CLINICAL STUDY

Effects of a Proximal Seal System on Neurologic Outcomes of Off-Pump Coronary Artery Bypass Grafting

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Summary

Severe aortic atherosclerosis is a risk factor for stroke during coronary artery bypass grafting (CABG). The purpose of this study was to evaluate the incidence of postoperative neurologic complications after off-pump CABG (OPCAB) with a proximal seal system (Heartstring).

From January 2011 to December 2014, 729 patients underwent isolated OPCAB. The cohort was divided into two groups (Heartstring [HS] and aortic no-touch [NT]). The severity of aortic atherosclerosis (Katz grade) was evaluated by intraoperative epiaortic ultrasonography (EUS). The primary endpoints were postoperative neurologic complications (early stroke and minor events (delirium, transient ischemic attack, and syncope)), and the secondary endpoints were late major adverse cardiac and cerebrovascular events (MACCEs) and death.

The mean age of all patients was 65.1 ± 9.5 years, and a severe Katz grade (IV or V) was demonstrated to be an independent risk factor of long-term mortality (HR 3.53; 95% CI 1.06-11.75; P = 0.04) and MACCEs (HR 2.41; 95% CI 1.19-4.92; P = 0.02), but no significant differences were found for early stroke (0.9% versus 1.7%; P = 0.53) and minor neurologic complications (14.6% versus 9.9%; P = 0.05) between the groups regardless of the Katz grade. The 5-year overall survival rate did not differ significantly between the groups (90.9% versus 87.6%; P = 0.61).

Although a higher Katz grade was identified as an independent risk factor of death and MACCEs, the HS group was not inferior in terms of neurologic complications regardless of the Katz grade. Therefore, the Heartstring system might be safely and efficiently used with EUS to decrease the incidence of neurologic complications.

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Key words: Atherosclerosis, Myocardial revascularization, Stroke

Severe aortic atherosclerosis is a risk factor for stroke and neurocognitive dysfunction during coronary artery bypass grafting (CABG).[1-4] The avoidance of aortic manipulation and cross-clamping and the use of clampless anastomotic devices is associated with a significant reduction in the risk of intraoperative embolic events.[5,6] Multiple studies have reported postoperative stroke rates between 1% and 5%.[6-9] Although aortic no-touch techniques, in which the internal thoracic artery (ITA) is used in situ and/or composite T or Y grafting is performed with no clamping during off-pump CABG (OPCAB), have resulted in lower stroke rates than conventional CABG[10], these methods may not be applicable for every case, including urgent and emergent cases. In addition, this surgical strategy is more technically demanding than graft anastomosis to the ascending aorta and may not supply sufficient blood flow to the entire ischemic myocardium because it is dependent on a single inflow from the left ITA. To overcome the limitations of the aortic no-touch technique, we designed this study and considered the aortocoronary configuration, particularly in OPCAB.

Recently, the Heartstring proximal seal system (Maquet Cardiovascular, San Jose, CA) has been used to minimize the risk of stroke and to accomplish a proximal aortic anastomosis to the diseased ascending aorta without partial clamping.[11-13] Indeed, intraoperative epiaortic ultrasonography (EUS) has also been recommended as superior to transesophageal echocardiography for the detection of the calcified ascending aorta and aortic arch during cardiac surgery.[14-16] This change in the surgical approach might result in improved postoperative neurologic outcomes. The purpose of this study was to evaluate the incidence of postoperative neurologic complications after OPCAB between the group in which the Heartstring system

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was used and the aortic no-touch group.

Methods

Study population: We retrospectively analyzed 803 consecutive patients who had undergone primary isolated OPCAB by two experienced surgeons at Severance Cardiovascular Hospital, Younsei University College of Medicine from January 2011 to December 2014. Seventy-four patients who had undergone on-pump CABG, emergent surgery, or minimally invasive surgery were excluded from the study. Of the 729 patients who were included, the Heartstring proximal anastomotic device was used in 323 patients (HS group), and the aortic no-touch technique was performed in 406 (NT group). Preoperative risk factors included age, sex, body mass index, preoperative comorbidities, a history of percutaneous coronary intervention with stenting, New York Heart Association functional class, left main coronary artery stenosis of 50% or greater, logistic Euroscore, and echocardiographic indicators such as the left ventricular ejection fraction. Perioperative variables recorded included in-hospital death, renal failure, pulmonary complications, reoperation for bleeding, and neurologic complications.

Epiaortic ultrasound scanner: After median pericardiotomy, EUS was routinely used as an intraoperative tool to assess the atherosclerotic plaque in the ascending aorta and was performed with a 7- to 14-MHz biplane linear ultrasound probe (Acuson 15 L8 probe) connected to an echocardiography ultrasound scanner (Acuson Sequoia Ultrasound System, Siemens Medical Solutions USA, Mountain View, CA). The embolic potential of the ascending aorta in the proximal, middle, and distal segments, the proximal aortic arch, and the descending aorta was evaluated by EUS under the direction and interpretation of the attending cardiac anesthesiologists. The degree of aortic atherosclerosis was graded according to the classification of Katz and colleagues:[15,17] grade I is normal, grade II is nonprotruding intimal thickening of the entire lumen and atheroma greater than 2 mm, grade III is atheroma less than 4 mm, grade IV is atheroma greater than 4 mm, and grade V is any mobile or ulcerated plaques.

We considered the location of the atherosclerotic lesion to determine whether to perform aortic manipulation. For cases in which the severity of ascending aortic atherosclerosis was less than grade III, we considered manipulation of the aorta using the Heartstring system to be safe. In cases with grade IV or V disease, we considered a restricted condition. The Heartstring system was used if atherosclerotic lesions were located on the posterior wall of the ascending aorta or the proximal aortic arch or if diffuse atheroma lesions were located sufficiently far from the site of manipulation. Although grade V disease was located on the mobile plaque of the descending aorta, the Heartstring system was used in non-diseased segments of the ascending aorta. The image of the aortic wall was confirmed by the surgeons and anesthesiologists according to the results of EUS.

Heartstring device: The proximal graft anastomoses were performed on non-diseased segments of aorta as assessed by EUS. The Heartstring system consists of an aortic cutter to create a circular aortotomy, a coiled device delivered through the aortotomy to form a hemostatic seal, and a proximal seal to unfold within the aorta. When the anastomosis is completed, the Heartstring is removed from the aorta before the suture is tightened.

Surgical technique: All OPCAB operations were performed via a standard median sternotomy. One or both ITAs were harvested routinely in a semi-skeletonized method. If necessary, the radial artery from the nondominant forearm (using a pedicle method) and a long saphenous vein graft were simultaneously harvested. Heparin (100 U/kg) was administered to maintain a target activated clotting time of greater than 300 seconds during the operation. The revascularization strategy was decided according to the size and degree of stenosis of the target coronary vessel and the atherosclerotic status of the ascending aorta. We routinely used intraoperative EUS before surgical manipulation of the aorta. The proximal anastomosis was performed with the Heartstring in the noncalcified segment of the ascending aorta. For cardiac displacement and stabilization, an Octopus tissue stabilizer Positioner (Medtronic, Minneapolis, MN) or a Maquet stabilizing device was used to safely expose the target vessel. Visualization of the sites of aortotomy during construction of the anastomosis was enhanced with a humidified carbon dioxide blower (Medtronic Clear View; Medtronic, Inc.) and irrigation with warm saline solution. The patency of all grafts was confirmed by flow measurements at the end of the bypass procedures.

Outcome measures: Postoperative neurologic complications were classified as early stroke or minor events (delirium, transient ischemic attack (TIA), and syncope). Early stroke was defined as a newly appearing neurologic deficit after the OPCAB procedure that remains at least partially evident for more than 24 hours after its onset. Overall neurologic complications were diagnosed before hospital discharge. Our definition of overall neurologic complications included TIA, defined as a fully reversible neurologic deficit that lasts less than 24 hours; delirium, defined as a transient and serious disturbance in attention and cognition that develops over a short period of time according to DSM-5 criteria; and early stroke, defined as events that last more than 24 hours and less than 30 days. In addition to clinical symptoms, diagnoses were confirmed by a neurologist on the basis of brain imaging.

Long-term outcomes were assessed by all-cause mortality and major adverse cardiac and cerebrovascular events (MACCEs), which were defined as death from any cause, nonfatal myocardial infarction, target vessel revascularization, or stroke. Target vessel revascularization was defined as any reintervention to treat luminal stenosis in the initially treated vessels.

Data collection: Preoperative and perioperative data were obtained from the cardiac research databases at our institution and reviewed in the hospital charts. Follow-up was performed during patient visits or by telephone. The median follow-up duration was 38.0 months (range, 0.4 to 63.9 months). Institutional review board approval from the Yonsei University College of Medicine was obtained for this retrospective study. Individual patient consent was waived because this study did not interfere with patient

Table I. Patient Characteristics and Perioperative Data

Variable	HS Group (*n* = 323)	NT Group (*n* = 406)	*P*
Age (y)	64.5 ± 9.4	65.5 ± 9.6	0.167
Female	77 (23.8)	112 (27.6)	0.251
Body mass index (kg/m^2)	24.2 ± 3.0	24.5 ± 3.2	0.324
Smoking	180 (55.7)	218 (53.7)	0.584
Hypertension	243 (75.2)	317 (78.1)	0.366
Diabetes mellitus	160 (49.5)	186 (45.8)	0.317
Dyslipidemia	147 (45.5)	180 (44.3)	0.751
Cerebrovascular accidents	41 (12.7)	56 (13.8)	0.664
Chronic obstructive pulmonary disease	12 (3.7)	10 (2.5)	0.326
Peripheral artery occlusive disease	37 (11.5)	31 (7.6)	0.078
Chronic kidney disease	52 (16.1)	61 (15.0)	0.690
Previous PCI	58 (18.0)	65 (16.0)	0.486
NYHA ≥ III	98 (30.3)	119 (29.3)	0.763
Euroscore	4.77 ± 3.2	4.74 ± 2.9	0.915
Three-vessel disease	277 (85.8)	336 (82.8)	0.271
Left main disease	112 (34.7)	104 (25.6)	0.008
Left ventricular ejection fraction (%)	55.0 ± 15.1	54.7 ± 14.4	0.778
Number of distal anastomoses	3.43 ± 0.81	3.05 ± 0.75	< 0.001
Total arterial graft	25 (7.7)	254 (62.6)	< 0.001
Composite Y graft	131 (40.6)	393 (96.8)	< 0.001
Complete revascularization	290 (89.8)	350 (86.2)	0.143
Free graft			
Saphenous vein	293 (90.7)	155 (38.2)	< 0.001
Radial artery	131 (40.6)	246 (60.6)	< 0.001
Katz grade			
I-II	52 (16.1)	63 (15.5)	0.830
III	117 (36.2)	148 (36.5)	0.949
IV-V	154 (47.7)	195 (48.0)	0.925

Values are mean ± SD or *n* (%). NYHA indicates New York Heart Association; and PCI, percutaneous coronary intervention.

treatment.

Statistical analysis: Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). All data are presented as the mean ± SD or frequencies and percentages. Comparisons of patients were performed with Student's *t*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Long-term survival and freedom from MACCEs were estimated by the Kaplan-Meier method, and comparisons between groups were performed with the log-rank test. Multivariable logistic regression analysis was used to calculate odds ratios (ORs) to determine the independent predictors of postoperative neurologic complications. The Cox proportional hazard regression model was used to analyze risk factors for time-related events (overall survival, MACCEs, and late-onset stroke), and *P* values of less than 0.05 were considered to indicate statistical significance.

Results

Patient characteristics and perioperative data: Preoperative and perioperative patient characteristics and echocardiographic data are summarized in Table I. The mean of all patients' ages was 65.1 ± 9.5 years, and the incidences of other preoperative risk factors were similar except for left main coronary artery disease (34.7% in the HS group versus 25.6% in the NT group; $P = 0.01$). Aorta atherosclerotic status was graded as normal or mild (Katz grade I or II) in 15.8%, moderate (grade III) in 36.4%, and severe (grades IV and V) in 47.9%. The mean number of distal anastomoses per patient was 3.43 ± 0.81 in the HS group and 3.05 ± 0.75 in the NT group ($P < 0.01$). The number of proximal anastomoses per patient was 1.03 ± 0.17. Only 10 patients (3.1%) had two proximal anastomoses using radial artery and saphenous vein grafts.

Early and late clinical outcomes: As seen in Table II, no statistically significant differences between groups were found in early complications or in-hospital mortality. Patients in the HS group showed a slightly higher tendency of minor (14.6% versus 9.9%; $P = 0.05$) and overall neurologic complications (15.2% versus 10.6%; $P = 0.06$) than those who underwent no-touch procedures, but these findings did not reach statistical significance.

The 5-year overall survival rate and the rate of freedom from MACCEs were 90.9 ± 1.8% and 88.2 ± 2.1% in the HS group and 87.6 ± 2.1% and 81.2 ± 2.6% in the NT group, respectively (Log-rank $P = 0.61$ and $P = 0.18$). These rates did not differ significantly between groups (Figure 1). The incidences of stroke according to aortic grade were I ($n = 0$, 0%), II ($n = 3$, 0.4%), III ($n = 4$, 0.5%), IV ($n = 13$, 1.8%), and V ($n = 2$, 0.3%). The frequency of stroke was similar between the groups regard-

Table II. Early and Late Clinical Outcomes

Variable	HS Group (n = 323)	NT Group (n = 406)	P
Early results			
In-hospital death	3 (0.9)	4 (1.0)	> 0.999
Reoperation for bleeding	2 (0.6)	2 (0.5)	> 0.999
Newly required dialysis	7 (2.2)	6 (1.5)	0.485
Overall neurologic complication	49 (15.2)	43 (10.6)	0.064
Early stroke	3 (0.9)	7 (1.7)	0.525
Minor neurologic complication	47 (14.6)	40 (9.9)	0.052
Delirium	44 (13.6)	39 (9.6)	0.090
Transient ischemic attack	2 (0.6)	0 (0.0)	0.196
Syncope	2 (0.6)	1 (0.2)	0.587
Pulmonary complication	32 (9.9)	43 (10.6)	0.763
Postoperative atrial fibrillation	87 (26.9)	89 (21.9)	0.116
Wound problems	34 (10.5)	43 (10.6)	0.977
Operative time (minutes)	248.5 ± 41.8	222.6 ± 36.3	< 0.001
Intensive care unit stay (hours)	76.9 ± 107.5	83.0 ± 155.6	0.548
Late results			
MACCEs	32 (9.9)	59 (14.5)	0.061
Death	24 (7.4)	39 (9.6)	0.299
Nonfatal MI	0 (0.0)	2 (0.5)	0.506
Stroke	7 (2.2)	15 (3.7)	0.231
Target vessel revascularization	3 (0.9)	8 (2.0)	0.362

Values are mean ± SD or n (%). MACCEs indicates major adverse cardiac and cerebrovascular events; and MI, myocardial infarction.

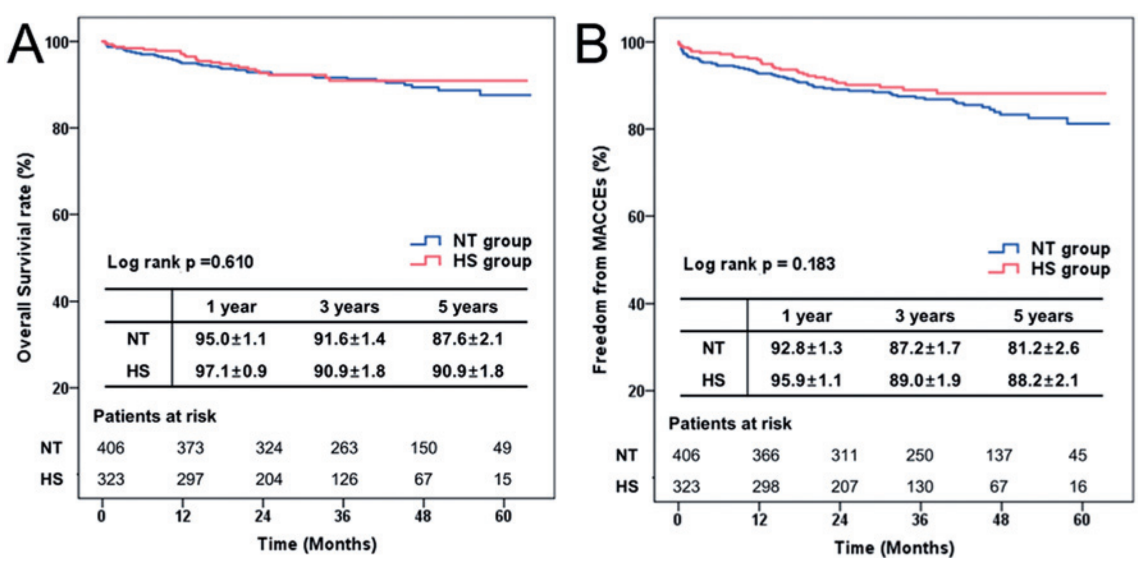

Figure 1. Overall survival rates (**A**) and rates of freedom (**B**) from major adverse cardiac and cerebrovascular events in the Heartstring (HS) group (red lines) and no-touch (NT) group (blue lines).

less of the Katz grade (n = 7, 2.2% in the HS group versus n = 15, 3.7% in the NT group, P = 0.23).

In the HS group, 4 patients had Katz grade 2 (one with syncope and 3 with delirium), 22 patients had Katz grade 3 (one with early stroke, one with syncope, and 21 with delirium), 19 patients had Katz grade 4 (one with early stroke, one with TIA, and 17 with delirium), and 5 patients had Katz grade 5 (one with early stroke, one with TIA, and 3 with delirium). In the NT group, 4 patients had Katz grade 2 (two with early strokes and 3 with delirium), 8 patients had Katz grade 3 (two with early strokes and 8 with delirium), 26 patients had Katz grade 4 (two with early strokes, one with syncope, and 23 with delirium), and 5 patients had Katz grade 5 (one with early stroke and 5 with delirium).

Regardless of Katz grade, the rate of freedom from stroke at 5 years was 97.7 ± 0.9% in the HS group and 94.5 ± 1.8% in the NT group (Log-rank P = 0.31, Figure 2).

Predictors of survival and MACCEs: Multivariable lo-

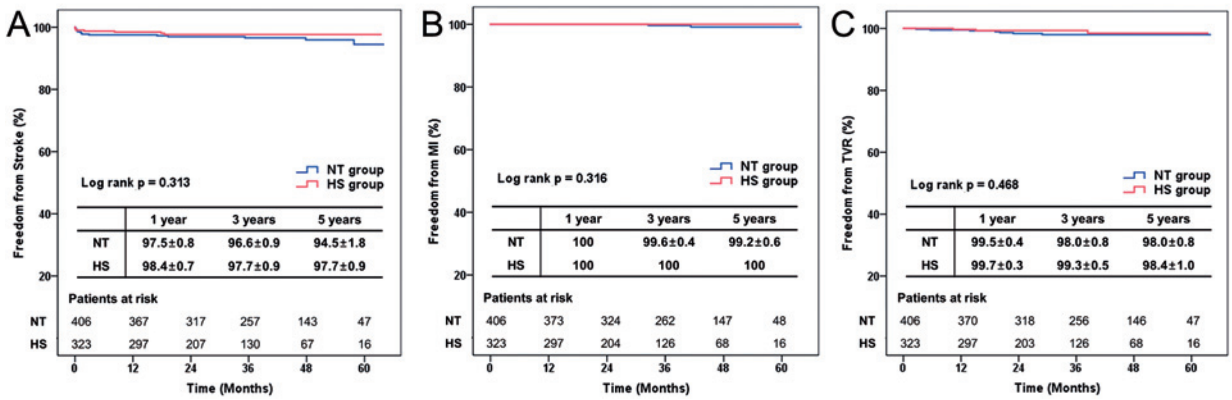

Figure 2. Rates of freedom from stroke (**A**), nonfatal myocardial infarction (**B**), and target vessel revascularization (**C**) in the Heartstring (HS) group (red lines) and no-touch (NT) group (blue lines).

Table III. Predictors of Early Stroke, Minor, and Overall Neurologic Complications

Variable	Early stroke		Minor neurologic complications		Overall neurologic complications	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age			1.10 (1.06 to 1.14)	< 0.001	1.09 (1.05 to 1.13)	< 0.001
Previous PCI			1.95 (1.10 to 3.48)	0.023	1.76 (1.00 to 3.10)	0.052
Left main disease	6.17 (1.55 to 24.57)	0.010				
Heartstring	0.44 (0.11 to 1.75)	0.245	1.67 (1.03 to 2.70)	0.038	1.60 (1.00 to 2.55)	0.049
Postoperative AF			3.04 (1.88 to 4.94)	< 0.001	3.07 (1.91 to 4.92)	< 0.001
Katz score						
moderate	0.80 (0.13 to 4.93)	0.805	1.05 (0.42 to 2.63)	0.922	0.93 (0.39 to 2.23)	0.875
severe	0.79 (0.15 to 4.17)	0.778	0.99 (0.40 to 2.45)	0.989	1.01 (0.43 to 2.36)	0.990

AF indicates atrial fibrillation; CI, confidence interval; OR, odds ratio; and PCI, percutaneous coronary intervention.

Table IV. Multivariate Cox Proportional Hazard Regression Analysis for Long-Term Survival, MACCEs, and Stroke

Variable	Overall Survival			MACCEs			Stroke		
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate	
	P	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*
Age	< 0.001	1.04 (1.00 to 1.07)	0.049	0.002	1.02 (0.99 to 1.05)	0.164			
Chronic kidney disease	0.001	3.09 (1.83 to 5.23)	< 0.001	< 0.001	2.11 (1.32 to 3.38)	0.002			
Postoperative AF	0.008	1.37 (0.81 to 2.34)	0.242	0.035	1.27 (0.80 to 2.01)	0.306			
Heartstring	0.610	0.99 (0.59 to 1.65)	0.960	0.184	0.79 (0.51 to 1.22)	0.283	0.317	0.63 (0.26 to 1.55)	0.316
Katz mild (reference)									
moderate	0.588	1.01 (0.27 to 3.72)	0.990	0.903	0.88 (0.39 to 1.95)	0.743	0.443	0.55 (0.12 to 2.44)	0.427
severe	0.003	3.53 (1.06 to 11.75)	0.040	0.014	2.41 (1.19 to 4.92)	0.015	0.403	1.67 (0.48 to 5.76)	0.419

AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; and MACCEs, major adverse cardiac and cerebrovascular events.

gistic regression analysis for minor neurologic complications revealed that age (OR, 1.10; 95% CI, 1.06 to 1.14; $P < 0.01$), a history of previous percutaneous coronary intervention (OR, 1.95; 95% CI, 1.10 to 3.48; $P = 0.02$), use of the Heartstring system (OR, 1.67; 95% CI, 1.03 to 2.70; $P = 0.04$), and postoperative atrial fibrillation (OR, 3.04; 95% CI, 1.88 to 4.94; $P < 0.01$) were independent predictors (Table III). Left main coronary artery disease was independently associated with an increased incidence of early stroke (OR, 6.17; 95% CI, 1.55 to 24.57; $P = 0.01$).

Cox regression multivariate analysis demonstrated that the independent risk factors of long-term mortality were chronic kidney disease (hazard ratio [HR], 3.09; 95% CI, 1.83 to 5.23; $P < 0.01$) and severe Katz grade (IV or V; HR, 3.53; 95% CI, 1.06 to 11.75; $P = 0.04$). The independent predictors of MACCEs were chronic kidney disease (HR, 2.11; 95% CI, 1.32 to 3.38; $P < 0.01$) and severe Katz grade (HR, 2.41; 95% CI, 1.19 to 4.92; $P = 0.02$). In subgroup analysis, a severe Katz grade was demonstrated to be an independent risk factor of long-term mortality and MACCEs (Table IV and Figure 3).

Discussion

Cerebrovascular accidents and neurocognitive dysfunction have been recognized as major issues in patients who undergo CABG, which is associated with high morbidity and mortality rates.[9,18] This study evaluated the efficacy of the Heartstring system with EUS for prevention of

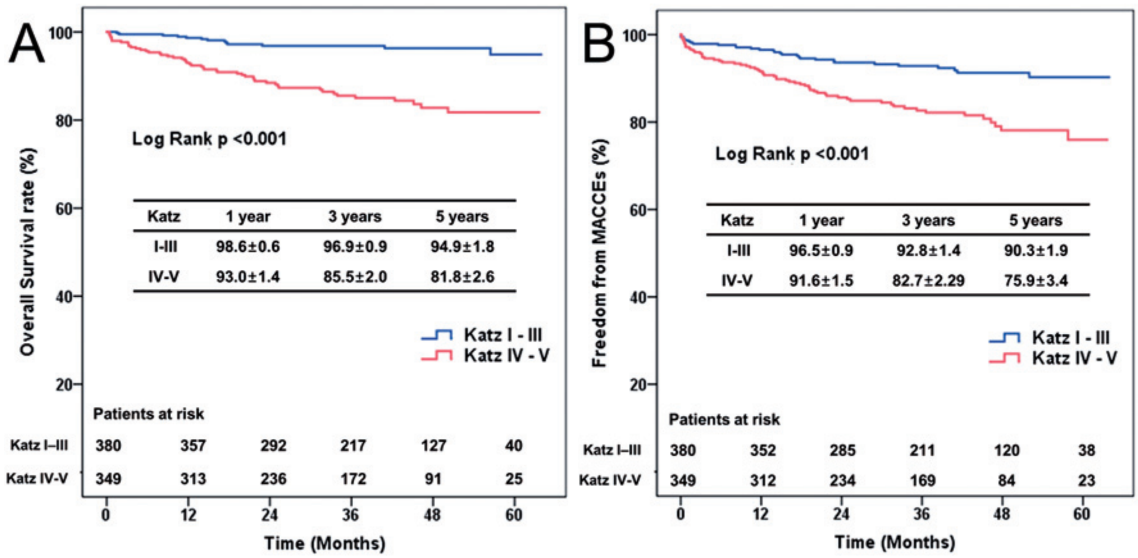

Figure 3. Overall survival rates (**A**) and rates of freedom (**B**) from major adverse cardiac and cerebrovascular events in group with Katz score of IV to V group (red lines) compared with group with Katz score of I to III (blue lines).

postoperative neurologic complications in patients who underwent isolated OPCAB. We showed that the Heartstring system does not increase early morbidity rates, overall mortality rates, or the incidence of MACCEs and stroke when compared with aortic no-touch techniques.

Intraoperative EUS has recently been recommended as a diagnostic tool to assess the diseased ascending aorta. Several studies have shown that EUS is superior to assessment by palpation and transesophageal echocardiography for the detection of atherosclerotic lesions over the ascending aorta and proximal aortic arch.[14,15,19,20] Joo, *et al*. reported that the early stroke rate for patients in whom EUS was used was similar between the groups with partial clamping and nonaortic clamping (0.8% versus 0.7%).[21] These results demonstrated that EUS bestows a significant benefit by reducing the early stroke rate in cases of aortic manipulation during OPCAB. In our study, intraoperative transesophageal echocardiography or EUS have been used routinely to evaluate atherosclerosis of the ascending aorta, proximal aortic arch, and descending aorta. The use of EUS with the Heartstring system could contribute to better long-term outcomes than aortic no-touch techniques, including the 5-year overall survival rate ($P = 0.61$) and freedom from stroke rate ($P = 0.31$).

Our study aimed to compare clinical outcomes between groups. Evidence has shown that the use of composite Y/T grafts to avoid any manipulation of the diseased ascending aorta results in a low stroke rate. Although OPCAB with total arterial revascularization has been proposed as the gold standard approach to reduce neurocognitive dysfunction only for patients with severe atherosclerosis,[10,22] this no-touch procedure may not be routinely applied, particularly in emergent cases. Left ITA to Y graft anastomosis is more technically demanding than that of the ascending aorta and can result in a potential steal phenomenon of the left ITA by the anastomosed graft because most of the coronary circulation is supplied through a single inflow from the left ITA. Therefore, for these reasons, direct aortic anastomosis using the Heartstring system was considered to be an effective alternative method when composite grafts are not available, particularly in cases with a moderately stenotic target vessel (< 90%) and insufficient length to reach most targets.

Importantly, our study shows no difference in the incidence of stroke ($P = 0.23$) and MACCEs ($P = 0.06$) between the groups. These findings are in accordance with the results of previous studies[16] that compared total arterial revascularization versus the Heartstring system and reported that the in-hospital mortality (1.8% versus 1.1%; $P = 0.42$) and stroke rates (2.8% versus 0.5%; $P = 0.09$) did not differ between groups.

Several studies have reported the increased stroke risk associated with advanced age, hypertension, cerebrovascular disease, diabetes, and aortic atherosclerosis.[2,9] Severe atherosclerosis is one of the most important predictors of neurologic deficits after CABG.[4,23,24] Postoperative delirium, a common complication after cardiac surgery, is also associated with increased mortality rates and cognitive decline.[25-27] New ischemic lesions created by cerebral microemboli have been considered to be significant risk factors for delirium,[28] and inflammation due to emboli has been considered to alter the permeability of the blood-brain barrier, activate microglia, and influence cognitive impairment.[29,30] Carotid artery stenosis of more than 50%, advanced arteriosclerosis, and myocardial infarction also play important roles in delirium after OPCAB.[27]

We found that left main coronary artery stenosis was a risk factor for early stroke (OR, 6.17), similar to other studies. Charlesworth, *et al*. found that left main coronary artery stenosis was associated with an increased risk of stroke (left main coronary artery stenosis 50% to 89%: OR, 1.41; stenosis of 90% or more: OR. 1.60; $P < 0.001$).[31] Left main coronary artery disease has also been identified as a marker for carotid stenosis.[32] Advanced age, smoking, extensive peripheral vascular disease, female gender, history of stroke or TIA, and left main coronary stenosis are correlates of carotid disease, which is an important cause of preoperative stroke.[33,34] Moreover, the various mechanisms of stroke include arteriosclerotic emboli from the aorta, hypotension from ventricular dysfunction, and reactive thrombocytosis. Carotid artery disease and cerebral microvascular disease have also been implicated.[35]

In our study, minor neurologic complications were independently associated with the use of the Heartstring system. Although the patients in whom the Heartstring system was used had a higher rate of delirium, the difference in the incidence of minor neurologic complications was not statistically significant between the groups (P = 0.05). Therefore, the use of the Heartstring system to prevent atherosclerotic emboli might result in improved postoperative neurologic outcomes.

The incidences of early and late stroke were 0.9% and 2.2%, respectively. Similar results have been reported by other investigators.[2,8,36] To the best of our knowledge, cerebral microembolization of atheromatous material during manipulation of the aorta is the main cause of postoperative stroke.[23,24] Neurologic derangement after CABG has been attributed to hypoxia, embolism, hemorrhage, and metabolic abnormalities. Although various mechanisms have been recognized for the development of stroke in patients who undergo CABG, embolic dislodgment of atherosclerotic plaques during surgical aortic manipulation remains the major cause of stroke. The Heartstring system resulted in a significant reduction in the proportion of solid microemboli compared with the partial clamping group (1% versus 23%; $P < 0.001$).[3,37] The largest analysis of 1,380 patients who underwent CABG with the Heartstring system showed no significant difference in the rate of postoperative stroke according to aortic atherosclerosis grade (1.2%, P = 0.83). Using grade I as the reference group, the adjusted OR of stroke was 0.97 (95% CI, 0.26 to 3.66) with grade II, 0.84 (95% CI, 0.22 to 3.25) with grade III, and 0.94 (95% CI, 0.10 to 8.46) with grade IV.[4] Our study shows no significant association between Katz grades and the incidence of postoperative stroke because the use of the Heartstring system with intraoperative EUS allowed the safe detection of severe atherosclerotic aortic lesions.

This study is limited by its single-center, nonrandomized, and retrospective nature. Selection bias may have occurred because the distribution of the groups was based on the surgeons'decision making. In our study, a perioperative surgical strategy was objectively determined that targeted native coronary arteries with greater than 80% stenosis at least 1 mm in diameter. Although every patient underwent OPCAB with EUS to detect aortic atherosclerosis at the site of anastomosis, we did not have a comparison group with partial clamping. The heterogeneous distribution of free grafts also makes a fair comparison difficult. Finally, this was a relatively small study and with short-term follow-up. The long-term graft patency should be evaluated with coronary angiography or computed tomography.

Conclusions

Although a higher Katz grade was identified as an independent risk factor of mortality and MACCEs, the HS group was not inferior in terms of neurologic complications regardless of the Katz grade. In conclusion, the use of the Heartstring system with the assistance of EUS during OPCAB can safely and efficiently decrease neurologic complications regardless of the atherosclerotic grade of the ascending aorta.

Disclosure

Conflicts of interest: None.

References

1. Nakamura M, Okamoto F, Nakanishi K, *et al*. Does intensive management of cerebral hemodynamics and atheromatous aorta reduce stroke after coronary artery surgery? Ann Thorac Surg 2008; 85: 513-9.
2. Hilker M, Arlt M, Keyser A, *et al*. Minimizing the risk of perioperative stroke by clampless off-pump bypass surgery: a retrospective observational analysis. J Cardiothorac Surg 2010; 5: 14.
3. El Zayat H, Puskas JD, Hwang S, *et al*. Avoiding the clamp during off-pump coronary artery bypass reduces cerebral embolic events: results of a prospective randomized trial. Interact Cardiovasc Thorac Surg 2012; 14: 12-6.
4. Thourani VH, Razavi SA, Nguyen TC, *et al*. Incidence of postoperative stroke using the Heartstring device in 1,380 coronary artery bypass graft patients with mild to severe atherosclerosis of the ascending aorta. Ann Thorac Surg 2014; 97: 2066-72.
5. Emmert MY, Grunenfelder J, Scherman J, *et al*. HEARTSTRING enabled no-touch proximal anastomosis for off-pump coronary artery bypass grafting: current evidence and technique. Interact Cardiovasc Thorac Surg 2013; 17: 538-41.
6. Moss E, Puskas JD, Thourani VH, *et al*. Avoiding aortic clamping during coronary artery bypass grafting reduces postoperative stroke. J Thorac Cardiovasc Surg 2015; 149: 175-80.
7. Sedrakyan A, Wu AW, Parashar A, Bass EB, Treasure T. Off-pump surgery is associated with reduced occurrence of stroke and other morbidity as compared with traditional coronary artery bypass grafting: a meta-analysis of systematically reviewed trials. Stroke 2006; 37: 2759-69.
8. Douglas JM Jr, Spaniol SE. A multimodal approach to the prevention of postoperative stroke in patients undergoing coronary artery bypass surgery. Am J Surg 2009; 197: 587-90.
9. Emmert MY, Seifert B, Wilhelm M, Grunenfelder J, Falk V, Salzberg SP. Aortic no-touch technique makes the difference in off-pump coronary artery bypass grafting. J Thorac Cardiovasc Surg 2011; 142: 1499-506.
10. Halbersma WB, Arrigoni SC, Mecozzi G, *et al*. Four-year outcome of OPCAB no-touch with total arterial Y-graft: making the best treatment a daily practice. Ann Thorac Surg 2009; 88: 796-801.
11. Calafiore AM, Bar-El Y, Vitolla G, *et al*. Early clinical experience with a new sutureless anastomotic device for proximal anastomosis of the saphenous vein to the aorta. J Thorac Cardiovasc Surg 2001; 121: 854-8.
12. Vicol C, Oberhoffer M, Nollert G, *et al*. First clinical experience with the HEARTSTRING, a device for proximal anastomoses in coronary surgery. Ann Thorac Surg 2005; 79: 1732-7.
13. Schoettle GP Jr, Jones CB. Hand-sewn proximal anastomoses in off-pump coronary artery bypass without the need for partial occlusion clamping: Experience with the heartstring II proximal

seal system. Innovations (Phila) 2007; 2: 198-200.

14. Davila-Roman VG, Phillips KJ, Daily BB, Davila RM, Kouchoukos NT, Barzilai B. Intraoperative transesophageal echocardiography and epiaortic ultrasound for assessment of atherosclerosis of the thoracic aorta. J Am Coll Cardiol 1996; 28: 942-7.
15. Wilson MJ, Boyd SY, Lisagor PG, Rubal BJ, Cohen DJ. Ascending aortic atheroma assessed intraoperatively by epiaortic and transesophageal echocardiography. Ann Thorac Surg 2000; 70: 25-30.
16. Manabe S, Fukui T, Miyajima K, *et al*. Impact of proximal anastomosis procedures on stroke in off-pump coronary artery bypass grafting. J Card Surg 2009; 24: 644-9.
17. Katz ES, Tunick PA, Rusinek H, Ribakove G, Spencer FC, Kronzon I. Protruding aortic atheromas predict stroke in elderly patients undergoing cardiopulmonary bypass: experience with intraoperative transesophageal echocardiography. J Am Coll Cardiol 1992; 20: 70-7.
18. Roach GW, Kanchuger M, Mangano CM, *et al*. Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 1996; 335: 1857-63.
19. Sylivris S, Calafiore P, Matalanis G, *et al*. The intraoperative assessment of ascending aortic atheroma: epiaortic imaging is superior to both transesophageal echocardiography and direct palpation. J Cardiothorac Vasc Anesth 1997; 11: 704-7.
20. Rosenberger P, Shernan SK, Loffler M, *et al*. The influence of epiaortic ultrasonography on intraoperative surgical management in 6051 cardiac surgical patients. Ann Thorac Surg 2008; 85: 548-53.
21. Joo HC, Youn YN, Kwak YL, Yi GJ, Yoo KJ. Intraoperative epiaortic scanning for preventing early stroke after off-pump coronary artery bypass. Br J Anaesth 2013; 111: 374-81.
22. Nicolini F, Agostinelli A, Spaggiari I, *et al*. Current trends in surgical revascularization of multivessel coronary artery disease with arterial grafts. Int Heart J 2014; 55: 381-5.
23. Davila-Roman VG, Murphy SF, Nickerson NJ, Kouchoukos NT, Schechtman KB, Barzilai B. Atherosclerosis of the ascending aorta is an independent predictor of long-term neurologic events and mortality. J Am Coll Cardiol 1999; 33: 1308-16.
24. Eldaif SM, Thourani VH, Puskas JD. Cerebral Emboli Generation During Off-Pump Coronary Artery Bypass Grafting With a Clampless Device versus Partial Clamping of the Ascending Aorta. Innovations (Phila) 2010; 5: 7-11.
25. McKhann GM, Grega MA, Borowicz LM Jr, *et al*. Encephalopathy and stroke after coronary artery bypass grafting: incidence, consequences, and prediction. Arch Neurol 2002; 59: 1422-8.
26. Gottesman RF, Grega MA, Bailey MM, *et al*. Delirium after coronary artery bypass graft surgery and late mortality. Ann Neurol 2010; 67: 338-44.
27. Miyazaki S, Yoshitani K, Miura N, *et al*. Risk factors of stroke and delirium after off-pump coronary artery bypass surgery. Interact Cardiovasc Thorac Surg 2011; 12: 379-83.
28. Omiya H, Yoshitani K, Yamada N, *et al*. Preoperative brain magnetic resonance imaging and postoperative delirium after off-pump coronary artery bypass grafting: a prospective cohort study. Can J Anaesth 2015; 62: 595-602.
29. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry 2013; 21: 1190-222.
30. Soeki T, Sata M. Inflammatory biomarkers and atherosclerosis. Int Heart J 2016; 57: 134-9.
31. Charlesworth DC, Likosky DS, Marrin CA, *et al*. Development and validation of a prediction model for strokes after coronary artery bypass grafting. Ann Thorac Surg 2003; 76: 436-43.
32. Rao V, Christakis GT, Weisel RD, *et al*. Risk factors for stroke following coronary bypass surgery. J Card Surg 1995; 10: 468-74.
33. Berens ES, Kouchoukos NT, Murphy SF, Wareing TH. Preoperative carotid artery screening in elderly patients undergoing cardiac surgery. J Vasc Surg 1992; 15: 313-21.
34. Puskas JD, Winston AD, Wright CE, *et al*. Stroke after coronary artery operation: incidence, correlates, outcome, and cost. Ann Thorac Surg 2000; 69: 1053-6.
35. Sato K, Fujiyoshi K, Hoshi K, *et al*. Low stroke rate of carotid stenosis under the guideline-oriented medical treatment compared with surgical treatment. Int Heart J 2016; 57: 80-6.
36. Biancari F, Yli-Pyky S. Meta-analysis on the use of the Heartstring anastomotic device to prevent stroke in patients undergoing off-pump coronary artery bypass grafting. Eur J Cardiothorac Surg 2011; 40: 1236-40.
37. Guerrieri Wolf L, Abu-Omar Y, Choudhary BP, Pigott D, Taggart DP. Gaseous and solid cerebral microembolization during proximal aortic anastomoses in off-pump coronary surgery: the effect of an aortic side-biting clamp and two clampless devices. J Thorac Cardiovasc Surg 2007; 133: 485-93.