

Avoidance of Aortic Side-Clamping for Proximal Bypass Anastomoses: Better Short-term Outcome?

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ABSTRACT

Objectives: The benefit of off-pump coronary artery bypass (OPCAB) surgery may be reduced by strokes caused by microemboli produced after aortic side-clamping for proximal bypass anastomoses. The Heartstring device allows constructing proximal bypass anastomoses without side-clamping of the aorta.

Methods: This retrospective study describes 260 consecutive patients who underwent OPCAB surgery; 442 proximal anastomoses were performed with the Heartstring device in this series. Ten percent of the patients were randomly sampled before discharge to undergo a coronary angiogram for assessment of graft patency.

Results: Intraoperative Doppler measurements confirmed regular bypass function. Early mortality occurred in 4 patients (1.5%), and stroke occurred in 2 patients (0.8%). Device-related bleeding was negligible, and there were no cases of aortic dissection. Perioperative ischemia occurred in 8 patients (3.1%). PredischARGE coronary angiography evaluations in 25 of the patients (of 260) showed that all 42 Heartstring-assisted anastomoses (of 442) were patent.

Conclusions: Clampless performance of proximal bypass anastomoses combined with OPCAB is associated with a very low incidence of stroke complications. Short-term follow-up has shown excellent results regarding bypass patency and other adverse events. Prospective randomized trials are required to confirm the advantage of this technique.

INTRODUCTION

Patients undergoing conventional coronary artery bypass grafting (CABG) using cardiopulmonary bypass can achieve excellent cardiac outcomes. However, success may be limited by postoperative neurocognitive dysfunction, which persists

in up to 40% of patients 5 years after surgery [Mark 2002]. Lower overall cognitive function is associated with reduced general health and a less productive working status that significantly affect the quality of life [Newman 2001].

This type of negative neurologic outcome has been suggested to be due to cerebral microembolism occurring after aortic cannulation, clamping, and clamp removal. Off-pump CABG (OPCAB) surgery, which does not use cardiopulmonary bypass, has been associated with a lower incidence of cerebral microemboli and an improved neurologic and cognitive outcome [Murkin 1999]. Some embolic risk remains with OPCAB, however, if the aorta is side-clamped to perform proximal bypass anastomoses [Barbut 1994]. Various devices, including the Heartstring device (Guidant Corporation, Santa Clara, CA, USA), have therefore been developed to avoid side-clamping of the aorta [Medalion 2004]. We describe our experience with this device in the largest series of OPCAB patients reported to date.

MATERIALS AND METHODS

Study Design

This retrospective descriptive study was designed to evaluate the Heartstring device during surgery and in the early postoperative period (up to 30 days). The local Institutional Review Board approved the retrospective collection of patient data.

Patients

Proximal anastomoses (n = 442) were performed with the Heartstring device in 260 consecutive OPCAB patients. The inclusion criterion was OPCAB as intention to treat; the patients were consecutive. There was no absolute exclusion criterion besides on-pump CABG.

Surgical Procedure

All patients were scheduled for isolated OPCAB. After sternotomy and harvesting of grafts (including the left and right internal mammary arteries [IMAs], the left radial artery, and veins [endoscopically] from the lower extremity), heparin was given at a dosage of 200 IU/kg with the aim of achieving an activated clotting time >300 seconds. Anastomoses were performed following placement of temporary pacemaker wires on the right atrium and the right ventricle. An Octopus

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Figure 1. The Heartstring device (unfolded).

device (Medtronic, Minneapolis, MN, USA) was used to stabilize the heart. The left anterior descending artery was anastomosed first, followed by the right coronary artery and, finally, the left circumflex artery. IMAs were either left in situ or used as T grafts, but they were not implanted into the aorta. The Heartstring device was used for implanting radial arteries and veins proximally into the ascending aorta without side-clamping (Figure 1). This device is a commercially available proximal seal system that allows the construction of proximal bypass anastomoses in a standard hand-sewn fashion without the use of clamps. Intraoperative assessment of graft function was made via Doppler measurement (CardioMed Flowmeter; Medi-Stim, Oslo, Norway) after bypass completion. Heparin was antagonized with an equivalent dose of protamine. After the placement of drains, the sternum was fixed with wires, and the soft tissues were adapted plane by plane in the common fashion. If the patient did not tolerate mobilization of the heart despite an optimal volume and inotropic management, an intra-aortic balloon pump was inserted via percutaneous puncture of the femoral artery. This procedure was required in 8 patients (3.1%). If hemodynamic instability persisted, extracorporeal circulation was established through cannulation of the ascending aorta and the right atrium, and the surgery was continued under a “beating heart” technique without aortic cross-clamping. This protocol was necessary in 6 patients (2.3%).

Insertion of Heartstring Device

A hole was punched into the ascending aorta, without side-clamping, and the seal was inserted (Figure 2). The delivery



Figure 2. Schematic drawing of the Heartstring device after insertion into the aortic lumen.

tube was pulled back, releasing the seal, which then temporarily occluded the hole from inside the aorta. The anastomosis between the aorta and the graft was constructed in a standard fashion with 6-0 Prolene running suture (Ethicon, Somerville, NJ, USA). Optimal visibility during construction of the anastomosis was ensured via use of a blower that applied CO₂ to prevent ambient air emboli. After completion of the anastomosis, the seal was removed.

Transit-Time Flow Measurement

Blood flow through the grafts was assessed intraoperatively via transit-time flow measurement (CardioMed Flowmeter). The pulsatile index (PI) is proportional to the vascular resistance and is expressed as follows: (Maximum Flow – Minimum Flow)/(Mean Flow Volume). A PI <5 is considered to indicate good bypass function [Di Giammarco 2006].

Postoperative Treatment

The patients received 500 mg aspirin intravenously 2 hours after the end of surgery, followed by 100 mg orally once a day. A 300-mg loading dose of clopidogrel was given on the first postoperative day, and clopidogrel administration was continued at a daily dosage of 75 mg. Heparin therapy was started 2 hours postoperatively at a thromboprophylactic dosage.

Postoperative Assessments

Perioperative ischemia was assessed by measuring creatine kinase (CK), the CK-MB isoform of CK, and troponin I;

Table 1. Preoperative Patient Characteristics*

Male/female sex, %	81/19
Age, y	66.0 ± 9.8
Height, cm	169.8 ± 12.5
Weight, kg	80.2 ± 14.9
EuroSCORE	5.4 ± 3.7
Ejection fraction, %	57 ± 16
Presence of intra-aortic balloon pump, %	7.7
Cardiovascular risk factors, %	
Diabetes mellitus	26.5
Hypertension	73.1
Smoking	63.8
Familial disposition	34.2
Urgency, %	
Elective	70.4
Urgent	19.2
Emergent	10.4

*Data are presented as the mean ± SD where indicated.

electrocardiography and echocardiography evaluations were also performed. Perioperative ischemia was diagnosed if the CK value was >1000 U/L along with a CK-MB fraction of >10% and/or a troponin I concentration >10 g/L, combined with newly detected Q waves on the electrocardiogram and/or wall motion abnormalities in the echocardiogram. The decision to perform re sternotomy because of bleeding was guided by hemodynamic instability, the need for transfusion of blood products, and detection of hemodynamically relevant pericardial effusion in the echocardiography evaluation. Neurologic tests included clinical examination and cranial computed tomography and electroencephalography evaluations.

After informed consent was obtained, 25 patients were randomly selected to undergo additional coronary angiography assessment of postoperative graft patency. Cardiac catheterization was performed in a standard fashion. Both native coronary arteries and all bypass grafts were selectively visualized in multiple projections via 6F diagnostic catheters in the right femoral artery. For the purposes of the study, graft patency was defined as either occluded or patent (a graft was considered patent when the angiographic assessment indicated freedom from stenosis of 50%).

Statistical Analysis

Values are presented as the mean ± SD or as a percentage of the entire cohort. The study was descriptive, and hence no statistical tests were conducted.

RESULTS

Patients

The preoperative characteristics are shown in Table 1. The mean age of the patients was 66.0 years, and the majority of

Table 2. Revascularization Profile

Distal Anastomoses	Total No.	No. per Patient*
All	981	3.8 ± 0.9
Arterial (left or right IMA, † left radial artery)	353	1.4 ± 0.6
Venous	628	2.4 ± 0.9

*Data are presented as the mean ± SD.

†IMA indicates internal mammary artery.

Table 3. Intraoperative Evaluation of Bypasses Performed with Heartstring-Assisted Proximal Anastomoses*

	Bypass to:		
	Diagonal Branch of Left Anterior Descending Artery	Left Circumflex Coronary Artery	Right Coronary Artery
Flow, mL/min	32.3 ± 24.3	26.8 ± 18.5	31.1 ± 22.1
Pulsatile index	2.5 ± 1.0	2.6 ± 1.1	2.8 ± 1.8

*Data are presented as the mean ± SD.

the patients were male. The mean EuroSCORE was 5.4. The most common cardiovascular risk factors were hypertension and smoking, each of which was reported in approximately two thirds of the patients.

Revascularization

The numbers and types of grafts used are summarized in Table 2. A total of 442 proximal anastomoses were performed with the aid of the Heartstring device, with a mean of 1.7 ± 0.5 grafts per patient. These grafts comprised 435 venous grafts and 7 radial artery grafts. The 442 grafts were used for 635 distal anastomoses (628 venous and 7 radial artery anastomoses). The left IMA was used in 98% of the patients, and the right IMA was used in 32%.

Insertion of the Heartstring Device

Intraoperative handling of the Heartstring device was uncomplicated. There were no failures of the device that necessitated aortic side-clamping.

Intraoperative Graft Assessment

Intraoperative Doppler measurements of bypass flow and the PI showed that the grafts for which proximal anastomoses were performed with the Heartstring device functioned normally (Table 3).

Perioperative Mortality and Morbidity

Perioperative mortality and morbidity data are summarized in Table 4. Four patients died within 30 days of surgery: 1 patient from multiorgan failure after 6 days, 1 patient from hypoxic brain injury after 4 days, and 2 patients from acute myocardial failure (one after several hours and the other after 1 day). Autopsy revealed open bypasses in both of the patients who died from myocardial failure.

Table 4. Clinical Outcomes (N = 260)

30-Day mortality, % (n)	1.5 (4)
Stroke, % (n)	0.8 (2)
Perioperative myocardial ischemia, % (n)	3.1 (8)
Resternotomy due to bleeding, % (n)	4.6 (12)
Aortic dissection, % (n)	0 (0)

Two patients experienced stroke. One experienced hypoxic brain injury and subsequently died. In this patient, the procedure had been switched from the off-pump procedure to an on-pump protocol because of hemodynamic instability and the need for cannulation of a severely atherosclerotic aorta. The other patient developed mild right-arm paresis and dysidiadochokinesia, and a cranial computed tomography revealed no intracerebral lesions.

Eight patients experienced perioperative myocardial ischemia, and they all recovered uneventfully. One underwent an angiography evaluation, which showed an open Heartstring-assisted bypass.

Twelve patients underwent a resternotomy procedure because of bleeding. One patient who exhibited a coagulation disorder postoperatively was found to have a small bleed from a proximal Heartstring-assisted anastomosis. There were no cases of aortic dissection.

Postoperative Graft Evaluation by Coronary Angiography

Coronary angiography evaluations in the early postoperative period showed patency of all 42 Heartstring-assisted proximal anastomoses (Table 5).

DISCUSSION

Stroke may reduce the benefit of OPCAB procedures considerably. In conventional CABG, which uses extracorporeal circulation and cross-clamping of the aorta, the stroke rate amounts to 2% to 3% [Zangrillo 2005]. Controversy remains as to whether OPCAB, which does not use a heart-lung machine, has a positive impact on the stroke rate. Several studies have shown that OPCAB surgery reduces the incidence of neurologic complications [Kapetanakis 2004], whereas other studies have not supported this finding [Berson 2004]. It appears that OPCAB does not improve the neurologic outcome as much as expected. Many studies of OPCAB have not differentiated between clampless and side-clamping techniques for proximal bypass anastomoses; therefore, it remains unclear whether the continued use of side-clamping could have been responsible for the absence of a reduction in stroke rate. Doppler measurements have shown that both cross-clamping and side-clamping of the aorta for proximal bypass anastomoses produce embolic signs that correlate with neurologic complications, such as stroke and neuropsychological deficits [Barbut 1994; Pugsley 1994; Kapetanakis 2004]. Thus, in order to reduce the stroke rate, efforts have been undertaken to avoid side-clamping of the aorta. One strategy is complete arterial revascularization with a technique involving “no touch” of the aorta, and another

Table 5. Postoperative Patency of Proximal Bypass Anastomoses Performed with the Heartstring Device

Patients, n	25
Proximal anastomoses with Heartstring, n	42
Postoperative days after surgery, d*	5.4 ± 2.4 (2-15)
Patency of proximal anastomoses, %	100

*Data are presented as the mean SD (range).

is the use of proximal-anastomosis devices. The incidence of stroke was reported to be significantly reduced in a series of patients in whom the aorta was left untouched by creating arterial conduits arranged in T grafts or in situ configurations [Kapetanakis 2004]. However, depending on the coronary anatomy, the availability of arterial grafts, and the patient's preoperative condition, not all patients qualify for complete arterial revascularization with aortic no-touch techniques. In such cases, bypasses need to be implanted into the aorta.

For avoiding side-clamping of the aorta for proximal anastomoses, various anastomotic devices have been developed. All studies have reported safe handling of the devices with no major neurologic complications, although neurocognitive assessments were not performed [Scarborough 2003; Athanasiou 2006; Guerrieri Wolf 2007].

There has been very little description in the literature of experiences with the Heartstring device. Several authors have described small numbers of OPCAB patients (1-31) in whom the Heartstring has been used [Medalion 2004; Vicol 2005; Kanemitsu 2006; Guerrieri Wolf 2007], although some studies investigated the use of the device only in patients with diseased aortas [Medalion 2004]. Three strokes were reported, 1 stroke due to air embolism and 2 due to potential atheroembolism in patients with diseased aortas [Vicol 2005; Kanemitsu 2006]. In the current report, we present the largest reported series of patients in whom OPCAB techniques were combined with a clampless approach to proximal bypass anastomoses. We switched to the Heartstring device as a proximal-anastomosis tool after we experienced complications (including early graft occlusion and aortic dissection) with the Symmetry Aortic Connector System (St. Jude Medical, St. Paul, MN, USA) [Reuthebuch 2004]. One of the potential advantages of the Heartstring device is that no foreign material remains in the aortic wall after its use, and therefore it cannot cause intimal hyperplasia or graft occlusion [Cavendish 2004]. With the Heartstring device, the proximal anastomosis is constructed in a classic fashion with a conventional 6/0 Prolene running suture. The 0.8% incidence of stroke in our series compares favorably with the stroke rate reported for on-pump CABG surgery (approximately 2% to 3%) and with the stroke rate in some OPCAB studies that failed to demonstrate a reduction in neurologic events compared with on-pump surgery [Berson 2004; Zangrillo 2005]. One might expect an even lower rate of stroke in our study, however. Indeed, the rate of neurologic events is reduced to 0.4% if we no longer consider the patient with hypoxic brain injury as an OPCAB patient after the patient's conversion to on-pump

surgery; therefore, this patient would have been excluded from the study. After the first 2 anastomoses were performed with the OPCAB technique, this patient was switched to an on-pump beating heart procedure because of hemodynamic instability. The severely diseased aorta was cannulated under emergency conditions; consequently, this situation did not allow exploration for a plaque-free area in the aorta. The 2 proximal bypass anastomoses were constructed on pump. Thus, it is not clear whether the cerebral injury was due to cannulation of the calcified aorta, which appears likely, or to the performance of the proximal bypass anastomosis. The symptoms were mild in the other patient who experienced a stroke, and the lack of ischemic signs in the cranial computed tomography results indicated a good long-term recovery. Only overt neurologic events, such as stroke, were recorded in the present study; subtle postoperative neurologic deficits and neurocognitive dysfunction were not assessed. Even with the use of proximal-anastomosis devices, microemboli associated with subtle neurologic deficits may occur, predominantly when the aorta is punched for creation of the bypass ostium [Martens 2004].

No other severe adverse events that could be attributed to the use of the Heartstring device occurred in our patients. Two other groups have reported air embolism with use of the Heartstring device [Nollert 2003; Vicol 2005]. We did not experience this complication because we used a CO₂ blower. Furthermore, no cases of aortic dissection have been observed thus far. This result is in contrast to other reports that have described this complication after use of a different proximal-anastomosis device or following aortic side-clamping. One injury of the aorta posterior wall with an automatic aortic cutter prior to inserting the Heartstring [Syburra 2009] has been reported thus far. Bypass stenosis or occlusion appears to occur very rarely following use of the Heartstring device. Coronary angiography evaluations performed in a sample of 25 randomly selected patients showed an early patency rate of 100%. This result corresponds with findings from other studies that used the Heartstring device, which found patency rates before hospital discharge of between 97.5% and 100% [Vicol 2005]. In contrast, occlusion and stenosis rates of 4% to 38% have been reported a few months after surgery with the most frequently used proximal-anastomosis device, the Symmetry aortic connector [Carrel 2003; Traverse 2003; Cavendish 2004; Reuthebuch 2004; Kiramura 2005]. The rate of perioperative ischemia was comparable to that seen in other studies with OPCAB in which conventional methods were used for proximal bypass anastomoses [Wijesundera 2005]. This finding therefore indicates that use of the Heartstring device at least did not lead to an increased rate of graft occlusion compared with conventional hand-sewn proximal bypass anastomoses, although this result requires confirmation in prospective randomized trials comparing the 2 methods. Bleeding from the proximal bypass anastomoses was negligible.

The current study, nevertheless, has several limitations. The data originate from a retrospective survey, and only short-term follow-up data are available. A prospective, randomized study with an extended follow-up would be required to fully

demonstrate a potential benefit of the Heartstring device. The neurologic assessments should also include neurocognitive-function tests. Angiographic evaluation of the grafts was limited in the current study, and future studies of graft patency should include a larger number of patients. In addition, the patency rate should be assessed as a continuous variable instead of as a categorical one. Such an assessment may be facilitated by the availability of the latest developments in computed tomography cardiac-scanning techniques.

In summary, use of the Heartstring device for performing proximal bypass anastomoses during OPCAB surgery is associated with a very low rate of stroke. The early rates of patency and bypass function are excellent, and adverse events have been negligible. Prospective randomized studies are required to further evaluate graft patency and the occurrence of adverse events over a long-term follow-up.

REFERENCES

- Athanasios T, Ashrafian H, Krasopoulos G, et al. 2006. Clamless arterial coronary artery bypass grafting with the use of magnetic coupling devices. *J Card Surg* 21:69-74; discussion 75-6.
- Barbut D, Hinton RB, Szatrowski TP, et al. 1994. Cerebral emboli detected during bypass surgery are associated with clamp removal. *Stroke* 25:2398-402.
- Berson AJ, Smith JM, Woods SE, Hasselfeld KA, Hiratzka LF. 2004. Off-pump versus on-pump coronary artery bypass surgery: does the pump influence outcome? *J Am Coll Surg* 199:102-8.
- Carrel TP, Eckstein FS, Englberger L, Windecker S, Meier B. 2003. Pitfalls and key lessons with the Symmetry proximal anastomotic device in coronary artery bypass surgery. *Ann Thorac Surg* 75:1434-6.
- Cavendish JJ, Penny WF, Madani MM, et al. 2004. Severe ostial saphenous vein graft disease leading to acute coronary syndromes following proximal aorto-saphenous anastomoses with the symmetry bypass connector device: is it a suture device or a "stent"? *J Am Coll Cardiol* 43:133-9.
- Di Giammarco G, Pano M, Cirmeni S, Pelini P, Vitolla G, Di Mauro M. 2006. Predictive value of intraoperative transit-time flow measurement for short-term graft patency in coronary surgery. *J Thorac Cardiovasc Surg* 132:468-74.
- Guerrieri Wolf L, Abu-Omar Y, Choudhary BP, Pigott D, Taggart DP. 2007. Gaseous and solid cerebral microembolization during proximal aortic anastomoses in off-pump coronary surgery: the effect of an aortic side-biting clamp and two clamless devices. *J Thorac Cardiovasc Surg* 133:485-93.
- Kanemitsu S, Tanaka K, Suzuki H, Tokui T, Kinoshita T. 2006. The HEARTSTRING proximal seal system is a possible source of atheroembolism. *Circ J* 70:638-40.
- Kapetanakis EI, Stamou SC, Dullum MK, et al. 2004. The impact of aortic manipulation on neurologic outcomes after coronary artery bypass surgery: a risk-adjusted study. *Ann Thorac Surg* 78:1564-71.
- Kitamura H, Okabayashi H, Hanyu M, et al. 2005. Early and midterm patency of the proximal anastomoses of saphenous vein grafts made with a Symmetry Aortic Connector System. *J Thorac Cardiovasc Surg* 130:1028-31.
- Mark DB, Newman MF. 2002. Protecting the brain in coronary artery bypass graft surgery. *JAMA* 287:1448-50.

- Martens S, Dietrich M, Herzog C, et al. 2004. Automatic connector devices for proximal anastomoses do not decrease embolic debris compared with conventional anastomoses in CABG. *Eur J Cardiothorac Surg* 25:993-1000.
- Medalion B, Meirson D, Hauptman E, Sasson L, Schachner A. 2004. Initial experience with the Heartstring proximal anastomotic system. *J Thorac Cardiovasc Surg* 128:273-7.
- Murkin JM, Boyd WD, Ganapathy S, Adams SJ, Peterson RC. 1999. Beating heart surgery: why expect less central nervous system morbidity? *Ann Thorac Surg* 68:1498-501.
- Newman MF, Grocott HP, Mathew JP, et al. 2001. Report of the sub-study assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. *Stroke* 32:2874-81.
- Nollert G, Oberhoffer M, Reichart B, Vicol C. 2003. Combination of the HEARTSTRING proximal seal system with a blower mister: a possible source of gas emboli. *J Thorac Cardiovasc Surg* 126:1192-4.
- Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S. The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. *Stroke* 25:1393-9.
- Reuthebuch O, Kadner A, Lachat M, Kunzli A, Schurr UP, Turina MI. 2004. Early bypass occlusion after deployment of nitinol connector devices. *J Thorac Cardiovasc Surg* 127:1421-6.
- Scarborough JE, White W, Derilus FE, Mathew JP, Newman MF, Landolfo KP. 2003. Combined use of off-pump techniques and a sutureless proximal aortic anastomotic device reduces cerebral microemboli generation during coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 126:1561-7.
- Syburra T, Reuthebuch O, Graves K, Genoni M. 2009. Aortic posterior wall perforation with automatic aortic cutter during routine off-pump coronary bypass grafting. *Interact Cardiovasc Thorac Surg* 9:840-1.
- Traverse JH, Mooney MR, Pedersen WR, et al. 2003. Clinical, angiographic, and interventional follow-up of patients with aortic-saphenous vein graft connectors. *Circulation* 108:452-6.
- Vicol C, Oberhoffer M, Nollert G, et al. 2005. First clinical experience with the HEARTSTRING, a device for proximal anastomoses in coronary surgery. *Ann Thorac Surg* 79:1732-7; discussion 1737.
- Wijeysundera DN, Beattie WS, Djaiani G, et al. 2005. Off-pump coronary artery surgery for reducing mortality and morbidity: meta-analysis of randomized and observational studies. *J Am Coll Cardiol* 46:872-82.
- Zangrillo A, Crescenzi G, Landoni G, et al. 2005. Off-pump coronary artery bypass grafting reduces postoperative neurologic complications. *J Cardiothorac Vasc Anesth* 19:193-6.