Cerebrovascular accidents in patients with a ventricular assist device

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Objective: A cerebrovascular accident is a devastating adverse event in a patient with a ventricular assist device. The goal was to clarify the risk factors for cerebrovascular accident.

Methods: Prospectively collected data, including medical history, ventricular assist device type, white blood cell count, thrombelastogram, and infection, were reviewed retrospectively in 124 patients.

Results: Thirty-one patients (25%) had 48 cerebrovascular accidents. The mean ventricular assist device support period was 228 and 89 days in patients with and without cerebrovascular accidents, respectively ($P < .0001$). Sixty-six percent of cerebrovascular accidents occurred within 4 months after implantation. Actuarial freedom from cerebrovascular accident at 6 months was 75%, 64%, 63%, and 33% with the HeartMate device (Thoratec Corp, Pleasanton, Calif), Thoratec biventricular ventricular assist device (Thoratec Corp), Thoratec left ventricular assist device (Thoratec), and Novacor device (WorldHeart, Oakland, Calif), respectively. Twenty cerebrovascular accidents (42%) occurred in patients with infections. The mean white blood cell count at the cerebrovascular accident was greater than the normal range in patients with infection ($12,900/\text{mm}^3$) and without infection ($9500/\text{mm}^3$). The mean maximum amplitude of the thrombelastogram in the presence of infection (63.6 mm) was higher than that in the absence of infection (60.7 mm) ($P = .0309$).

Conclusions: The risk of cerebrovascular accident increases with a longer ventricular assist device support period. Infection may activate platelet function and predispose the patient to a cerebrovascular accident. An elevation of the white blood cell count may also exacerbate the risk of cerebrovascular accident even in patients without infection. Selection of device type, prevention of infection, and meticulous control of anticoagulation are key to preventing cerebrovascular accident.

Cerebrovascular accident (CVA) is a devastating complication after ventricular assist device (VAD) implantation. Investigators have reported that the incidence of CVA in patients with a VAD ranges from 14% to 47%.¹⁻³ The incidence of CVA was 1.6% to 4.6% after cardiac surgery, including coronary artery bypass grafting and valve surgery. Several authors have reported risk factors for

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Dr Tsukui is partially supported as the Thomas Burnett Ventricular Assist Device Fellow by the Thoratec Corporation. Dr Kormos reports consulting fees from Ventracor. Dr Tsukui reports grant support from Thoratec.

Poster Presentation at the Twenty-sixth Annual Meeting of the Western Thoracic Surgical Association, Sun Valley, Idaho, June 21–24, 2006.

Received for publication June 19, 2006; revisions received Dec 2, 2006; accepted for publication Feb 14, 2007.

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J Thorac Cardiovasc Surg 2007;134:114-23
0022-5223/\$32.00

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doi:10.1016/j.jtcvs.2007.02.044

Abbreviations and Acronyms

CVA	= cerebrovascular accident
HIT	= heparin-induced thrombocytopenia
INR	= international normalized ratio
LVAD	= left ventricular assist device
MA	= maximum amplitude
POD	= postoperative day
PTT	= prothrombin time
TEG	= thromboelastogram
TIA	= transient ischemic attack
VAD	= ventricular assist device

CVA: older age, female sex, history of CVA, peripheral vascular disease, diabetes, hypertension, renal insufficiency, atrial fibrillation, previous cardiac surgery, preoperative infection, prolonged cardiopulmonary bypass time, need for intraoperative hemofiltration, and high transfusion requirement.⁴⁻⁶ However, these risk factors are not always the same as those in patients receiving VAD, and the mechanism of CVA is not fully understood. In the era of destination therapy with a VAD, a solution for this complication is important.

Materials and Methods

From January 2000 to September 2005, 124 patients (98 males, age 7–72 years, mean 49.6 ± 15.6 years) underwent VAD implantation at the University of Pittsburgh Medical Center. We have been developing our artificial heart program since 1986 and have performed implantation in more than 300 patients. Because Novacor continued to change its conduit and valve until 2000 to prevent CVA (as described later), and the outcome of patients who received a VAD improved after 2000 because of some modifications including anticoagulation and wound care,⁷ we collected data after 2000 to simplify the comparison among devices. The preoperative diagnoses were idiopathic cardiomyopathy in 36 patients (29%), ischemic cardiomyopathy in 36 patients (29%), acute cardiogenic shock including acute myocardial infarction and postcardiotomy failure in 33 patients (27%), and other causes in 19 patients (15%). Sixty-four patients received a left ventricular assist device (LVAD), including 22 HeartMate left ventricular assist systems (Thoratec Corp, Pleasanton, Calif), 19 Thoratec LVADs (Thoratec Corp), 5 Thoratec implantable ventricular assist devices, 13 Novacor devices (WorldHeart Inc, Oakland, Calif), and 5 HeartMate II devices (Thoratec Corporation), whereas 60 patients underwent biventricular assist device (BiVAD) implantation with 57 Thoratec BiVADs and 3 HeartMate left ventricular assist systems followed by a Thoratec right ventricular assist device because of delayed right ventricular failure.

Selection of Device Type

Selection of the device was made on the basis of the patients' preoperative hemodynamics. We have used the BiVAD strategically in the last 10 years in patients with significant right ventricular dysfunction and in patients in whom we believed the risk of

right ventricular failure would be high perioperatively on the basis of our early experience using a single-ventricle strategy.⁷ Patients who had the following conditions underwent BiVAD implantation: acute cardiogenic shock with multiorgan failure with coagulopathy, intractable ventricular arrhythmia or persistent ventricular fibrillation, severe right ventricular dysfunction characterized by central venous pressure greater than 18 mm Hg and/or mean pulmonary artery pressure less than 25 mm Hg or diastolic pulmonary artery pressure less than 15 mm Hg on inotropic support and an intraaortic balloon pump, giant cell myocarditis, acute biventricular myocardial infarction with or without a ventricular septal defect, acute biventricular postcardiotomy failure, and LVAD flow less than 2.0 L/min/m² and central venous pressure greater than 18 mm Hg after LVAD implantation in the operating room. In the selection of LVAD type, the Thoratec LVAD was implanted in smaller patients and those with acute cardiogenic shock because implantable VADs were not feasible. In the selection between HeartMate and Novacor devices, we preferred to use the Novacor device, which has a higher durability, for patients who had less chance of heart transplantation because of size mismatch, blood type, or the existence of unacceptable antibodies. A pivotal study of HeartMate II implantation was started from April 2004 if the patient fitted its criteria.

Postoperative Anticoagulation

Postoperative anticoagulation in patients who underwent VAD implantation except with the HeartMate was started with dextran 40% at 25 mL/h 6 hours after admission to the intensive care unit if bleeding was less than 100 mL/h. Subsequently, heparin was started when postoperative bleeding from the chest tubes was less than 50 mL/h over 3 consecutive hours. The goal for prothrombin time (PTT) was 40 to 51 seconds for at least the first 72 hours or until the risk of bleeding from more aggressive anticoagulation was thought to be acceptable. Heparin was then increased to maintain a PTT of 42 to 62 seconds. Coumadin was introduced on postoperative day (POD) 10 to keep the international normalized ratio (INR) between 2.5 and 3.5. Heparin was discontinued after obtaining an INR of at least 2.5. The philosophy of anticoagulation was to maintain heparin until the patient demonstrated a low risk of bleeding complications and there had been a period of stable gastrointestinal tract function and diet. This usually occurred approximately 10 to 14 days postimplantation. A daily dose of 81 to 325 mg aspirin and/or 75 mg clopidogrel (Plavix, Sanofi-Aventis, Bridgewater, NJ) was also started approximately 48 hours after implantation. Since August 2004, aspirin and/or clopidogrel (Plavix) was started if the maximum amplitude (MA) of the thromboelastogram (TEG) was greater than 70 mm, and the dosage was adjusted to maintain MA at 60 to 70 mm. After discharge, the INR was assessed a minimum of twice per week in stable patients. In patients who received a HeartMate device, 81 to 325 mg aspirin was started on POD 1 if bleeding was minimal. In patients with atrial fibrillation with a HeartMate device, heparin followed by Coumadin with the INR controlled at 2.0 to 3.0 was given after VAD implantation.

Data including patients' medical history, demographics, and blood parameters (white blood cell [WBC] count and TEG)

TABLE 1. Patient demographics

	CVA group	%	Non-CVA group	%	P value	Total	%
No. of patients	31	25	93	75		124	
Gender							
Male	24	77	74	80	NS	98	79
Female	7	23	19	20	NS	26	21
	31	100	93	100		124	100
Age (y)	51.0 ± 13.5		48.1 ± 16.3		.3747	49.6 ± 15.6	
Diagnosis							
Ischemic cardiomyopathy	10	32	26	28	NS	36	29
Idiopathic cardiomyopathy	8	26	28	30	NS	36	29
Acute cardiogenic shock	9	29	24	26	NS	33	27
Others	4	13	15	16	NS	19	15
Medical history							
Atrial fibrillation	6	19	24	26	NS	30	24
Abnormality of coagulation	4	13	1	1	.0138	5	4
Diabetes	8	26	24	26	NS	32	26
Hypertension	14	45	25	27	NS	39	31
Peripheral vascular disease	4	13	10	11	NS	14	11
Previous CVA	1	3	5	5	NS	6	5
Implanted VAD type							
Thoratec BiVAD	13	42	44	47		57	46
Thoratec LVAD	4	13	15	16		19	15
Thoratec IVAD	1	3	4	4		5	4
Novacor	8	26	5	5		13	10
HeartMate	4	13	18	19		22	18
HeartMate II	1	3	4	4		5	4
HeartMate + Thoratec RVAD	0	0	3	3		3	2
	31	100	93	100		124	100
VAD support period							
Mean (d)	228.5 ± 169.1		89.4 ± 86.0		<.0001		
<30 d	1	3	29	31			
30–120 d	8	26	35	38			
121–365 d	17	55	27	29			
>365 d	5	16	2	2			
Device outcomes							
Transplantation	12	39	58	62		70	56
Weaned off device	2	6	8	9		10	8
Died on device	11	35	20	22		31	25
On device	6	19	7	8		13	10

BiVAD, Biventricular assist device; IVAD, implantable ventricular assist device; LVAD, left ventricular assist device; RVAD, right ventricular assist device; CVA, cerebrovascular accident; VAD, ventricular assist device; NS, not significant.

were collected and retrospectively compared between the groups who had postoperative CVAs including stroke and transient ischemic attack (TIA) (31 patients: CVA group) and those who did not have a postoperative CVA (93 patients: non-CVA group). Neurologic events were divided into 2 categories. A stroke was a focal brain event with signs and symptoms lasting more than 24 hours; TIA was a focal ischemic brain event lasting less than 24 hours with a negative brain image. This study including patients' data was approved by the Institutional Review Board of the University of Pittsburgh Medical Center, and individual consent for the study was waived because individual patients were not identified.

Analysis

Data were expressed as mean ± standard deviation. Data were analyzed univariately by unpaired Student *t* test for continuous variables and by chi-square or Fisher exact test for categorical variables between the groups using a commercially available statistics package: Statview (ver5.0, SAS Institute Inc, Cary, NC).

Results

Thirty-one patients (25%) had 48 CVAs, including 31 strokes and 17 TIAs after VAD implantation (Table 1). The mean age was 51.0 ± 13.5 years in the CVA group and 48.1 ± 16.3 years in the non-CVA group (*P* = .3747).

TABLE 2. Device outcomes in each device

CVA	Thoratec BiVAD		Thoratec LVAD		Thoratec IVAD		Novacor		HeartMate		HeartMate II		HeartMate + Thoratec RVAD		All devices	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
No. of patients	13	44	4	15	1	4	8	5	4	18	1	4	0	3	31	93
Mean VAD support (d)	254	78	145	94	43	86	223	106	257	121	69	30	n/a	102	229	89
(range)	8–625	0–259	43–204	9–282		18–250	41–428	41–223	40–598	3–368		20–48		17–229	8–625	0–368
Device outcome																
Transplant	6	25	1	11	0	2	4	3	1	14	0	1	0	2	12	58
Died on device	6	13	1	2	0	0	1	1	2	2	1	1	0	1	11	20
Weaned from device	0	5	1	2	1	1	0	0	0	0	0	0	0	0	2	8
On device	1	1	1	0	0	1	3	1	1	2	0	2	0	0	6	7
Cause of death																
CVA	2	0	0	1	0	0	1	0	1	0	1	0	0	0	5	1
Infection	3	0	1	1	0	0	0	0	0	1	0	0	0	0	4	2
Multiorgan failure	0	10	0	0	0	0	0	0	0	0	0	1	0	1	0	12
Respiratory failure	1	1	0	0	0	0	0	1	0	0	0	0	0	0	1	2
Liver failure	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Graft failure	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Unknown	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1

BiVAD, Biventricular assist device; LVAD, left ventricular assist device; IVAD, implantable ventricular assist device; RVAD, right ventricular assist device; CVA, cerebrovascular accident.

Thirty-one patients with CVA included 13 with Thoratec BiVADs, 8 with Novacor devices, 4 with Thoratec LVADs, 4 with HeartMate devices, 1 with a Thoratec implantable ventricular assist device, and 1 with a HeartMate II device. There was no significant difference between the CVA and non-CVA groups in medical history, including atrial fibrillation ($P = .6291$), diabetes ($P > .9999$), hypertension ($P = .0744$), peripheral vascular disease ($P = .7481$), and previous CVA ($P > .9999$). Abnormalities of the coagulation system including heparin-induced thrombocytopenia (HIT) and lupus anticoagulant were found in 4 patients and 1 patient in the CVA and non-CVA groups, respectively ($P = .0138$). Three of 4 patients with lupus anticoagulant had multiple CVAs; a patient with a Thoratec LVAD had 3 CVAs on PODs 85, 93, and 94, a patient with a Thoratec BiVAD had 2 CVAs on PODs 32 and 559, and a patient with a Novacor device had 2 CVAs on PODs 208 and 216. A patient with HIT with a Thoratec LVAD had 2 CVAs on PODs 8 and 118. Mean VAD support period was 228.5 ± 169.1 days (range: 8–625 days) and 89.4 ± 86.0 days (range: 0–368 days) in the CVA and non-CVA groups, respectively ($P < .0001$). The mean period from implantation to the first CVA onset was 62.4 days, and 66% of CVAs occurred within 4 months (<30 days: 31%, 31–120 days: 35%, 121–365 days: 31%, >365 days: 3%). The results of each device are shown in Table 2. Actuarial freedom from CVA at 6 months was 75%, 64%, 63%, and 33% for the HeartMate device, Thoratec BiVAD, Thoratec LVAD, and the Novacor device, respectively (Figure 1). The mean incidence of stroke with all devices was 0.879 per patient-

year, and the results were 1.023, 0.976, 1.568, and 1.579 for the HeartMate device, Thoratec BiVAD, Thoratec LVAD, and Novacor device, respectively. Detailed data on CVA are shown in Table 3. The 31 patients with stroke included 19 with embolism (61%), 8 with hemorrhage (26%), and 4 with unknown causes (13%). CVA significantly affected the device outcome (Table 1). In the non-CVA group, 58 of 93 patients (62%) underwent heart transplantation, whereas

Figure 1. Actuarial freedom from CVA in each VAD. CVA, cerebrovascular accident; VAD, ventricular assist device; BiVAD, Biventricular assist device; LVAD, left ventricular assist device.

TABLE 3. Demographics of patients with cerebrovascular accident

	Thoratec BiVAD	%	Thoratec LVAD	%	Thoratec IVAD	%	Novacor	%	HeartMate	%	HeartMate II	%	All devices	%
No. of patients with CVA	13		4		1		8		4		1		31	
Incidence of stroke/patient-year	0.976		1.568		0.941		1.579		1.023		1.028		0.879	
Type of CVA														
Stroke	13	72	7	78	0	0	7	70	5	56	0	0	32	67
TIA	5	28	2	22	1	100	3	30	4	44	1	100	16	33
Total	18	100	9	100	1	100	10	100	9	100	1	100	48	100
Source of CVA														
Embolism	7	39	5	56	0	0	5	50	3	33	0	0	20	42
Hemorrhage	4	22	3	33	0	0	3	30	1	11	0	0	11	23
Unknown	7	39	1	11	1	100	2	20	5	56	1	100	17	35
Timing of CVA onset														
<30 d	6	33	2	22	0	0	4	40	3	33	0	0	15	31
30–120 d	7	39	4	44	1	100	2	20	2	22	1	100	17	35
121–365 d	4	22	3	33	0	0	4	40	4	44	0	0	15	31
>365 d	1	6	0	0	0	0	0	0	0	0	0	0	1	2

BiVAD, Biventricular assist device; LVAD, left ventricular assist device; IVAD, implantable ventricular assist device; CVA, cerebrovascular accident; TIA, transient ischemic attack.

only 12 of 31 patients (39%) underwent heart transplantation in the CVA group ($P = .0354$). Mortality was higher in the CVA group (11 patients, 36%) than in the non-CVA group (20 patients, 21%) ($P = .1511$). In the non-CVA group, 12 patients (60%), including 10 with BiVADs, died of multiorgan failure without CVA. This means that patients who received BiVAD were too sick to recover. In the CVA group, 5 of 11 patients (45%) died of CVA itself, and no patient died of multiorgan failure, which implies that CVA directly affected the mortality after VAD implantation. The details of the device outcome and cause of death for each device are shown in Table 2.

An infection developed in 27 of 31 patients (87%) in the CVA group, including 23 bloodstream, 20 respiratory, 29 urinary tract, and 15 device-related infections during VAD support, whereas 51 of 93 patients (55%) in the non-CVA group had an infection, including 26 bloodstream, 28 respiratory, 29 urinary tract, and 24 device-related infections ($P = .0012$). Twenty CVAs (42%) occurred during infection, including 7 bloodstream, 5 device-related, 4 urinary tract, and 4 respiratory infections. The mean WBC count at the time of CVA exceeded the normal range in patients with infection ($12,900/\text{mm}^3$) and without infection ($9500/\text{mm}^3$) ($P = .7256$). Information on the infections in each patient with CVA (infection source and WBC count) when they had a CVA are shown in Table 4.

Anticoagulation and antiplatelet therapy for each patient at the time of CVA are shown in Table 4. Twenty-two of 48 CVAs (46%) occurred when anticoagulation therapy was out of the therapeutic range, including 9 cases of hypertherapeutic and 13 cases of hypotherapeutic anticoagulation due to bleeding, accident, or patient noncompliance. Not all of the cases of hypotherapeutic and hypertherapeutic anti-

coagulation resulted in embolism and hemorrhage, respectively. Despite appropriate anticoagulation therapy, the rest of the patients experienced CVAs. The mean MA of TEG in periods with infection (63.6 ± 9.1 mm) was higher than that in those without infection (60.7 ± 7.4 mm) ($P = .0309$).

Discussion

CVA is one of the major complications after VAD implantation. The Mechanical Circulatory Support Device Database of the International Society for Heart and Lung Transplantation in 2005 reported that 14% of patients with VADs had neurologic dysfunction, and there were 18 cumulative thromboembolic events per 100 patients at 6 months after device implantation.¹ Lazar and colleagues⁸ reported that 16% of patients with an LVAD had a stroke, with a rate of 0.19 per year. Other authors reported 14% to 47% CVA occurrence.^{1–3} In our study, CVA occurred in 25% of patients and greatly affected the device outcomes, including heart transplantation and mortality. Therefore, the prevention of CVA is key to obtaining a good outcome after VAD implantation. The incidence of CVA was 1.6% to 4.6% after cardiac surgery, including coronary artery bypass grafting and valve surgery.^{4–6} Risk factors in patients who underwent cardiac surgery were not always the same as those in patients receiving VAD. In our study, common risk factors for CVA in association with cardiac surgery (ie, diabetes, hypertension, atrial fibrillation, peripheral vascular disease, and history of CVA) were not risk factors for CVA after VAD implantation, which may imply that patients who undergo VAD need particular strategies to prevent CVA.

Schmid and associates² reported that the incidence of CVA did not correlate strongly with the duration of VAD support, and that the majority of CVAs (43%) occurred

during the interval from 30 to 100 days after VAD implantation. In our study, the mean VAD support period in the CVA group (228.5 days) was significantly longer than that in the non-CVA group (89.4 days). There is no doubt that the longer the VAD support period, the higher the risk of CVA, but we should pay attention to the fact that the non-CVA group included 20 patients with a device who mainly died of multiorgan failure (60%) with a mean support period of 61 days, and 10 of 20 patients died within 30 days after VAD implantation. This decreased not only the mean VAD support period but also the chance of CVA during VAD support. Sixty-six percent of CVAs occurred within 4 months after VAD implantation, and then the risk of CVA decreased as shown in Figure 1. This means that appropriate anticoagulation in the early phase after VAD implantation is important. Also, 46% of CVAs occurred when anticoagulation control was out of the therapeutic range (Table 4). Embolism (42%) was predominant over hemorrhage (23%) as a cause of CVA; however, it would be premature to emphasize strong anticoagulation immediately after VAD implantation because embolism and hemorrhage are always directly opposed phenomena. Tailor-made anticoagulation therapy depending on the patient and the device is required to prevent CVA, as described below.

In terms of the difference in actuarial freedom from CVA among all VADs, the HeartMate device was superior to others despite a mild anticoagulation strategy with aspirin alone. In accordance with other authors' data, Novacor had a high CVA risk despite aggressive anticoagulation and changes in the conduit and valve.^{2,3,9-12} Novacor used a Cooley double-velour graft (Cooley, Meadox Medical, Oakland, NJ) for the inflow and outflow conduits until 1988, which were woven, low-porosity, crimped, unsupported polyester prostheses. Suboptimal mural flow in combination with radial pulsation made it prone to develop a poorly attached, friable pannus that could cause particulate emboli. From 1998 to 2000, the Vasculour II (Sulzer Vascutek, Renfrewshire, Scotland) was used for the inflow conduit. This conduit was made of knitted gel-sealed uncrimped polyester and was integrally supported with a polypropylene stent. The incidence of CVA became significantly less with the Vasculour II conduit (6%–12%) than with the Cooley conduit (21%–23%).^{13,14} However, a thin, adherent pannus could be observed in the Vasculour II conduit. Two lengths of conduits, 6 cm and 9 cm, were available, but no significant difference in the incidence of CVA was found between Vasculour II conduit lengths.¹⁴ The expanded polytetrafluoroethylene (ePTFE, Edwards Lifesciences, Irvine, Calif) inflow conduit was introduced in 2000. This conduit has an uninterrupted luminal surface and is not penetrated by sutures. An outer impermeable fluorinated ethylene-propylene coating reduces the risk of leaks or bleeding through the wall, blocks transmural penetration by inflammatory medi-

ators, and prevents adhesions; the fibrous tissue capsule readily separates. Two lengths of conduits, 6 cm and 9 cm, are available. A significant decrease in CVA was found in patients who received an ePTFE conduit, with a linearized rate of 0.025 events/patient-month versus 0.034 events/patient-month in patients who received a Vasculour II conduit (rate ratio: 0.76).¹⁵ Also, a bovine pericardial valve was used initially; however, Novacor implemented a change to a porcine xenograft valve that resulted in better flow characteristics. Because our data were collected since 2000, all our patients with Novacor devices received an ePTFE inflow conduit and porcine xenograft.

There was a discrepancy between the results of actuarial freedom from CVA and the incidence of stroke per patient-year of device support in patients with Thoratec LVADs and Novacor devices. In actuarial freedom from CVA at 6 months, the Thoratec LVAD (63%) showed better results than the Novacor device (33%), but the incidence of stroke per patient-year of device support was almost the same: 1.568 with the Thoratec LVAD and 1.579 with the Novacor device. Multiple CVAs during Thoratec LVAD support in a patient with lupus anticoagulant (3 CVAs) and a patient with HIT (2 CVAs) increased the incidence of stroke per patient-year. This means that even in patients who receive a VAD with a higher rate of freedom from CVA, coagulation abnormalities may increase the risk of CVA. Abnormal coagulation system diseases, such as HIT and lupus anticoagulant, are devastating problems in patients with VAD and more challenging to control appropriately after VAD implantation. HIT is caused by the development of an immunoglobulin (Ig)G antibody that recognizes multimolecular complexes of platelet factor 4 and heparin. If HIT develops, the platelet count typically begins to decrease 5 to 10 days after starting heparin. Half of the patients will have associated thrombosis. The incidence of HIT is approximately less than 1% in medical patients but is higher in surgical patients (5% in orthopedic patients).¹⁶ Lupus anticoagulant is caused by antiphospholipid antibodies (IgG, IgM, or a mixture of both) and is associated with cerebral, deep venous, or renal thromboses, as well as pulmonary emboli or arterial occlusions, particularly stroke. Some 2% to 4% of the US population is affected, and the incidence of thrombotic complications in patients with lupus anticoagulant ranges from 5% to 20%. Reports indicate that lupus anticoagulant is found in 8% to 14% of patients with deep venous thrombosis and in approximately one third of patients with stroke who are aged less than 50 years. There is also evidence that the type of recurrent thrombotic event, venous or arterial, tends to be persistent over time in the same patient. Lupus anticoagulant is characterized by a prolonged activated partial thromboplastin time. In our series, uncontrollable thromboembolic events were experienced, including CVA, pulmonary, liver, and renal emboli in 1 patient with HIT and in 3

TABLE 4. Data at the time of cerebrovascular accident in each patient

Patient	Device type	Period from implant to CVA (d)	Type of CVA	Source of CVA	Antiplatelet therapy	Anticoagulation therapy	INR	PTT	Anticoagulation control	Infection	WBC count (×1000)
1	HeartMate	110	TIA	Unknown	Aspirin 325 mg BID	None	1.2			None	5.4
2	HeartMate	1	Stroke	Embolism	None	None	1.4			None	4.9
		299	TIA	Unknown	Aspirin 325 mg BID	None	1.0			None	11.7
		324	TIA	Unknown	Aspirin 325 mg QD	Heparin Coumadin	1.3	32.5	Low	None	7.9
		339	Stroke	Unknown	Aspirin 325 mg BID Clopidogrel 75 mg QD	None	1.1			None	9.3
		351	Stroke	Hemorrhage	Aspirin 325 mg BID Clopidogrel 75 mg BID	Heparin	1.1	35.1	Low	None	11.6
3	HeartMate	67	TIA	Unknown	Aspirin 325 mg BID	Coumadin	2.2			None	5.6
4	HeartMate	5	Stroke	Embolism	None	None	1.1			None	14.8
		20	Stroke	Embolism	None	None	1.2			None	8.1
5	HeartMate II	64	TIA	Unknown	Aspirin 81 mg QD Dipyridamole 75 mg TID	Coumadin	2.7			Blood Urine	11.9
6	Novacor	23	Stroke	Unknown	Aspirin 81 mg QD Clopidogrel 75 mg QD	Heparin		14.2	Low	None	6.7
7	Novacor	16	Stroke	Embolism	Aspirin 81 mg QD Clopidogrel 75 mg QD	Heparin Coumadin	1.5	65.4	High	None	10.6
8	Novacor	20	Stroke	Hemorrhage	Aspirin 81 mg QD Clopidogrel 75 mg QD	Heparin		81.0	High	None	10.4
9	Novacor	153	Stroke	Embolism	Aspirin 325 mg QD	Heparin	1.3	68.0	High	Blood	19.2
		166	TIA	Hemorrhage	Aspirin 325 mg QD	Heparin	1.2	67.9	High	Blood	7.5
10	Novacor	106	TIA	Unknown	None due to bladder bleeding	Heparin	1.1	40.0	Low	None	4.3
11*	Novacor	208	Stroke	Embolism	Aspirin 81 mg QD Clopidogrel 75 mg QD	Coumadin	2.2		Low	Device	6.5
		216	Stroke	Embolism	None	Heparin	1.2	53.4		Device	9.8
12	Novacor	17	TIA	Embolism	Aspirin 81 mg QD	Heparin	1.3	34.6	Low	Respiratory	15.7
13	Novacor	36	Stroke	Hemorrhage	Aspirin 81 mg QD	Heparin		55.2		Device	8.4
14	Thoratec BiVAD	65	TIA	Unknown	Aspirin 81 mg QD	Coumadin	3.8		High	None	6.9
		66	TIA	Unknown	Aspirin 81 mg QD	Coumadin	3.4			None	n/d
		70	Stroke	Hemorrhage	Aspirin 81 mg QD	Coumadin	3.5			None	n/d
15	Thoratec BiVAD	26	Stroke	Unknown	Aspirin 325 mg QD	Coumadin	2.3		Low	None	9.3
16	Thoratec BiVAD	25	TIA	Unknown	None due to recent bleeding	Dextran	1.2	33.7	Low	Respiratory	8.6
17	Thoratec BiVAD	6	Stroke	Hemorrhage	Aspirin 325 mg QD	Heparin		53.7		Respiratory	21.5
18	Thoratec BiVAD	0	Stroke	Unknown	None due to immediately after surgery	Dextran	1.1		Low	None	17.5
19	Thoratec BiVAD	4	Stroke	Embolism	None	Heparin		56.3		None	17.7
		86	Stroke	Embolism	None	Heparin		28.9	Low	None	14.6
20	Thoratec BiVAD	7	Stroke	Embolism	None	Heparin		45.6		Respiratory	19.9
21	Thoratec BiVAD	330	Stroke	Embolism	Aspirin 325 mg QD	Coumadin	3.9		High	Blood	13.1
22	Thoratec BiVAD	59	TIA	Unknown	Aspirin 81 mg QD	Heparin	1.2	43.2		Urine	12.2
23*	Thoratec BiVAD	32	TIA	Unknown	Aspirin 325 mg QD	Heparin Coumadin	1.1	55.8		None	9.1
		559	Stroke	Embolism	Aspirin 325 mg QD Clopidogrel 75 mg QD	Heparin	1.2	39.3	Low	Blood	7.5
24	Thoratec BiVAD	41	Stroke	Hemorrhage	None	Heparin Coumadin	1.3	49.6		None	9.4
25	Thoratec BiVAD	133	Stroke	Hemorrhage	None	Coumadin	3.0			Urine	14.2

TABLE 4. Continued

Patient	Device type	Period from implant to CVA (d)	Type of CVA	Source of CVA	Antiplatelet therapy	Anticoagulation therapy	INR	PTT	Anticoagulation control	Infection	WBC count ($\times 1000$)
26	Thoratec BiVAD	131	Stroke	Embolism	Aspirin 81 mg QD	Coumadin	3.1			Device	7.0
		196	Stroke	Embolism	Aspirin 325 mg QD	Coumadin	4.1		High	Device	8.2
27	Thoratec IVAD	42	TIA	Unknown	None	Heparin		46.2		Blood	6.0
28	Thoratec LVAD	103	Stroke	Embolism	Aspirin 81 mg QD	Coumadin	2.9			None	8.4
29*	Thoratec LVAD	85	TIA	Hemorrhage	Aspirin 81 mg QD	Coumadin	3.2			None	7.3
		93	TIA	Hemorrhage	None	Heparin	2.1	38.4	Low	None	8.0
						Coumadin					
30†	Thoratec LVAD	94	Stroke	Hemorrhage	None	Heparin	1.6	83.2	High	None	8.0
						Coumadin					
						Coumadin					
		8	Stroke	Embolism	None	Bivalirudin	1.7	35.0		Urine	39.0
		188	Stroke	Embolism	Aspirin 325 mg QD	Heparin	1.5	43.7		None	12.0
31	Thoratec LVAD					Coumadin					
		9	Stroke	Embolism	None	Heparin	1.1	52.2		Respiratory	15.2
		192	Stroke	Unknown	Aspirin 325 mg QD	Coumadin	3.7		High	None	n/d
		226	Stroke	Embolism	Aspirin 325 mg QD	Coumadin	2.3		Low	Blood	6.8
					Clopidogrel 75 mg QD						

CVA, Cerebrovascular accident; INR, international normalized ratio; PTT, prothrombin time; WBC, white blood cell; BID, twice per day; CVA, cerebrovascular accident; n/d, no data; QD, once per day; TIA, transient ischemic attack; TID, 3 times per day; IVAD, implantable ventricular assist device; LVAD, left ventricular assist device; BiVAD, biventricular assist device; IVAD, implantable ventricular assist device; ASA, acetylsalicylic acid. *Lupus anticoagulant; †HIT.

patients with lupus anticoagulant after VAD implantation. On the basis of our experiences, we started preoperative tests for coagulation abnormalities, including HIT, lupus anticoagulant, factor V Leiden, antithrombin III deficiency, protein C deficiency, protein S deficiency, prothrombin gene mutation, hyperhomocysteinemia, and carotid artery Doppler for all patients and a head computed tomography scan for patients who had a history of CVA or an audible bruit of the carotid artery before VAD implantation. If a patient had positive results from these tests, the Novacor device was not selected because CVA greatly affects device outcomes, including heart transplantation achievement and mortality. In patients with HIT, postoperative anticoagulation therapy should be done with bivalirudin or hirudin,^{17,18} followed by Coumadin with an INR of 2.5 to 3.5 for all types of VADs. If a patient has lupus anticoagulant, postoperative anticoagulation is controlled with higher PTT (46–80 seconds) and INR (3.0–4.0) levels.

The selection of VAD type is a key to obtaining excellent outcomes. In our institute, the BiVAD was selected strategically for patients with significant right ventricular dysfunction and for patients who we believed were at risk of right ventricular failure peri- and postoperatively.⁷ Because this study showed that the incidence of CVA in patients with a Thoratec BiVAD was acceptably low, we do not think we have to question our BiVAD strategy with respect to CVA risk. It is reasonable to use the Thoratec LVAD, an extracorporeal type of VAD, for small patients and patients in acute cardiogenic shock because of its acceptable low CVA rate. Implantable LVAD type selection is still puzzling because of the variable durability (less with the Heart-

Mate device) and CVA rate (higher with the Novacor device). Because the freedom from CVA of the HeartMate device was reliably higher than that of the Novacor device, and CVA affected the outcome after VAD implantation, the HeartMate device would be desirable for all patients, especially in those with coagulation abnormalities. The Novacor device may be desirable for patients without coagulation abnormalities and for patients who have less possibility of undergoing heart transplantation because of size mismatch, blood type, or the existence of unacceptable antibodies and who undergo VAD implantation as destination therapy. It may be too early to say because we dealt with a small number of HeartMate II cases, but the HeartMate II device may become the best VAD in the future because it can be expected to have both a low CVA rate because of the same internal surface texture and conduits of the HeartMate device and a high durability because of its design without valves.

TEG was introduced at our institute in August 2004 for meticulous anticoagulation therapy in patients on VAD. TEG is a bedside monitor of coagulation and traces the viscoelasticity of the clot forming between a suspended pin and a cuvette wall; therefore, the result may be affected by various plasma and cellular components of coagulation. The following parameters were obtained from the TEG trace: R time: period of time from initiation of the test to the start of the trace and represents initial fibrin formation; alpha: the angle between the line in the middle of the TEG tracing and the line tangential to the developing TEG tracing and represents the kinetics of fibrin cross-linking; MA: reflects strength of a clot that is dependent on the number and

function of platelets and its interaction with fibrin but is insensitive to the effect of aspirin; LY-30: measures the rate of amplitude reduction 30 minutes after MA and represents the stability of the clot. We especially focused on the MA level to examine platelet function after VAD implantation. It is too early to state conclusively because of the small number of experiences at our institute, but we observed a fluctuating MA level immediately after VAD implantation and stabilized MA level in the late phase. This phenomenon may support our result that 66% of CVAs occurred within 4 months after VAD implantation. We consider that tailor-made antiplatelet therapy based on TEG may be effective to prevent CVA in patients with a VAD.

The relationship between CVA and a high WBC count and/or infection has been studied. Several investigators reported an association between CVA and elevated WBC count and C-reactive protein.¹⁹⁻²² Albert and colleagues²³ reported that WBC count was significantly higher preoperatively and postoperatively in patients with CVA. The risk of perioperative CVA increased starting with a preoperative WBC count of 9000/mm³ ($P = .044$) and further increased at higher WBC counts. In our study, patients with CVA had a high WBC count exceeding the normal range ($>9000/\text{mm}^3$) regardless of the presence or absence of infection (patients with infection: 12,900/mm³; patients without infection 9500/mm³). Furthermore, 42% of CVAs occurred in patients with infection. The relationship between infection and CVA is still not fully understood. The basic mechanism may be altered rheology caused by an increased fibrinogen level induced by infection²⁴ or blood viscosity, erythrocyte rigidity, fibrinogen concentration,²⁵ protein C,²⁶ protein S, and platelet aggregation.²⁷ Grau and colleagues²¹ reported recent bacterial and viral infection as a risk factor for CVA. Recently, we routinely checked not only INR but also TEG, controlling the level of MA at approximately 60 to 70 with aspirin and/or clopidogrel (Plavix). Our data showed that mean MA in periods with infection (63.6 mm) was higher than that without infection (60.7 mm) ($P = .0309$) under the same protocol, which may clinically support the hypothesis that infection activates platelet aggregation. We check TEG when a patient has symptoms of CVA or infection to adjust antiplatelet therapy.

Limitations

Limitations of this study include those related to a retrospectively performed analysis at a single center. Not all data from every patient were available or data could not be obtained because of the critical illness of the patients studied. The number of patients was relatively low.

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