confounding intraluminal anastomosis damage, nor ventriculography, to reduce catheterization risk.

The protocol was approved by the Animal Experimentation Committee of the Utrecht University. The animals 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 authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Starting 72 hours before surgery, all animals received 325 mg acetylsalicylic acid and 75 mg clopidogrel bisulphate daily until euthanized.

**Coronary Connector and Delivery System**

The S²AS is a micro-stapler that intraluminally delivers 8 stainless steel staples, mounted on a thin expandable ring (thickness 70 μm [<0.003 inch] in axial direction; Figure 1). A simple deployment procedure creates a side-to-side anastomosis without wall eversion. Intended vessels sizes have an inner diameter of 1.8 to 2.5 mm and ≥2.2 mm for coronary artery and graft, respectively. The key feature of the system is the distinct sequence of radial expansion of the connector followed by closure of the staples, effecting precise vessel wall positioning between the anvils before final fixation by stapling. The side-to-side anastomosis is converted to an end-to-side configuration by clipping off the distal free end of the graft (Figure 2 foreground).

**Anesthesia and Euthanasia**

Anesthesia was induced with ketamine (10 mg·kg⁻¹), midazolam (0.2 mg·kg⁻¹) and thiopental sodium (4 mg·kg⁻¹) intramuscularly. Once intubated and mechanically ventilated, anesthesia and analgesia were maintained with midazolam (0.7 to 1.0 mg·kg⁻¹·h⁻¹) and sufentanil citrate (4 μg·kg⁻¹·h⁻¹), in combination with muscle relaxation with pancuronium bromide (0.1 mg·kg⁻¹·h⁻¹) intravenously. Euthanasia was effected with pentobarbital sodium (20 mg·kg⁻¹) intravenously after partial heparinization (ACT ≥250 seconds; Hemotec, Inc, Englewood, Col).

**Surgery**

After a partial median sternotomy and LITA harvesting, the LAD was immobilized with the Octopus 3 Tissue Stabilizer (Medtronic Inc, Minneapolis, Minn). With 2-dimensional ECUS (ProSound SSD-5000; Aloka Co, Wallingford, Conn), using a linear array,
15×9×6-mm mini-transducer (up to 13 MHz in B-mode), anastomotic sites were chosen with inner diameters in the lower part of the intended range in anticipation of some animal growth.

After ischemic myocardial preconditioning, the anastomotic procedures were performed using partial heparinization as specified, reversed at the end of the procedure with protamine hydrochloride. The LAD was ligated 10 mm proximal to the anastomosis.

**Anastomotic Procedure with the S\(^2\)AS**

After making a small arteriotomy in the LITA (Sharpey 15° blade; Surgical Specialties Corporation, Reading, Pa), followed by insertion of a conical tool, the LITA was loaded on the S\(^2\)AS. A similar arteriotomy in the LAD was sharply cut to ∼3 mm with standard micro-instruments and checked for size with a conical tool. The preloaded S\(^2\)AS was subsequently inserted into the LAD, activated, and withdrawn, and the distal graft was closed with a clip (medium Atraumatic clip; Pilling Inc, Fort Washington, Pa). All anastomoses were constructed by M.P.B.

**Hand-Sutured Anastomotic Procedure**

Routine surgical techniques were used, including cutting the end of the graft at a 30° angle and extending the opening by a small longitudinal incision, making a 5-mm-long arteriotomy in the LAD, inserting an intracoronary shunt, and using a 7-0 or 8-0 Prolene (Ethicon Inc, Somerville, NJ) running suture technique. All suture anastomoses were constructed by an experienced cardiothoracic surgeon (A.B.R.).

In both groups, anastomoses were checked using ECUS (vide supra). \(^6\) LITA blood flow was measured with a calibrated transit time flow probe (size 3S) connected to a flowmeter (T208; Transonic Systems Inc, Ithaca, NY) at a mean blood pressure of 80 mm Hg.

**Follow-Up Catheterization**

After anesthetizing each animal as described, selective coronary angiography of the LITA and native LAD was performed via the femoral artery using a C-arm (Pulsera; Philips, Eindhoven, the Netherlands), followed by left ventriculography, according to Table 1.

**Per Anastomosis Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Connector</th>
<th>Suture</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel inner diameter, mm</td>
<td>2.71±0.31</td>
<td>2.55±0.24</td>
<td>0.12</td>
</tr>
<tr>
<td>LITA</td>
<td>2.15±0.14</td>
<td>2.01±0.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anastomosis construction time, minutes</td>
<td>3.7±0.7</td>
<td>16.5±2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anastomosis success rate</td>
<td>90%</td>
<td>71%</td>
<td>0.19</td>
</tr>
<tr>
<td>Immediate hemostasis</td>
<td>0.14</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Extra stitches required per anastomosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outflow tract diameter stenosis &gt;50%</td>
<td>0</td>
<td>2</td>
<td>0.15</td>
</tr>
<tr>
<td>Anastomosis dimensions, mm, ECUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transverse (Plane A*)</td>
<td>2.37±0.10</td>
<td>2.78±0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Longitudinal (Plane A*)</td>
<td>2.37±0.10</td>
<td>4.58±0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (Plane B*)</td>
<td>4.71±0.48</td>
<td>4.36±0.58</td>
<td>0.11</td>
</tr>
<tr>
<td>LITA graft flow, mL/minute</td>
<td>14.4±7.1</td>
<td>12.9±4.9</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*Planes correspond to Figure 2; †derived from histomorphometry.

**Statistical Analysis**

Data are presented as mean±SD. The difference between continuous variables was analyzed using the \(t\) test. The differences between dichotomous variables were analyzed using the Fisher exact test. \(P<0.05\) was considered to indicate a significant difference.

**Results**

**Surgery**

Construction of the connector anastomosis took 3.7±0.7 minutes, less than one-fourth the time required for construction of the suture anastomosis (16.5±2.6 minutes). All vessel diameters were within the intended range, with the sutured anastomoses tending toward the lower side \((P<0.001)\). In the relatively fragile porcine tissue, 2 connector and 4 suture cases required up to 2 extra stitches to address bleeding (Table 2).

Intraoperative ECUS showed that all 21 connector anastomoses were fully patent, whereas 2 of 14 conventional anastomoses showed >50% luminal diameter narrowing at the outflow tract. In one case, the stenosis was successfully dilated using a 1.5-mm probe, introduced through a side branch in the LITA. The other case was accepted. Graft flows were comparable in both groups. Anastomosis dimensions were significantly bigger in the suture group in plane A according to Figure 2 (Table 2).

**Follow-Up**

The suture animal, with the accepted stenosis, died soon after the operation as a result of persistent blood loss. Three additional animals died, all showing fully open anastomoses at autopsy: 2 suture pigs because of arrhythmias during angiography and 1 connector pig because of a cage construction accident. Consequently, follow-up was completed for 20
TABLE 3. Functional Results

<table>
<thead>
<tr>
<th></th>
<th>Connector</th>
<th>Suture</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular apical wall motion disturbance (number/total)</td>
<td>90 days</td>
<td>1/10</td>
<td>3/5</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>1/10</td>
<td>5/6</td>
</tr>
<tr>
<td>Overall</td>
<td>2/20 (10%)</td>
<td>8/11 (73%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FFR ( fractional flow reserve)</td>
<td>90 days*</td>
<td>0.93±0.04</td>
<td>0.96±0.03</td>
</tr>
<tr>
<td></td>
<td>180 days†</td>
<td>0.94±0.01</td>
<td>0.97±0.02</td>
</tr>
<tr>
<td>CFR ( coronary flow reserve)</td>
<td>90 days*</td>
<td>3.9±0.9</td>
<td>4.4±1.4</td>
</tr>
<tr>
<td></td>
<td>180 days†</td>
<td>4.1±1.1</td>
<td>4.5±1.1</td>
</tr>
</tbody>
</table>

* n=20 (connector), n=11 (suture); † n=10 (connector), n=6 (suture).

connector and 11 suture animals (Table 1). Animal weight (73±8 kg, mean age 17 weeks) increased comparably in both groups by 21±8 kg at 180 days (P=0.99).

Angiography and Ventriculography
Angiography revealed FitzGibbon grade A anastomoses in all cases with rapid run-off. No competitive native LAD flow was observed beyond the clips that isolated the grafted distal part of the vessel. Left ventriculograms showed significantly less hypokinetic or dyskinetic apical regions in the connector group (Table 3). In the presence of a fully open graft, regional wall motion disturbances were considered to represent myocardial damage.

FFR, CFR, and Graft Flow Measurements
FFR and CFR values are listed in Table 3. The CFR values were comparable between the 2 groups at 90 and 180 days.

In all animals, the FFR was ≥0.93 at 180 days, indicating clinically unobstructed bypass flow. A tiny difference of the mean FFR in favor of the suture group reached statistical significance.

TABLE 4. IVUS Measurements and Calculated Parameters

<table>
<thead>
<tr>
<th></th>
<th>Connector*</th>
<th>Suture*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intimal hyperplasia at joining line, mm</td>
<td>90 days</td>
<td>0.12±0.04</td>
<td>0.30±0.17</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>0.10±0.04</td>
<td>0.31±0.13</td>
</tr>
<tr>
<td>Lumen loss: MLD† decrease since day 0, %</td>
<td>90 days</td>
<td>9.6±4.3</td>
<td>9.1±25</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>−0.6±6.5</td>
<td>21.6±19</td>
</tr>
<tr>
<td>PDS, %‡</td>
<td>0 days</td>
<td>−10±6</td>
<td>−38±23</td>
</tr>
<tr>
<td></td>
<td>90 days</td>
<td>−1±5</td>
<td>21±7</td>
</tr>
<tr>
<td></td>
<td>180 days</td>
<td>−9±8</td>
<td>24±24</td>
</tr>
</tbody>
</table>

*90, 180 days respectively: n=10, 9 (connector), n=3, 6 (suture) because no measurements were possible in 1 connector and 2 suture animals because of poor visualization.
† Minimum lumen diameter, related to intra operative measurements with ECUS (see Table 2).
‡ Percent diameter stenosis: PDSx0 (day x) = [ LADx (day x) − MLD at day 0] × 100/ LADx (day 0)

In both groups, mean graft flow (14.4±7.1 and 12.9±4.9 mL/min) remained similar over time (P=0.30 and P=0.40 at 90 and 180 days, respectively).

Anastomosis Dimensions
Neointimal tissue at the level of the connector and the suture line was significantly thinner in the connector group, and virtually did not change from 3 to 6 months (IVUS; Table 4).

Lumen loss inside the anastomosis, calculated by comparing the minimum lumen diameter (MLD) at day 0 (acquired with ECUS) and at follow-up (acquired with IVUS), was significantly less in the connector group (Table 4). Percent diameter stenosis (PDS) was calculated from the intraoperative LAD dimensions to exclude the effect of animal growth, negative values meaning anastomoses larger than the target vessels (Table 4). The initial difference (P<0.001), indicating substantially larger anastomoses in the suture group, lost statistical significance (P=0.19 at 180 days), indicating convergence toward more similar geometry.

Changes along the flow pathway, measured similarly with ECUS and IVUS, showed a comparable pattern: (1) the LITA diameter shrank significantly (P<0.01) toward the target vessel size (−9±10% in the connector group versus −14±15% in the suture group at 180 days; P=0.37); and (2) the LAD diameter increased (P=0.07, by 6±12% in the connector group versus 3±15% in the suture group at 180 days, P=0.75), most likely the result of animal growth.

Remodeling: Gross Pathology and Casts
Both techniques resulted in a remarkably smooth flow pathway, illustrated by the elastomeric luminal resin casts (Figures 3 and 4). The blind sac, created by closing the LITA in
the connector group, had been completely remodeled. The segment of the LAD, upstream of the anastomosis to the ligating clip, was also significantly obliterated.

**Histology**

In both groups, repair tissue filled excess space, resulting in a smooth inner surface. Metal parts were covered with a thin layer of flattened cells, containing connective tissue (myofibroblasts). Neointimal tissue was markedly less abundant along the connector than along the suture. Complete endothelium-like lining of the anastomoses was observed in both groups; occasional minor gaps were considered a tissue-processing artifact.

**Vessel Wall Apposition**

In the majority of sutured anastomoses, wall apposition could not be precisely characterized. Vessel wall eversion was specifically looked for, but was generally not found. Most connector anastomoses showed inverted vessel walls.

**Tissue Inflammation**

In the connector group, tissue reaction was negligible to mild, being of 2 types: foreign body reaction (lymphocytes, occasional giant foreign body cells) near metal parts and infiltrates located in the adventitia. In the suture group, tissue reaction was more marked, with more abundant infiltrates in the adventitial layer, as well as infiltrates around the suture. In both groups, the adventitial infiltrates were interpreted to be the result of tissue handling.

**Necrosis**

Both near the staples and around the suture bites, minor to mild levels of tissue necrosis were observed, most likely caused by compressive forces.

**Discussion**

The principal findings of this study are: (1) the connector technique fully met current standards on patency and function, despite the presence of an endoluminal, noncompliant metal ring, inverting wall apposition and a blind lumen pouch; (2) in the initially smaller connector anastomosis, remodeling resulted in significantly less lumen loss and less neointima formation than in the suture group; and (3) connector anastomosis construction was faster, tended to be more consistent, and resulted in better preservation of myocardial contractility.

Some of these findings cast a new light on current controversies on anastomosis healing.

**Anastomosis Remodeling**

A striking observation was the apparently controlled formation of intraluminal repair tissue in all cases, producing a remarkably smooth flow pathway. This remodeling process explains the excellent hemodynamics, reflected by all FFRs being >0.90. The sutured anastomosis was initially larger than the connector anastomosis, the result of the surgical habit to oversize; however, significantly more neointima formation and, therefore, more lumen loss resulted, causing the initially diverging geometries to converge toward similarly optimized configurations. This process is likely shear rate-controlled, aimed at establishing laminar flow. Quantitative clinical observations suggest that a comparable mechanism exists in humans as well, because sutured anastomotic MLDs of 1.8±0.6 to 2.0±0.5 mm were reported at angiography after 3 to 6 months, targeting mean LAD sizes of 1.8 to 1.9 mm with LITA grafts of 2.1 to 2.4 mm. Because lumen loss was confined to the anastomotic plane, the use of intracoronary shunts is unlikely to be a factor as these devices have their tightest fit in the anastomosis outflow tract.

**Other Aspects**

Introducing a limited foreign body load, as well as a noncompliant plane to the anastomosis, did not interfere with favorable remodeling. The remarkably mild neointimal response had stabilized at 3 months, indicating a completed healing response and supporting expectations of enduring patency. This observation contradicts the hypothesis that noncompliance inherently induces more intimal hyperplasia by not responding to pulsatile pressure. The ≈3% lower mean FFR in the connector group might be compliance related, but it is not expected to be clinically relevant.

Established opinion is that vessel wall egression with intima–intima apposition is a prerequisite for good results. This configuration, however, could not be identified in the suture group. In the S2AS group, an inverting configuration was typically found. These observations indicate that, contrary to broad belief, routine expert coronary anastomosis suturing does not necessarily result in any specific type of wall apposition, but that this does not appear to affect the result.

The blind pouch, formed by the conversion of the side-to-side anastomosis to an end-to-side configuration, effectively disappeared. For 6 months, CFR values remained stable. Thus, coronary run-off was preserved. The low incidence of myocardial damage seen in the left ventriculogram further supports the inference that the connector anastomosis did not generate (micro) emboli. The cause of the increased incidence of myocardial damage in the suture group is unclear. Porcine myocardium is more vulnerable to ischemia than human myocardium, probably because of the virtual absence of collaterals. Inadequate flow through the intracoronary shunt or blocking of side branches during anastomosis construction may have played a role.

**Advantages of the Connector Technique**

When validated clinically, the simplification of anastomosis construction, coupled to improved consistency, may guide more surgeons toward off-pump revascularization of all regions of the heart and may facilitate limited access procedures.

**Limitations of the Study**

All procedures were standardized, but observations at 3 and 6 months were mostly performed in different animals. Therefore, the time frame may not be the only factor explaining the observed differences.

The current experiment was limited to 6-month follow-up in the porcine model, which is regarded as correlating with a
1.5- to 3-year healing response in the human coronary artery.11

For lack of a viable porcine venous graft model, the current study was limited to arterial grafts. The validity of our findings for venous grafts remains to be established.

Conclusions
In arterial grafting, the tested connector rivaled suturing in terms of patency and function. The noncompliant intraluminal ring, unconventional wall apposition, and the initial blind pouch did not interfere with favorable anastomosis remodeling and healing. By simplifying and accelerating anastomosis construction, coronary connectors may help to expand off-pump coronary bypass surgery and stimulate the development of limited and port access procedures.

Acknowledgments
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Disclosures
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References
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