Risk of stroke early after implantation of a left ventricular assist device

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ABSTRACT

Objective: Stroke is one of the major adverse events after left ventricular assist device implantation. Risk of stroke is the highest immediately after left ventricular assist device implantation and then increases again in chronic periods. There is no study that has analyzed risk factors for stroke in acute phase. We investigated the risk factors for stroke in the acute phase after left ventricular assist device implantation in the present study.

Methods: Between October 2005 and December 2016, 158 consecutive patients (mean age, 43 ± 14 years; 34% were women) underwent continuous-flow left ventricular assist device (50 HeartMate II [Abbott Medical, Abbott Park, Ill], 38 DuraHeart [Terumo Heart, Ann Arbor, Mich], 33 Jarvik2000 [Jarvik Heart, New York, NY], 23 EVAHEART [Sun Medical, Moriyama City, Japan], 14 HeartWare [Framingham, Mass]) implantation in our institution. We analyzed the risk factors for a symptomatic stroke within 90 days after left ventricular assist device implantation.

Results: Stroke occurred in 28 patients in the acute phase after left ventricular assist device implantation. Multivariate analysis revealed that low cardiac output (odds ratio, 0.25; 0.07-0.92; $P = .024$) during postoperative 12 to 24 hours was the only independent risk factor for stroke in the acute phase. Patients with stroke in the acute phase had higher serum lactate dehydrogenase levels at any point until postoperative 14 days. Patients with the HeartMate II device particularly showed a statistically significant negative relationship between cardiac output during postoperative 12 to 24 hours and serum lactate dehydrogenase levels at postoperative 14 days ($r = -0.313$, $P = .03$).

Conclusions: Our study demonstrated that patients with perioperative lower cardiac output and higher lactate dehydrogenase level developed stroke in the acute phase after left ventricular assist device implantation. These results suggested that maintenance of sufficient left ventricular assist device flow is important in prevention of stroke, which may be related to subclinical pump thrombosis. (J Thorac Cardiovasc Surg 2019;157:259-67)

Postoperative course of the minimum cardiac output in patients with stroke versus stroke-free patients.

Central Message

Perioperative lower cardiac output is strongly related to stroke in the acute phase after LVAD implantation.

Perspective

Patients with perioperative lower cardiac output and higher LDH level developed stroke in the acute phase after LVAD implantation. These results suggested that maintenance of sufficient LVAD flow plays a critical role in prevention of stroke, which may be related to subclinical pump thrombosis.

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The evolution of implantable continuous-flow left ventricular assist devices (LVADs) has resulted in the prevailing treatment option for patients with end-stage heart failure.^{1,2} Although a continuous-flow LVAD is associated with a lower

Scanning this QR code will take you to a supplemental table and video for the article.

Abbreviations and Acronyms

aPTT	= activated partial thromboplastin time
CT	= computed tomography
INR	= international normalized ratio
LDH	= lactate dehydrogenase
LVAD	= left ventricular assist device
PT-INR	= prothrombin time international normalized ratio

rate of stroke than the older pulsatile LVAD, stroke remains a major adverse event.^{3,4} A previous report revealed that the risk for stroke after LVAD implantation showed a bimodal reversed J-shaped curve with the highest risk immediately after LVAD implantation, which then increases again at postoperative 9 to 12 months.⁵ This result implies that the cause of stroke should be divided into 2 phases: the acute phase and the chronic phase. We have previously revealed that systemic bacteremia was an independent risk factor for hemorrhagic stroke in the chronic phase.⁴ We have also reported that age was an independent risk factor for stroke in the acute phase.⁴ However, in the previous study, we were not able to include data on postoperative hemodynamic and laboratory parameters in data analysis; therefore, we could not demonstrate how to perform postoperative management in the acute phase to prevent stroke. In the present study, we analyzed the risk factors for stroke after LVAD implantation in the acute phase, along with postoperative hemodynamic parameters and laboratory parameters.

MATERIALS AND METHODS

Patients

The ethical committee of our hospital approved this study. Between January 2005 and December 2016, 158 patients (mean age, 43 ± 14 years, 53 women) underwent continuous-flow LVAD implantation for end-stage heart failure at Osaka University Hospital. We evaluated the incidence of stroke in these patients and analyzed the risk factors for symptomatic stroke within 90 days after LVAD implantation. All patients and their family members provided informed consent to participate in related clinical studies before LVAD implantation.

Devices and Surgical Procedures

The type of LVAD used in each patient was decided at the preoperative conference, although available devices have changed over the years in Japan. Briefly, the DuraHeart (Terumo Heart, Ann Arbor, Mich) and EVAHEART (Sun Medical, Moriyama City, Japan) were approved in October 2011, the HeartMate II (Abbott Medical, Abbott Park, Ill) was approved in April 2013, and the Jarvik2000 (Jarvik Heart, New York, NY) was approved in May 2014, whereas the HeartWare (HeartWare, Framingham, Mass) is presently available only for clinical trial use. Before 2010, the DuraHeart and Jarvik2000 were primarily used at Osaka University in a clinical trial subsidized by the Ministry of Health and Labor of Japan.

A detailed method of continuous-flow LVAD implantation has been described.^{6,7} Generally, patients underwent LVAD implantation thorough

a median sternotomy with a systemic cardiopulmonary bypass, during which the inflow cannula was inserted into the apex of the left ventricle and the outflow graft was anastomosed to the ascending aorta. Three patients underwent Jarvik2000 implantation through a left thoracotomy with a descending aorta anastomosis of the outflow graft because of the previous cardiac surgery. In patients with mild or greater aortic insufficiency, aortic valve closure with bovine pericardial patch or replacement with a tissue valve was performed, whereas mitral valve repair was done in patients with severe functional mitral regurgitation at the discretion of the surgeons. We typically perform a tricuspid valve procedure in cases with moderate or greater tricuspid regurgitation. The decision regarding concomitant right ventricular assist device insertion was made individually for each patient by the attending surgeons.

Anticoagulant and Medical Therapy During Left Ventricular Assist Device Support

After LVAD implantation, all patients received a standardized heart failure prevention medical regimen, including neurohormonal antagonists, diuretics, and antiarrhythmic agents, as needed. Aspirin (100 mg daily) monotherapy was also started from the day after LVAD implantation and was maintained throughout LVAD support, unless major bleeding occurred. Anticoagulation therapy with warfarin was also initiated 24 hours after surgery and maintained at the target international normalized ratio (INR) of 2.0 to 2.5 for patients with a HeartMate II or DuraHeart, and 2.5 to 3.0 for those with a HeartWare, EVAHEART, or Jarvik2000. These different anticoagulation thresholds depend on the company's recommendation. Systemic heparinization was initiated when drainage became less than 100 mL in the previous 3 hours. We checked the activated partial thromboplastin time (aPTT) twice per day and managed to achieve a target aPTT (50-60 seconds) before achieving the target INR. Perioperative antibiotic therapy was routinely managed by experienced intensive care unit physicians. Postoperative mean blood pressure was usually controlled under 85 mm Hg.

Definition and Management of Left Ventricular Assist Device–Related Adverse Events

Preoperative neurologic examination using physical examination and brain computed tomography (CT) was routinely performed in all patients. Postoperatively, if patients had any neurologic symptoms, including headache, dizziness, lightheadedness, syncope, or convulsion, we always performed brain CT without delay and referred to neurologists. A definition of stroke event has been described.⁴ A stroke event was defined as a neurologic symptom lasting for more than 24 hours with a compatible new lesion shown in brain CT scans. Stroke events are subdivided into ischemic and hemorrhagic stroke events. In the present study, hemorrhagic stroke included cerebral, cerebellum, and subarachnoid hemorrhaging, as well as subdural hematoma. Ischemic stroke was defined as a cerebral or cerebellum infarction without hemorrhagic lesions detected by brain CT scan. Headache or convulsion without any sustained neurologic deficit was not defined as an episode of stroke, unless patients had new lesions identified during neuroimaging. Furthermore, we defined the acute phase as within 90 days after LVAD implantation.⁴ Upon the occurrence of an LVAD-related stroke, treatment management was based on the discussion among experienced cardiologists, cardiovascular surgeons, neurosurgeons, and neurologists. The termination and reinitiation of antiplatelet or anticoagulation therapy was also managed after the discussion.

When our patients have any type of cerebral infarction, they are usually examined using CT angiography, and the indication of selective angiography or thrombectomy and the enforcement of antiplatelet and anticoagulant therapy are discussed with neurologists and neurosurgeons. On the other hand, when our patients have any type of intracranial hemorrhage lesion, antiplatelet and anticoagulant therapies are immediately ceased, normalization of INR using factor-IX or

fresh-frozen plasma is started, and closed consecutive follow-up brain CT is performed until complete hemostasis is confirmed.

Data Collection

All patient data were obtained from the electronic medical records, including baseline characteristics, comorbidities, types of LVAD, and duration of LVAD implantation. Baseline characteristics (demographics, etiologies), laboratory values, hemodynamics, carotid Doppler, intraoperative parameters (cardiopulmonary bypass time, operation time, amount of blood products used, concomitant cardiac procedures), and postoperative complications were also collected from the electronic medical records and operative records. Postoperative hemodynamic parameters (central venous pressure, cardiac output, cardiac index) of Swan-Ganz catheter were collected from the intensive care unit medical charts. We further subdivided these hemodynamic parameters into 4 periods: postoperative 0 to 12 hours, 12 to 24 hours, 24 to 36 hours, and 36 to 48 hours, and the maximum and minimum digits of these hemodynamic parameters were manually extracted. Postoperative laboratory values were routinely evaluated every day until postoperative day 7. Unless patients had no serious complications, routine postoperative transthoracic echocardiography, the parameters of which were adopted in the present study, was performed within 4 weeks after LVAD implantation.

Statistical Analysis

All statistical analyses were performed using JMP version 12.0 (SAS Institute Inc, Cary, Calif) software. Categorical variables were summarized as frequencies and percentages and compared among groups using a chi-square or Fisher exact test. Continuous variables are summarized as the mean $\pm$ standard deviation or median (interquartile range [IQR]) after testing for normality using the Shapiro–Wilk W test. All *P* values for statistical analysis were 2 tailed.

The incidence rate of stroke was estimated using Kaplan–Meier curves, and multiple regression analysis was used to identify the risk factors for stroke within 90 days after LVAD implantation. Baseline characteristics, laboratory values, hemodynamics, intraoperative parameters (cardiopulmonary bypass time, operation time, amount of blood products used, concomitant cardiac procedures), postoperative parameters (maximum central venous pressure within postoperative 48 hours, minimum cardiac output, and cardiac index within postoperative 48 hours), complications (the amount of blood products used within postoperative 24 hours, blood loss within postoperative 24 hours, reexploration of bleeding, and requirement for continuous venovenous hemodialysis or right ventricular assist device), postoperative laboratory values, and parameters of postoperative transthoracic echocardiography were used as factors for this analysis. Initially, univariate analysis was applied, and then factors with a *P* value less than .05 were considered for a multiple regression model to identify risk factors.

RESULTS

Baseline Characteristics

Patients' mortality with an LVAD at 90, 180, and 360 days after implantation was 5%, 8%, and 13%, respectively. A total of 40 patients (25%) underwent heart transplantation with a mean waiting duration of 29 ± 12 months. The preoperative characteristics of the 158 enrolled patients are shown in Table 1. The mean age was 43 ± 14 years, and 53 patients (34%) were women. Because of the strict indications and eligibility requirements for placement on the heart transplantation list, comorbidity prevalence was low. The majority of these patients had idiopathic-dilated cardiomyopathy, and 97% of the entire cohort underwent

LVAD implantation as a bridge-to-transplantation therapy, because destination therapy was not approved in Japan at the end of December 2016.

Incidence of Stroke and Comparison of Baseline Characteristics

Of these 158 patients, 28 (18%) developed stroke within 90 days of LVAD implantation. The rate of stroke at 7, 30, and 90 days was 4%, 7%, and 18%, respectively (Figure 1). The incidence of stroke within 90 days was more than half of that within 1 year, because the rate of stroke at 90, 180, and 360 days was 18%, 20%, and 32%, respectively, whereas that of stroke-related death was 5%, 5%, and 10%, respectively. Furthermore, hazard function of stroke showed a J-shaped curve with the highest risk immediately after LVAD implantation, which then increases again at postoperative 9 to 12 months (Figure 1, B). The details of stroke in the acute phase are summarized in Table E1. For those with stroke in the acute phase, cerebral infarction occurred in 8 patients, intracerebral hemorrhage occurred in 10 patients, subarachnoid hemorrhage occurred in 8 patients, and subdural hematoma occurred in 2 patients. Among patients with cerebral infarction, thrombectomy was performed in 2 patients, and 6 patients were managed by strengthening of the anticoagulation therapy. Every patient with cerebral infarction fully recovered without any permanent neurologic deficit. Among patients with intracerebral hemorrhage, all 10 patients were managed by infusion of factor-IX and fresh-frozen plasma transfusion. Three of them required decompressive craniectomy for salvage, although 5 (50%) of 10 patients died, including 1 patient who underwent craniectomy. Meanwhile, LVAD pump thrombosis occurred in 2 patients in the acute phase. Of these, 1 patient (case 17) who was supported by the HeartMate II device and developed severe hemolysis with the maximum serum lactate dehydrogenase (LDH) level of 3400 U/mL at postoperative 36 days required emergency exchange of the HeartMate II LVAD and experienced cerebral infarction 16 days after the conversion. The other patient who was supported by the HeartMate II device also developed hemolysis with the maximum serum LDH level of 2000 U/mL at postoperative 41 days and required emergency conversion of the HeartMate II LVAD. The patient did not develop stroke during the follow-up period.

The comparison of patient characteristics, operative details, and postoperative echocardiographic parameters between patients with and without stroke in the acute phase is detailed in Table 1. Patients with stroke were significantly older, and stroke was more prevalent in women. Body surface area was significantly smaller in patients with stroke. There were no statistical differences among the etiologies, types of LVAD, preoperative hemodynamic, and laboratory valuables, except for the preoperative blood

TABLE 1. Factors associated with stroke in acute phase (n = 158)

	All (n = 158)	Stroke (–) (n = 130)	Stroke (+) (n = 28)	P value
Age at LVAD implantation (y)	43 ± 14	42 ± 14	48 ± 17	.013
Female, n (%)	53 (34)	39 (30)	14 (50)	.049
Body surface area (m ²)	1.6 ± 0.2	1.6 ± 0.2	1.5 ± 0.2	.006
Body mass index (kg/m ²)	19.9 ± 3.1	20.1 ± 3.1	18.8 ± 3.3	.096
Complications				
Previous stroke, n (%)	10 (6)	8 (6)	2 (7)	.855
Diabetes mellitus, n (%)	24 (15)	19 (15)	5 (18)	.677
Hypertension, n (%)	12 (8)	8 (6)	4 (14)	.144
INTERMACS profile				
Profile I, n (%)	15 (10)	13 (10)	2 (7)	1.000
Profile II, n (%)	56 (35)	45 (35)	11 (39)	.667
Profile III, n (%)	59 (37)	49 (38)	10 (36)	1.000
Profile IV, n (%)	5 (3)	3 (2)	2 (7)	.215
Bridge to bridge, n (%)	23 (15)	20 (15)	3 (11)	.768
Cause				
Ischemic cardiomyopathy, n (%)	20 (13)	14 (11)	6 (21)	.128
Idiopathic dilated cardiomyopathy, n (%)	91 (57)	76 (58)	15 (54)	.676
Hypertrophic cardiomyopathy, n (%)	22 (14)	19 (15)	3 (11)	.767
Devices				
HeartMate II (Abbott Medical, Abbott Park, Ill), n (%)	50 (32)	42 (32)	8 (28)	.824
DuraHeart (Terumo Heart, Ann Arbor, Mich), n (%)	38 (24)	35 (27)	3 (11)	.088
Jarvik2000 (Jarvik Heart, New York, NY), n (%)	33 (20)	24 (19)	9 (32)	.125
EVAHEART (Sun Medical, Moriyama City, Japan), n (%)	23 (15)	18 (14)	5 (18)	.562
HeartWare (Framingham, Mass), n (%)	14 (9)	11 (8)	3 (11)	.715
Preoperative hemodynamics				
Central venous pressure (mm Hg)	8.1 ± 4.9	8.1 ± 5.0	8.5 ± 4.8	.524
Mean pulmonary artery pressure (mm Hg)	28.4 ± 10.1	28.3 ± 10.1	29.3 ± 10.5	.647
Pulmonary wedge capillary pressure (mm Hg)	20.5 ± 8.4	20.4 ± 8.7	21.2 ± 7.4	.561
Cardiac index (L/min/m ²)	2.1 ± 0.6	2.2 ± 0.6	2.1 ± 0.5	.584
Inotropes, n (%)	138 (88)	115 (88)	23 (85)	.745
Intra-aortic balloon pumping, n (%)	27 (17)	21 (16)	6 (21)	.579
Intubation, n (%)	28 (18)	22 (17)	6 (21)	.580
Use of extracorporeal LVAD, n (%)	29 (19)	6 (4)	2 (7)	.622
Preoperative echocardiographic parameters				
LVDd (mm)	69.0 ± 13.3	70.1 ± 13.1	65.0 ± 14.3	.061
LVDs (mm)	63.5 ± 14.0	64.5 ± 13.6	60.0 ± 15.7	.099
Left ventricular ejection fraction (LVEF, %)	20.7 ± 8.8	20.4 ± 8.2	22.2 ± 11.3	.695
Preoperative laboratory valuables				
Hemoglobin (g/dL)	11.2 (9.88-12.9)	11.6 (10.0-13.2)	10.8 (9.8-11.6)	.073
White blood cell count (×1000/mm ³)	6.6 (4.9-8.0)	6.6 (4.9-8.0)	6.5 (4.8-7.8)	.973
BUN (mg/dL)	19 (13-25)	18 (13-25)	21 (16-26)	.098
Creatinine (mg/dL)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.0 (0.7-1.5)	.681
eGFR (mL/min/1.73 m ²)	58 (44-82)	58 (45-83)	59 (36-76)	.495
Aspartate transaminase (IU/dL)	27 (21-36)	27 (21-36)	26 (20-36)	.573
Alanine transaminase (IU/dL)	23 (15-37)	24 (17-37)	18 (13-35)	.108
Total bilirubin (mg/dL)	1.0 (0.6-1.5)	1.0 (0.6-1.5)	0.8 (0.6-1.6)	.970
Albumin (mg/dL)	3.8 (3.2-4.1)	3.8 (3.2-4.2)	3.7 (2.9-4.1)	.400
LDH (IU/L)	248 (205-359)	248 (205-359)	263 (199-366)	.849

(Continued)

TABLE 1. Continued

	All (n = 158)	Stroke (–) (n = 130)	Stroke (+) (n = 28)	P value
Operative values				
Re-do surgery, n (%)	50 (32)	38 (31)	12 (43)	.181
CPB time (min)	150 ± 62	145 ± 59	174 ± 69	.028
Aortic valve surgery, n (%)	10 (6)	7 (6)	3 (11)	.375
Perioperative characteristics				
Blood loss within 24 h (mL)	1360 (964-1993)	1415 (976-2131)	1101 (882-1598)	.071
RBC transfusion in postoperative 24 h (mL)	483 (233-960)	538 (250-1031)	275 (10-745)	.094
FFP transfusion in postoperative 24 h (mL)	775 (477-1258)	800 (475-1257)	660 (488-1231)	.533
Postoperative echocardiographic parameters				
Postoperative LVDd (mm)	53.9 ± 14.7	49.6 ± 14.7	54.8 ± 15.0	.218
Postoperative LVDs (mm)	48.7 ± 15.4	43.9 ± 15.4	49.7 ± 15.6	.207
Postoperative LVEF (%)	22.8 ± 12.1	21.8 ± 11.9	25.0 ± 14.4	.441

Blood loss within 24 hours, total amount of drainage tube within 24 hours. LVAD, Left ventricular assist device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; CPB, cardiopulmonary bypass; RBC, red blood cell; FFP, fresh-frozen plasma.

urea nitrogen levels, although there was a trend of the left ventricle being smaller in patients with stroke. As for the operative and postoperative parameters, patients with stroke had significantly longer cardiopulmonary bypass time. There was a trend of less blood products required by patients with stroke compared with patients without stroke, and the total amount of drainage tube during the first 24 days was significantly less in patients with stroke.

Change of Laboratory and Hemodynamic Parameters

We compared the change of serum coagulant factor during the first 2 weeks (prothrombin time international normalized ratio [PT-INR], aPTT, and serum LDH) between patients with and without stroke in the acute phase (Figure 2, A-C). There were 57% and 62% of all patients whose PT-INR was in normal ranges at postoperative 7 days and 14 days, respectively. There was no significant difference in the change of PT-INR between patients with and without stroke throughout the first 2 weeks

(Figure 2, A). Although patients with stroke had higher aPTT levels at 2 and 3 postoperative days than patients without stroke, there was no statistical difference at 4 days postsurgery and thereafter (Figure 2, B). In contrast, patients with stroke in the acute phase had significantly higher LDH levels from the first postoperative day to 2 weeks postsurgery (Figure 2, C).

Figure 3 shows the change of postoperative minimum cardiac output (Figure 3, A) and minimum cardiac index (Figure 3, B) of Swan-Ganz catheter during the first 2 postoperative days. In the overall cohort, patients with stroke had significantly lower minimum cardiac output between 12 and 48 postoperative hours than patients without stroke (Figure 3, A). When we evaluated the minimum cardiac index, patients with stroke had a significantly lower cardiac index at 12 to 24 hours (Figure 3, B). Because our cohort included both axial and centrifugal LVADs, we subdivided LVADs into these 2 types (Figure 4). Seventeen patients with axial LVAD and 11 patients with centrifugal LVAD developed stroke in the

FIGURE 1. A, Incidence rates of overall stroke in the entire cohort. B, Hazard function of stroke after LVAD implantation. LVAD, Left ventricular assist device.

FIGURE 2. Postoperative course of (A) INR, (B) aPTT, and (C) serum LDH levels during the first postoperative 2 weeks. The horizontal line in the middle of each box indicates the median; the top and bottom borders of the box mark the 75th and 25th percentiles, respectively; and the whiskers mark the 90th and 10th percentiles. INR, International normalized ratio; CVA, cerebrovascular accident; LVAD, left ventricular assist device; aPTT, activated partial thromboplastin time; LDH, lactate dehydrogenase.

acute phase. In both types of LVADs, patients with stroke tended to have lower cardiac output and index than patients without stroke. The minimum cardiac output between 24 and 36 postoperative hours in patients with stroke was significantly lower than in patients without stroke (Figure 4, A and B).

Risk Factors for Stroke

The risk factors for stroke in the acute phase are summarized in Table 2. Parameters with a statistically

significant difference in comparison between patients with and without stroke in the acute phase were studied in the multivariate analysis. For postoperative minimum cardiac output, cardiac output during postoperative 12 to 24 hours was included because this period had the strongest odds ratio. Multivariate analysis revealed that low cardiac output (odds ratio, 0.25; 0.07-0.92; $P = .024$) during postoperative 12 to 24 hours was the only independent risk factor for stroke in acute phase after LVAD implantation (Table 2). Age, female sex, body surface area, and cardiopulmonary

FIGURE 3. Postoperative course of (A) the minimum cardiac output in patients with stroke (red line) versus stroke-free patients (blue line) and (B) minimum cardiac index in patients with stroke (red line) versus stroke-free patients (blue line) after LVAD implantation. CVA, Cerebrovascular accident; LVAD, left ventricular assist device.

FIGURE 4. Postoperative course of (A) the minimum cardiac output in patients with stroke (red line) versus stroke-free patients (blue line) after axial type LVAD implantation and (B) the minimum cardiac output in patients with stroke (red line) versus stroke-free patients (blue line) after centrifugal type LVAD implantation. CVA, Cerebrovascular accident; LVAD, left ventricular assist device.

bypass time were not considered as risk factors for stroke in the acute phase.

Relation Between Hemodynamic Parameters and Coagulant Factors

Because the minimum cardiac output at postoperative 12 to 24 hours was the exclusive risk factor for stroke in the acute phase and serum LDH level was significantly higher in patients with stroke, we further evaluated the relationship between the minimum cardiac output at 12 to 24 hours and the serum LDH level at postoperative 3, 7, and 14 days (Figure 5, A-C). To eliminate the device bias, we evaluated the mentioned relationship in 50 patients with the HeartMate II device. Although there was no significant correlation between the minimum cardiac output and the serum LDH level until 7 days, a significant negative correlation was present at 14 days ($r = -0.313$, $P = .03$).

DISCUSSION

In the present study, stroke rate at 90 days, 180 days, and 1 year was 18%, 20%, and 32%, respectively. More than one half of stroke events within 1 year occurred within 90 days postoperatively, whereas the stroke rate from postoperative 90 to 180 days was only 2%. Frontera and colleagues⁵ reported that the risk for stroke after LVAD implantation showed a bimodal J-shaped curve, with the highest risk immediately after LVAD implantation, which then increased again at postoperative 9 to 12 months. The

present study revealed a result similar to the previous study (Figure 1, B). The previous study and ours may imply that the cause of stroke could be divided into 2 phases: the acute phase and the chronic phase. We have also previously revealed that systemic bacteremia was an independent risk factor for hemorrhagic stroke in the chronic phase, whereas age was an independent risk factor for stroke in the acute phase.^{4,8} However, in our previous study, we could not include the data on the postoperative hemodynamic and laboratory parameters in the analysis. Therefore, in the previous study, it was not clear how to reduce the incidence of stroke in the acute phase.

In the analysis, PT-INR and aPTT during the first 2 weeks were almost similar, except for aPTT at 2 and 3 days, among patients with and without stroke. These results can imply that we cannot sufficiently prevent stroke in the acute phase only by meticulous management of anticoagulation with warfarin and heparinization. Instead, we revealed that patients with stroke in the acute phase had significantly higher serum LDH levels from postoperative day 1 to postoperative 2 weeks than patients without stroke. This result may indicate that stroke in the acute phase can be related to thrombotic or thrombolytic complications in the pump. Previous reports have noted that pump thrombosis often occurred in the acute phase after LVAD implantation, and evaluation of serum LDH levels provided good sensitivity and specificity to detect pump thrombosis.^{9,10} In detail, the hazard function of pump thrombosis in the

TABLE 2. Multivariable risk factors for stroke in acute phase (n = 158)

Parameters	Univariate P value	Stroke	
		Multivariate OR (95% CI)	P value
Age at LVAD implantation (y)	.013	1.04 (0.98-1.10)	.159
Female, n (%)	.049	2.02 (0.37-11.0)	.417
Body surface area (0.1 m ²)	.006	1.18 (0.74-1.89)	.485
Minimum cardiac output in postoperative 12-24 h (L/min)	.002	0.25 (0.07-0.92)	.024
CPB time (min)	.028	1.00 (0.99-1.01)	.630

OR, Odds ratio; CI, confidence interval; LVAD, left ventricular assist device; CPB, cardiopulmonary bypass.

FIGURE 5. The relationship between the minimum cardiac output and the LDH (A) at 3 days, (B) 7 days, and (C) 2 weeks after implantation of the HeartMate II (Abbott Medical, Abbott Park, Ill). LDH, Lactate dehydrogenase.

HeartMate II device peaked at approximately 2 months after LVAD implantation, and marked elevation of LDH at 1 month after LVAD implantation was a predictor of subsequent pump thrombosis.¹⁰⁻¹² Therefore, to prevent stroke in the acute phase, it is important to prevent LVAD thrombus formation during this period, although the mechanism and risk factor of thrombus formation in patients with LVADs were unclear. In the present study, we revealed that lower minimum cardiac output in the Swan-Ganz catheter, which is estimated to be almost the same as LVAD pump flow in the majority of patients, was the exclusive risk factor for stroke in the acute phase. To date, a negative correlation between the cardiac output and the incidence of stroke has not been reported. Several previous studies revealed predictors of stroke, including hypertension, female sex, and small body surface area, in the acute phase, although the detailed reasoning has not been discussed.^{12,13} All of these previously reported predictors, such as hypertension, female gender, and small body surface area, are also risk factors of low LVAD flow. Because experimental and fluid dynamic studies revealed that lower pump flow predisposes the pump to pump thrombosis (by shear stress and heat generation from pump rotor),^{14,15} we speculated that lower LVAD pump flow can precipitate subclinical pump thrombus and cause

subsequent stroke in patients with small body surface area, including women, even though cardiac index was adequately maintained. Figure 3, B, shows that patients had a higher risk for strokes, even though the cardiac index was maintained above 2.2. Therefore, we think that sufficient cardiac output or LVAD pump flow, not cardiac index, should be achieved to prevent stroke in the acute phase, particularly in patients with small body size. Blood pressure and afterload control have been considered important to prevent strokes.¹⁶⁻¹⁸ Because reduction of afterload increases LVAD pump flow, blood pressure control is also important to maintain adequate LVAD pump flow and prevent strokes.

To strengthen our hypothesis that lower LVAD pump flow can predispose the pump to subclinical pump thrombosis, which may cause strokes in the acute phase after LVAD implantation, we evaluated the correlation between cardiac output and serum LDH levels at 3, 7, and 14 days after LVAD implantation. Serum LDH levels, with LDH half-life depending on isozyme, seemed to be multifactorial, such as muscle injury during surgery especially in the postoperative super-acute phase. However, these intraoperative factors gradually declined, and thrombotic and thrombolytic factors became evident. Our analysis revealed a negative correlation between the

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James K. Kirklin, David C. Naftel, Francis D. Pagani, Robert L. Kormos, Lynne W. Stevenson, Elizabeth D. Blume, Susan L. Myers, Marissa A. Miller, J. Timothy Baldwin, James B. Young

Figure 10. Hazard function curves indicating the instantaneous risk of death over time for the major causes/modes of death. RHF, right heart failure; MSOF, multisystem organ failure. The Journal of Heart and Lung Transplantation, Volume 34, Issue 12, 2015, 1495–1504

VIDEO 1. The video briefly summarizes the important findings of this study. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)31765-3/fulltext](https://www.jtcvs.org/article/S0022-5223(18)31765-3/fulltext).

perioperative cardiac output and the serum LDH levels at 14 days. These results indicate that sufficient LVAD pump flow may be important to prevent subclinical thrombosis formation and avoid strokes in the acute phase after implantation. The threshold of “sufficient flow” in each device should be further evaluated in future studies with large numbers of patients.

Study Limitations

Our study has several limitations. First, this study is a retrospective study in a single center, and the number of patients with stroke in the acute phase is inevitably limited. Second, 5 different types of LVADs were included, because the available devices varied during the study period. Although there were no statistical differences among the various LVADs used, the numbers of each device were further limited, and the analysis might have been underpowered. Third, although we defined stroke in the acute phase as stroke that occurred within postoperative 90 days, we cannot conclude that all stroke events were caused by embolic events. Therefore, we could not completely eliminate cases of stroke caused by other factors such as spontaneous bleeding of the cerebral artery. Finally, our analysis could overlook some stroke events, because we did not perform brain CT in patients without headache or any neurologic symptoms.

CONCLUSIONS

More than one half of stroke events within 1 year after LVAD implantation occurred within 90 days, and stroke in the acute phase may be related to subclinical pump thrombus formation due to low and insufficient LVAD flow. Our study suggested that maintenance of sufficient LVAD flow, as well as anticoagulation therapy, plays a critical role in prevention of stroke in the acute phase after LVAD implantation (Video 1).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: left ventricular assist device, low cardiac output, pump thrombosis, stroke

TABLE E1. Patients with stroke

Case	Age (y)	Sex	Type of device	Days from surgery to CVA	LDH just before stroke (IU/L)	PT-INR just before stroke	Type of CVA	Location and size	Neurologic symptom	Neurologic outcome
1	65	F	Jarvik2000	1	710	1.26	Hemorrhagic infarction	Left frontal lobe	None	Aphasia
2	49	M	DuraHeart	4	319	1.13	Cerebral infarction	Right cerebellar	Dysarthria	Full recovery
3	61	F	Jarvik2000	4	622	1.25	Cerebral infarction	Right basal ganglia	Coma	Full recovery
4	20	M	EVAHEART	5	534	1.48	Subarachnoid hemorrhage	Left frontal lobe	Disordered consciousness	Full recovery
5	59	F	Jarvik2000	5	1488	2.02	Subcortical hemorrhage	Right frontal lobe, 40 × 55 × 60 mm	Headache	Full recovery
6	12	F	Jarvik2000	6	603	1.87	Subcortical hemorrhage	Right occipital lobe	Headache	Full recovery
7	61	M	HeartMate II	9	441	1.81	Subcortical hemorrhage	Right frontal lobe, 40 × 55 × 60 mm	Lose consciousness	Dead
8	61	F	HeartMate II	9	632	3.39	Left frontal lobe SDH	Left frontal lobe	Dysarthria	Full recovery
9	64	F	HeartMate II	15	756	1.83	Subcortical hemorrhage	Right frontal lobe	Coma	Dead
10	47	F	HeartWare	25	198	2.20	Subcortical hemorrhage	Left frontal lobe, 80 × 55 × 80 mm	Anisocoria	Dead
11	61	F	Jarvik2000	25	495	3.02	Subcortical hemorrhage	Left cerebellar, 40 × 55 × 60 mm	Headache	Full recovery
12	46	F	Jarvik2000	32	375	1.94	Subarachnoid hemorrhage	Anterior medulla oblongata	Headache	Full recovery
13	50	M	HeartMate II	32	445	2.10	Subcortical hemorrhage	Right temporal lobe, 78 × 49 × 70 mm	Headache	Dead
14	55	M	EVAHEART	34	192	1.81	Cerebral infarction	Left parietal lobe	Headache	Full recovery
15	59	M	DuraHeart	42	265	2.16	Right frontal lobe SDH	Right frontal lobe	Headache	Full recovery
16	11	M	HeartWare	49	298	2.42	Cerebral infarction	Right temporal lobe	Hemiplegia	Full recovery
17	64	F	HeartMate II	52	417	1.72	Subarachnoid hemorrhage	Frontal lobe	Seizures	Full recovery
18	53	F	EVAHEART	52	243	2.43	Cerebral infarction	Left thalamus	Aphasia, Hemiplegia	Full recovery
19	51	M	EVAHEART	53	265	2.74	Cerebral infarction	Left basal ganglia	Disordered consciousness	Full recovery
20	62	M	HeartMate II	55	405	1.83	Subcortical hemorrhage	Right frontal lobe, 40 × 55 × 60 mm	Coma	Dead
21	13	F	HeartWare	58	720	1.70	Subarachnoid hemorrhage	Left frontal lobe	Lose consciousness	Full recovery
22	35	F	EVAHEART	58	177	1.67	Cerebral infarction	Left temporal lobe	Aphasia, Hemiplegia	Full recovery
23	36	M	DuraHeart	59	241	2.13	Subarachnoid hemorrhage	Left temporal lobe	None	Full recovery
24	49	M	HeartMate II	63	573	1.4	Subcortical hemorrhage	Right frontal lobe	Hemiplegia	Hemiplegia
25	44	F	Jarvik2000	67	346	1.78	Subarachnoid hemorrhage	Left temporal lobe	Visual field defect	Full recovery
26	56	M	Jarvik2000	71	360	2.81	Subcortical hemorrhage	Left frontal lobe	Lose consciousness	Dead
27	55	M	Jarvik2000	86	554	2.08	Subarachnoid hemorrhage	Right frontal lobe	Lose consciousness	Full recovery
28	31	M	HeartMate II	88	298	2.85	Subcortical hemorrhage	Right frontal lobe	Headache	Full recovery

CVA, Cerebrovascular accident; LDH, lactate dehydrogenase; PT-INR, prothrombin time international normalized ratio; SDH, subdural hematoma.