モックサーキュレーションでの実習、LVAD装着患者の創部管理の実践、ブタ心臓を用いた植込み手術手技の実習を実践するとともに、看護師、臨床工学士らによって、実際の入院患者の処置見学と現場での管理上の要点について、質疑応答を交わした。

D. 考察

東北大学病院は広域医療圏である東北地方全域から重症心不全患者を受け入れ、心臓移植治療に向けてのブリッジ治療として植込み型補助人工心臓治療を行ってきた。今回の解析対象30例は東北6県から紹介されており、改めてこの広域医療圏をカバーしてゆく必要性を認識した。これまでも、緊急対応に備えて退院前に患者の居住区を訪れ、地域基幹病院、消防本部、職場の同僚などに対して、補助人工心臓治療についての講義を行い、緊急対応が問題なく施行されるよう活動していることが重要であると認識してきた。しかしながら、緊急時以外の恒常的なLVAD管理治療に関しては、基幹病院でのみ連続して継続しており、遠方から補助人工心臓センター外来を受診する患者とその家族、また、患者数増加に伴うセンタースタッフ、特に、看護師と臨床工学士の負担が増加している。負担軽減の方向に進めると、治療密度の低下に繋がり、きめ細かな管理治療が心臓移植への移行までの鍵となるこのLVAD治療にとっては、マイナスとなる懸念がある。従って、広域な地域全体にこの治療に関する知識の普及と技術の修得を図り、さらに、様々な治療経験の共有を推進することが、この領域の治療体系の確立に必須であると考えられる。

また、上記のLVAD管理スタッフの軽減を達成するため方略の一つとして、在宅患者、および、その家族と補助人工心臓センターとの通信速度と密度、さらに、秘匿性を担保した情報インフラのさらなる強化も重要な側面であることが判明した。

今年度は、試行的な事業として、第一回東北・北海道地区補助人工心臓研修コースを平成27年3月28日と29日の二日間にわたって、東北大学にて主催し得た。この二日間における実習の成果は比較的多く、多くの反響も得られた。次年度以降の連続開催を期待する声も大きい。このようなLVAD治療に関する知識と技術の不況、啓蒙活動を継続することで、在宅治療の拡充の拡充、安全な心臓移植医療への移行がさらに高い精度で実施できるようになるものと期待される。さらには、今後、人工心臓管理施設と呼称できるような補助人工心臓在宅治療管理が可能な施設が増設されることで、より広範囲の患者に対する治療が可能になると思われる。

E. 結論

広域医療圏における複数機種から成る植込み型LVAS長期在宅治療の拡充のためには、植込み施設の増加、患者の居住区に比較的近接する医療機関として、新たな一定の基準を充たす補助人工心臓管理施設の設置、それらの施設に対する恒常的な教育機会の提供による、在宅治療管理密度の上昇と管理の質の向上が必要と考えられた。

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G. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

附録

別冊

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CASE REPORT

Artificial Heart (Clinical)

Left coronary artery occlusion caused by a large thrombus on the left coronary cusp in a patient with a continuous-flow ventricular assist device

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Abstract Despite continual improvements in ventricular assist device (VAD) therapy, various clinical issues are emerging. Importantly, various types of thromboembolic complications have been reported to date. Recently, we encountered a rare continuous-flow VAD-related thromboembolic event that resulted in acute myocardial infarction. A 26-year-old female who just underwent HeartMate II® VAD implantation suddenly developed widespread anterolateral myocardial infarction on postoperative day 16. Echocardiography and aortography revealed a large thrombus on the left coronary cusp of the aortic valve that almost completely occluded the left coronary ostium. After VAD implantation, her aortic valve did not open, even at relatively low pump speeds; this was thought to be one of the causes for thrombus formation. Continuous suction of blood from the left ventricle and non-pulsatile flow into the ascending aorta resulted in a continuously closed aortic valve and stagnation of blood in the coronary cusp. Furthermore, both small body size (body surface area <1.3 m^2) and postoperative right ventricular failure may have exacerbated blood stagnation and thrombus formation in this patient. We should have adjusted the anticoagulation and antiplatelet therapy protocols based on the patient's condition. She underwent off-pump coronary artery bypass surgery and remained in clinically stable condition afterwards.

Keywords Ventricular assist device · Myocardial infarction · Thrombus · Off-pump coronary artery bypass surgery

Introduction

A ventricular assist device (VAD) is an alternative for patients with advanced heart failure who are candidates for heart transplantation. Recently, several types of implantable continuous-flow VADs have become available. The HeartMate II® (Thoratec Corporation; Pleasanton, CA, USA), currently the most widely used VAD worldwide, was approved for health insurance coverage in Japan in April 2013. Since the introduction of such implantable continuous-flow VADs, the incidence of VAD-related complications has decreased [1–4]. However, many patients still experience adverse events such as driveline infection, hemorrhage, and thromboembolism. Stroke is the most common thromboembolic event; however, myocardial infarction is uncommon. According to the most recent report by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), 0.07 % of patients on continuous-flow LVAD support have a new myocardial infarction in the first 12 months after implantation [5].

In this report, we present a rare case of an impressively large thrombus on the left coronary cusp (LCC) resulting in left coronary artery (LCA) occlusion and myocardial

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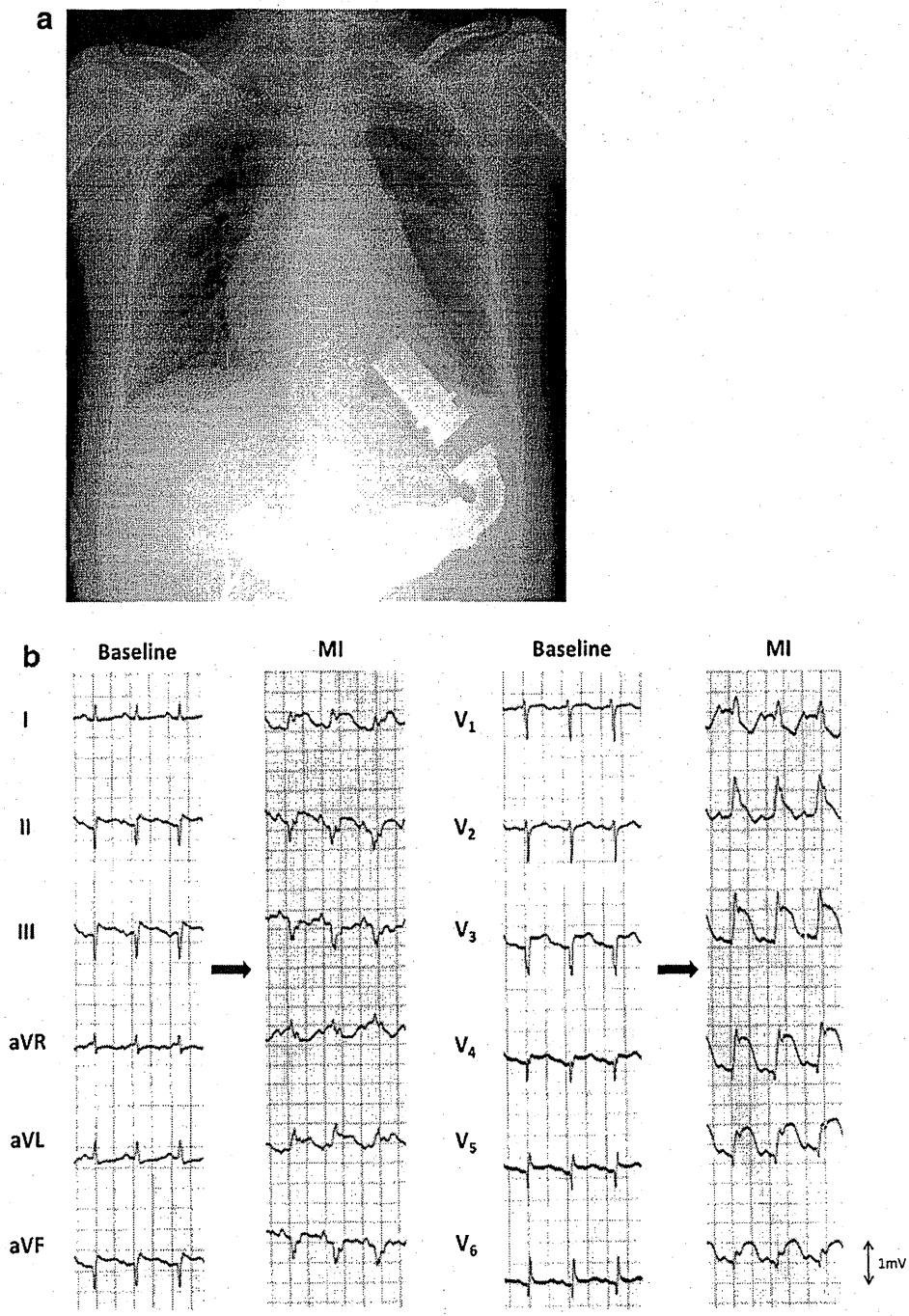

Fig. 1 Anteroposterior chest X-ray showing the inflow cannula connected to the left ventricular apex, the outflow cannula anastomosed to the ascending aorta, as well as the blood pump and the driveline (**a**). Twelve-lead electrocardiogram at baseline and at the onset of myocardial infarction (*MI*), which shows a heart rate of 131 beats per min, sinus rhythm, and ST-segment elevations in leads I, aVL, and V_2–V_6 (**b**)

infarction early after the implantation of a HeartMate II® continuous-flow VAD.

Case report

The patient was a 26-year-old woman with a body surface area (BSA) of 1.23 m^2 who was admitted to our hospital with advanced heart failure. Transthoracic echocardiography revealed severe left ventricular (LV) dysfunction with an LV ejection fraction of 17 % and mild LV dilatation (LV diastolic and systolic dimensions, 51 and 47 mm, respectively). Right ventricular (RV) contractility was mildly decreased. Coronary artery stenosis was ruled out by coronary angiography, and endomyocardial biopsy showed moderate myocardial replacement fibrosis with hypertrophic changes in the cardiomyocytes. Therefore, we made a diagnosis of dilated cardiomyopathy.

Despite continuous infusion of catecholamines and intra-aortic balloon pump support for 1 month, the patient's cardiac function did not recover, so she was registered as a candidate for heart transplantation. Subsequently, the HeartMate II® continuous-flow VAD was implanted as a bridge to transplant (Fig. 1a).

After VAD implantation, routine echocardiography revealed a decrease in LV dimensions (LV diastolic and systolic dimensions, 30 and 22 mm, respectively) and moderately reduced RV contractility. The aortic valve did not open, even at pump speeds of 8,600 rpm or lower, so the pump speed was kept at 8,600 rpm for this patient. Her central venous pressure was 15 mmHg or higher, implying the presence of postoperative RV failure. She required catecholamine infusion for more than 2 weeks. The LVAD parameters were as follows: pump speed, 8,600 rpm; pulse index, 4.5–5.5; and pump power, 4.5–5.5 W. Occasionally, the estimated pump flow rate was not displayed because it was <3.0 L/min. On postoperative day 1, we began warfarin without heparin bridge therapy and single antiplatelet therapy with 100 mg of aspirin a day. We maintained the international normalized ratio (INR) in the range of 1.5–2.0.

On postoperative day 16, she suddenly complained of severe chest discomfort with cold sweats at rest. ST-segment elevation in leads I, aVL, and V_2–V_6 were documented in the 12-lead electrocardiogram (ECG), implying widespread anterolateral ischemia (Fig. 1b). Echocardiography revealed an akinetic area in the anterolateral wall and a hyperechoic lesion filling the LCC. In retrospect, this hyperechoic lesion was present on the echocardiogram from the previous day, but it was smaller in size.

Since thromboembolism of the LCA was suspected, emergent catheterization was performed with the possibility of percutaneous coronary intervention (PCI). Before positioning a coronary catheter into the LCA, a low dose of contrast medium was injected into the LCC to confirm the presence of thrombus. As expected, a large thrombus (85 × 120 mm) was detected on the LCC, which was almost completely occluding the LCA (Fig. 2a). Although coronary revascularization seemed necessary for mitigating myocardial injury and preventing ventricular arrhythmias, PCI could not be performed for fear of systemic embolism induced by the coronary catheter. Therefore, the patient underwent off-pump coronary artery bypass surgery (with the VAD on) with a left internal thoracic artery to left anterior descending artery graft. We identified a mobile thrombus that occupied the LCC and partially extended to the noncoronary cusp (NCC) during intraoperative transesophageal echocardiography (Fig. 2b). Plasma creatine kinase MB isoenzyme (CK-MB) levels peaked at 351 IU/L 23 h after the onset of symptoms. A hypercoagulability workup was performed, which was negative for collagen diseases, congenital deficiencies of anticoagulants, and cancer. The thrombus on the LCC decreased in size after continuous infusion of low molecular weight heparin.

We maintained the INR in the range of 2.0–2.5. LV anterolateral motion recovered to preoperative levels and the patient remained in clinically stable condition 3 months after bypass surgery.

Discussion

In this case, a large thrombus generated on the LCC led to the development of anterolateral myocardial infarction. In patients with severely reduced LV contractility with implanted continuous-flow VADs, continuous suction of blood from the LV and non-pulsatile flow into the ascending aorta lead to fewer openings of the aortic valve and stagnation of blood on the coronary cusp, which can result in thrombus formation [6]. In our patient, there were no anatomical abnormalities in the aortic valve and the aortic root. Furthermore, the angle and the position of the outflow graft were also acceptable, so it is more likely that the combination of BSA less than 1.3 m^2 and postoperative RV failure might have exacerbated blood stagnation near the coronary cusp. Due to her small body size, a relatively higher volume of blood was suctioned from the LV even at low pump speeds, potentially worsening RV function through septal shift towards the LV with RV deformation. Persistent RV failure might contribute to stagnant blood flow around the coronary cusp through insufficient LV preload, followed by reduced pump flow to the ascending aorta. There have been few reports of LVAD implantation in patients with a small body size, and a limited number of pumps are available for such patients. Therefore, closer attention should be paid to device selection and pump speed settings in small patients.

The anticoagulation protocol after HeartMate II® implantation is currently in evolution. At the beginning of the clinical use, HeartMate II® recipients were bridged with heparin until anticoagulation with warfarin reached therapeutic levels (INR 2.0–3.0). However, several clinical trials demonstrated that patients are at low risk of thromboembolism, whereas postoperative bleeding was the most frequent adverse event [1–4]. Furthermore, there have been many reports of acquired von Willebrand disease occurring after HeartMate II® implantation [7]. These findings changed the clinical management of patients with HeartMate II® devices. At the time of implantation for this patient, the recommended INR range was 1.5–2.5 without a heparin bridge therapy [4, 8]. We maintained INR in the range of 1.5–2.0 during the early postoperative period based on the study by John et al. [3]. However, in retrospect we speculate that the patient's anticoagulation

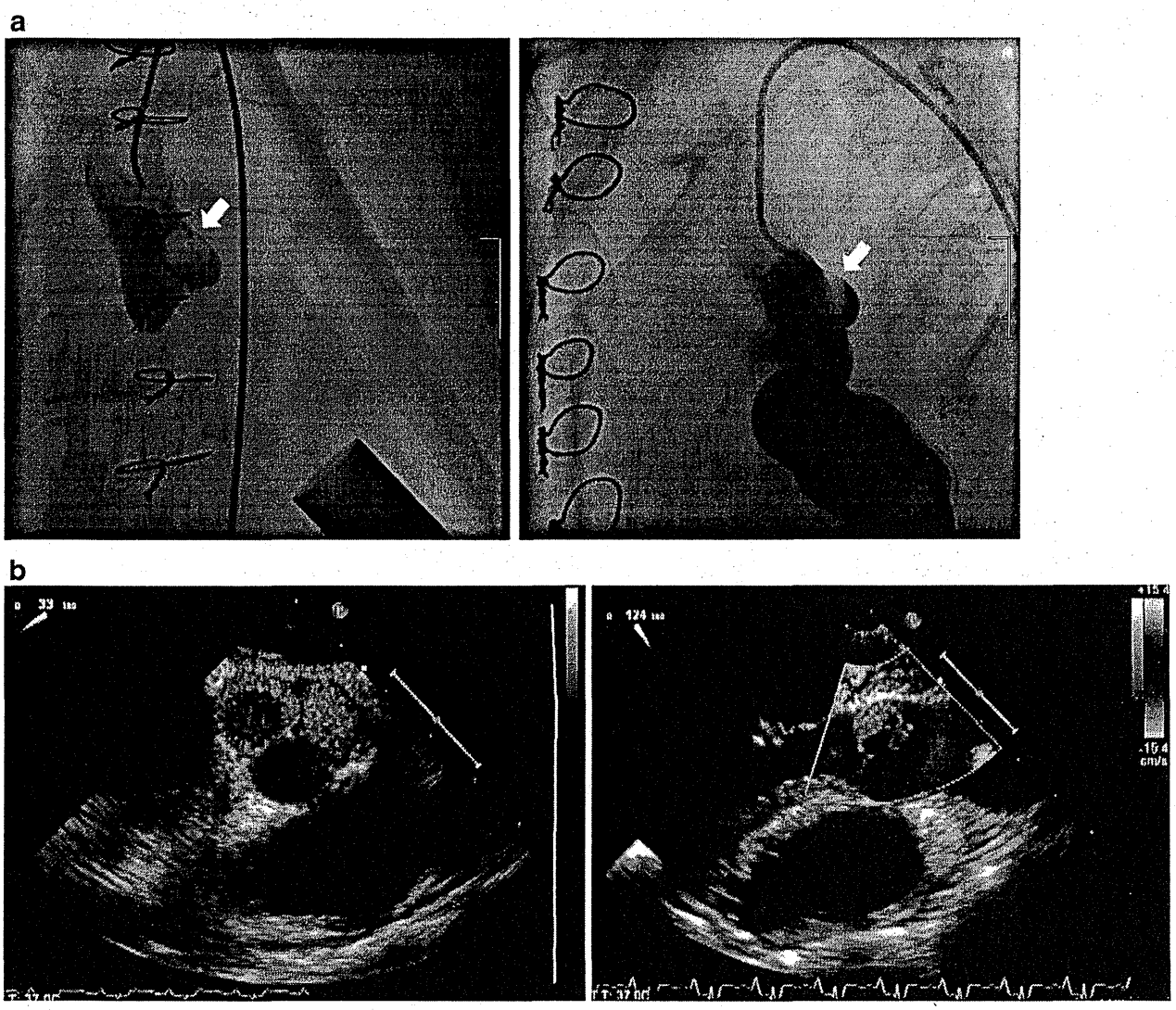

Fig. 2 Aortography showing a thrombus (85 × 120 mm) on the left coronary cusp (*white arrow*) and obstruction of the left main trunk (*left*) in the frontal view and (*right*) in the left anterior oblique/caudal view (**a**). Transesophageal echocardiography during bypass surgery showing a thrombus on the aortic valve that occupied the left coronary cusp and partially extended to the noncoronary cusp in the short-axis view (*left*) and in the long-axis view (*right*) (**b**)

regimen may have contributed to thrombus formation, and that we should have adjusted her anticoagulation and antiplatelet therapy based on her condition.

The strategy for treating thrombi on the coronary cusp in patients with VADs remains controversial. It is assumed that surgical removal of the thrombus with the aid of cardiopulmonary bypass would be highly invasive and only palliative if the precise etiology of thrombus formation is unknown. Demirozu et al. have reported a series of four HeartMate II® recipients with thrombus formation on the NCC. One patient underwent thrombectomy to relieve heart failure originating from thrombus-induced aortic insufficiency, while the others received only additional anticoagulant therapy [9].

We have encountered a similar case after EVAHEART® (Sun Medical, Nagano, Japan) implantation [10]. To date, thrombus formation on the coronary cusp seems to be a complication mainly observed in patients with continuous-flow pumps. It has not been reported in patients with pulsatile-flow pumps. Therefore, we believe this may be an emerging clinical issue in the era of continuous-flow VADs. Further investigation is needed to determine the mechanisms contributing to this complication and to establish both preventive and therapeutic strategies.

Conflict of interest The authors declare that they have no conflicts of interest.

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ORIGINAL ARTICLE

Pathological analysis of the aortic valve after long-term left ventricular assist device support

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Abstract

OBJECTIVES: Aortic insufficiency (AI) often develops during left ventricular assist device (LVAD) support and is related to a poor prognosis. As LVAD implantation and the support duration increase, the risk of acquired aortic valve lesions may increase. We investigated the pathological changes in the aortic valve and its function after long-term LVAD support.

METHODS: Thirty-five hearts removed at heart transplantation were investigated. Thirty-one patients were supported by extracorporeal pulsatile devices, and 4 were supported by implantable devices. We compared the histological changes in the aortic valve with the echocardiogram results.

RESULTS: The mean duration of LVAD support was 961 days. Before device implantation, all patients had a normal aortic valve opening, and only 5 had trivial AI. After LVAD support, trivial AI was observed in 18 patients, mild AI in 4 and mild-to-moderate AI in 2. Pathological examination revealed that the aortic valve had become thinner in all patients, ranging from 120 to 1400 μm. The aortic wall had also become thinner in most patients, ranging from 830 to 2220 μm. Left ventricular wall thickness was ranging from 4 to 13 mm, and aortic annular diameter was ranging from 17 to 27 mm. Partial aortic valve fusion was seen in 17 (48.6%) recipients, and curling with leaflet shortening was detected in 22 (62.9%) patients. Dense collagen accumulation in the spongiosa layer was also present. All aortic valves of the patients with mild and mild-to-moderate AI showed a scarce or no opening before explantation. Conversely, the AI grade of patients whose aortic valve frequently opened remained none or trivial. There was no close correlation between these pathological findings and the development of AI independently.

CONCLUSIONS: Degenerative aortic valve changes were recognized after long-term LVAD support. There was also an increasing prevalence of mild and mild-to-moderate AI, which may have been associated with continuous aortic valve closure. An optimal strategy to prevent AI development should be determined, and careful periodic echocardiographic follow-up is essential.

Keywords: Left ventricular assist device • Aortic insufficiency • Heart transplantation • Aortic commissural fusion

INTRODUCTION

Left ventricular assist device (LVAD) support has provided improved survival and a better quality of life for patients with end-stage heart failure [1, 2]. It is applied not only as a bridge to transplantation, but also as destination therapy (DT). The use of DT significantly increased in the USA after the REMATCH trial indicated that long-term mechanical support such as DT was effective, and the American Heart Association recommended the use of DT for patients with advanced heart failure (Class I) [3–5]. In Japan, on the other hand, implantable LVADs were introduced only a few years ago, and they have been applied only to heart transplantation candidates; that is, the use of DT involving implantable, non-pulsatile LVADs is not yet officially allowed, and the majority of patients with end-stage heart failure have undergone extracorporeal pulsatile LVAD installation. However, because the donor shortage is very serious in Japan, long-term support is mandatory for patients with LVADs.

The long-term effects of LVADs on native cardiac function, especially on native aortic valve function, are still unclear. The development of native aortic insufficiency (AI) during long-term LVAD support has been reported, and *de novo* AI developing during prolonged LVAD support is reportedly related to a poor prognosis [6, 7]. The mechanism of AI progression is not clear; however, some data have been reported. Anatomical and physiological alterations in the heart and great vessels have been observed after long-term LVAD support. Some reports described aortic valve commissural fusion in patients with the pulsatile HeartMate (Thoratec, Pleasanton, CA, USA) [8–12], and some demonstrated fusion of the native aortic valve and bioprosthesis in patients with the HeartMate II (Thoratec), a non-pulsatile LVAD [13–15].

The clinical implication of acquired commissural fusion is not well described or understood [16]. We here describe the pathological analysis results of the native aortic valve and their correlation

TX & MCS

with the clinical status in bridge-to-transplantation patients treated with an LVAD.

MATERIALS AND METHODS

The study was approved by the institutional review board and informed consent was obtained from each patients. From March 2006 to March 2013, a total of 38 patients underwent heart transplantations at our institute, 35 of whom had undergone LVAD implantation as a bridge to transplantation. Indication and operative procedure of LVAD implantation were previously described [17]. Prior to LVAD implantation, all patients were in New York Heart Association Class IV receiving i.v. inotropes. Twenty-five (71%) patients were supported by an intra-aortic balloon pumping system. At the time of LVAD implantation, 13 (37%) underwent tricuspid annuloplasty and 1 (3%) underwent coronary artery bypass grafting concomitantly. No patient needed bi-VAD support. After LVAD implantation, all 35 patients were stable, although 5 (14%) required inotrope support at 1 month after the operation. During support, the pump flow was typically adjusted as low as possible unless symptom of low output syndrome or right heart failure did not appear.

These 35 hearts removed at transplantation were investigated for evidence of aortic valve pathology. Clinical and echocardiographic data were collected retrospectively. Thirty-one patients were supported with an extracorporeal pulsatile device (Nipro-Toyobo LVAD; Nipro, Osaka, Japan), 1 was supported with an implantable pulsatile device (Novacor; World Heart, Oakland, CA, USA) and 3 were supported with an implantable non-pulsatile device [HeartMate II, Jarvik 2000 (Jarvik Heart, New York, NY, USA) and EVAHEART (Sun Medical, Nagano, Japan); 1 each].

Echocardiography was periodically performed before and after LVAD implantation, and each patient was analysed in terms of cardiac function and native aortic valve function. All studies were analysed by the cardiologists at the National Cerebral Cardiovascular Center using standard criteria to assess the degree of AI, which was graded on a scale of 1–4. The number of aortic valve openings per native heart rate was calculated to determine the frequency of the native aortic valve opening. Detailed gross pathological analysis of the aortic valve was performed after explantation at the time of transplantation. The extent and length of commissural fusion was recorded. Microscopic analysis was also performed with haematoxylin and eosin and Masson's trichrome staining. The thickness of the aortic cusp, aortic wall and left ventricular wall was measured. The perimeter of the aortic valve annulus was also measured, and then the annular diameter was calculated.

Data are expressed as mean ± standard deviation. We compared continuous variables using a *t*-test. χ^2 analysis was used to assess group differences involving discrete variables. The correlations among aortic valve thickness, duration of LVAD support, cardiac function, commissural fusion and AI grade were assessed using Pearson's correlation test. The relationship between late AI and other parameters was examined using logistic regression analysis. Statistical significance was considered at $P \leq 0.05$.

RESULTS

Patient characteristics are summarized in Table 1. The patients were relatively young with small body surface areas. Twenty-eight of the 35 patients were male, and most suffered from idiopathic non-ischaemic cardiomyopathy. The mean time on LVAD support was 961 ± 307 (range, 416–1697) days. No patient underwent aortic valve surgery at LVAD implantation or during LVAD support.

Echocardiographic data obtained before LVAD implantation and just before heart transplantation are summarized in Table 2. Before device implantation, all patients had a normal aortic valve opening, and only 5 had trivial AI. After slightly <3 years of LVAD support, 18 patients developed trivial AI, 4 developed mild AI and 2 developed mild-to-moderate AI. The AI was predominantly observed from the centre throughout both systole and diastole. Trivial AI observed before LVAD implantation remained trivial in 3 patients and improved to an absence of AI in 1 patient before transplantation. Thus, all patients with mild and mild-to-moderate AI ($n = 6$) were

Table 1: Baseline characteristics of the 35 patients

Variables	Mean ± SD or *n* (%)
Age, years	34.3 ± 12.5
Sex, female	7 (20.0)
BSA, m^2	1.63 ± 0.18
Duration of LVAD support, days	961 ± 307
Aetiology of heart failure	
DCM	25 (71.4)
dHCM	6 (17.1)
ICM	2 (5.7)
PMCM	2 (5.7)
Device	
Nipro-Toyobo	31 (88.6)
Novacor	1 (2.9)
HeartMate II	1 (2.9)
Jarvik 2000	1 (2.9)
EVAHEART	1 (2.9)

BSA: body surface area; LVAD: left ventricular assist device; DCM: dilated cardiomyopathy; dHCM: dilated phase of hypertrophic cardiomyopathy; ICM: ischaemic cardiomyopathy; PMCM: post-myocarditis cardiomyopathy; SD: standard deviation.

Table 2: Summary of pre-LVAD implantation and pre-transplantation echocardiographic data

	Pre-LVAD implantation	Pre-transplantation
LVDd, mm	74.1 ± 11.4	64.1 ± 15.9
LVDs, mm	67.8 ± 12.7	58.8 ± 16.9
FS, %	8.5 ± 5.2	9.6 ± 5.6
Aortic insufficiency		
None	30 (85.7)	11 (31.4)
Trivial	5 (14.3)	18 (51.4)
Mild	0	4 (11.4)
Mild-to-moderate	0	2 (5.7)
Aortic valve opening		
Every heartbeat	35 (100)	8 (22.9)
Sometimes	0	11 (31.4)
Seldom	0	5 (14.3)
No opening	0	11 (31.4)

Data are presented as mean ± SD or *n* (%).
LVAD: left ventricular assist device; LVDd: left ventricular diastolic dimension; LVDs: left ventricular systolic dimension; FS: fractional shortening; SD: standard deviation.

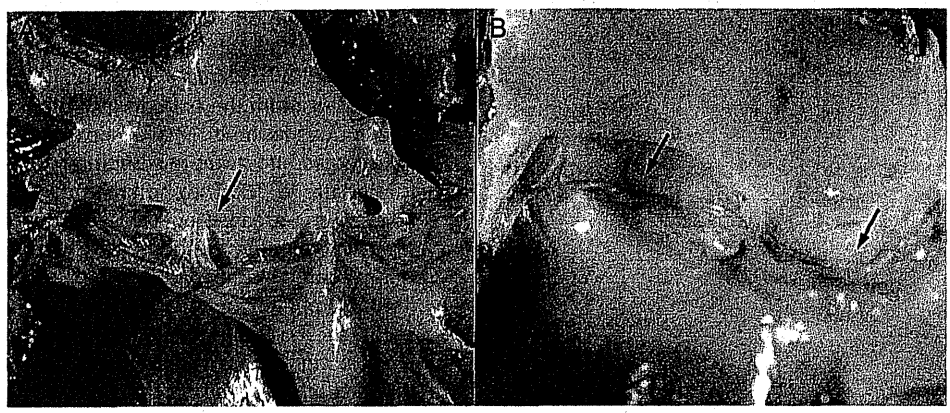

Figure 1: Representative gross appearance of the native aortic valve after long-term left ventricular assist device support. (**A**) Partial aortic valve commissural fusion (arrow). (**B**) Curling and shortening of the aortic valve cusp (arrows).

Table 3: Summary of histological analysis

Variables	Mean ± SD (range) or *n* (%)
Commissural fusion	17 (48.6)
3 commissures	1 (2.9)
1 commissure	16 (45.7)
Curling and shortening of aortic valve cusp	22 (62.9)
Thickness of aortic valve cusp, μm	680 ± 320 (120–1400)
Thickness of aortic wall, μm	1400 ± 390 (830–2220)
Thickness of left ventricular wall, mm	7.7 ± 2.1 (4–13)
Diameter of aortic annulus, mm	20.9 ± 2.9 (17–27)

SD: standard deviation.

determined to have so-called '*de novo*' AI. In terms of the type of LVAD, all 3 patients with implantable continuous-flow LVADs developed *de novo* AI during the study period: 2 (HeartMate II and Jarvik 2000) with trivial AI and 1 (EVAHEART) with mild AI. In terms of the aortic valve opening, a normal opening was observed in only 8 patients. The aortic valve sometimes opened in 11 patients, seldom opened in 5 and was continuously closed in 11. All aortic valves of patients with late mild or mild-to-moderate AI ($n = 6$) rarely showed an opening or showed no opening. Conversely, the AI grade of patients whose aortic valve frequently opened remained none or trivial ($n = 19$).

On gross pathological examination, 16 (45.7%) of 35 patients had one commissural fusion (Fig. 1A), and 1 (2.9%) had three commissural fusions. All examined aortic valves were tricuspid, and there was no predilection for fusion of specific cusps (between right and left coronary cusps, 3; between right and non-coronary cusps, 5; and between left and non-coronary cusps, 8). The fusion distance was within 5 mm in all cases of fusion, and there was no fresh thrombotic or post-inflammatory fusion. Leaflet curling and shortening (Fig. 1B) were seen in 22 (62.9%) patients (Table 3).

Histological examination revealed that the aortic valve leaflet had become thinner in all patients (Fig. 2A), ranging from 120 to 1400 μm compared with the normal value of 1500–2000 μm. The aortic wall had also become thinner in most patients, ranging from 830 to 2220 μm. The left ventricular wall thickness was thinner in the majority of cases, ranging from 4 to 13 mm. The aortic annular diameter was ranging from 17 to 27 mm (Table 3). Microscopically, dense collagen accumulation in the spongiosa layer (Fig. 2B) was observed in some patients. Microthrombi on the left ventricular side of fused leaflets were recognized in 1 patient. There was no significant sign of inflammation on the leaflets (Fig. 2C).

Statistically, there was no close correlation between aortic valve thickness, aortic annulus dimension, or aortic wall thickness and LVAD support duration, AI grade, or cardiac function. Closed or less frequently opening aortic valve was a significant predictor of late mild or mild-to-moderate AI. However, no other parameters such as female sex, age over 50 years, LVAD support duration over 1200 days, commissural fusion, cusp thickness <500 μm, aortic annular dilatation >25 mm and aortic wall thickness <1200 μm were proved to be no significant predictor of mild or mild-to-moderate AI after long-term LVAD support by logistic regression analysis. Additionally, there was no close correlation between commissural fusion and sex, age, LVAD support duration, cusp thickness, aortic valve opening or types of LVAD.

DISCUSSION

It is well known that native AI develops or progresses during LVAD support [6, 18]. This may be caused by dramatically altered haemodynamics after LVAD implantation. LVADs decrease the load on the ventricle and reduce ventricular wall stress, which encourages reverse remodelling and results in a reduced ventricular cavity size. The pressure load is shifted to the aortic valve and aortic root. The pressure difference between the aortic root and left ventricle thus increases. Consequently, the aortic valve leaflets are subjected to a constant high transvalvular pressure, which tends to induce deterioration and remodelling (including collagen proliferation) of the aortic valve and less frequent opening of the native aortic valve, and the aortic root tends to dilate [19, 20]. It is no wonder that constant high pressure on the aortic valve and remodelling of the aortic root and valve contribute to AI progression.

Other potential risk factors of AI development after LVAD implantation are reduced left ventricular function, continuous-flow LVAD and preoperative mitral regurgitation [6, 7, 21]. Each factor means low antegrade blood flow through the aortic valve, which can result in poor opening of the valve and development of AI.

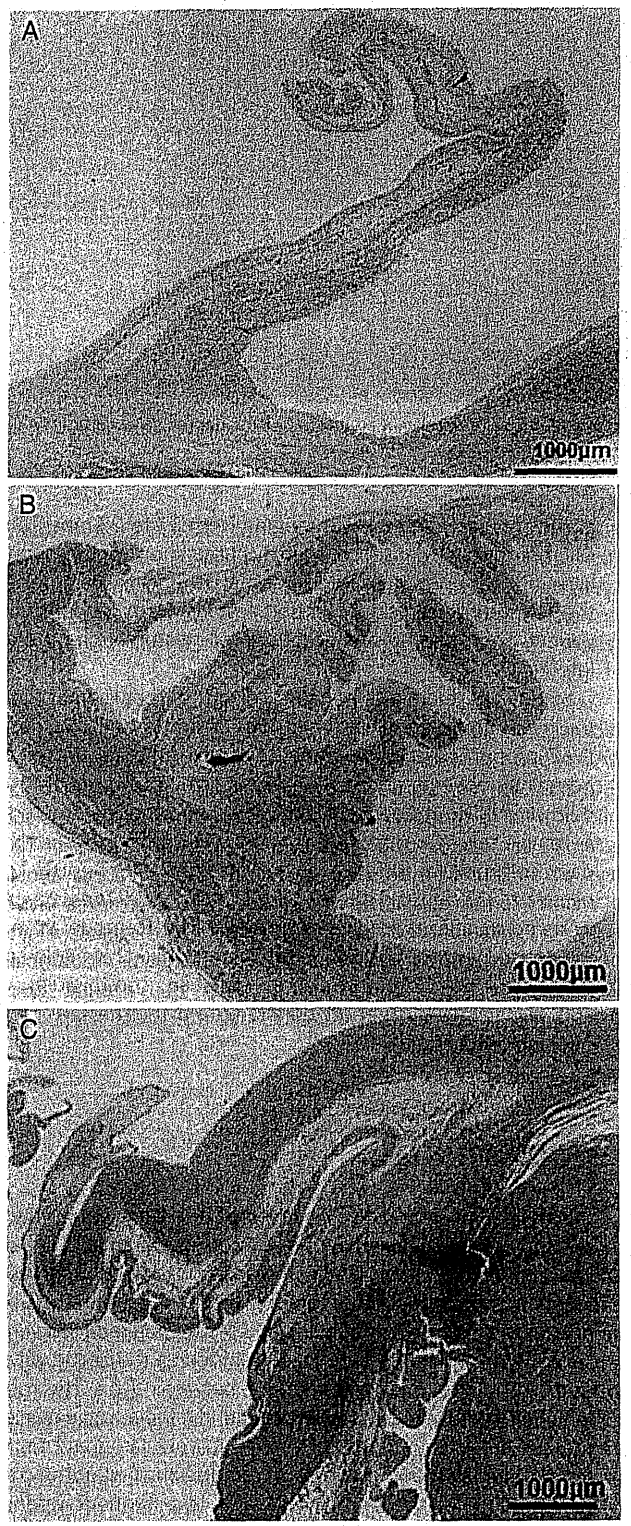

Figure 2: Microscopic appearance of the native aortic valve leaflet after long-term left ventricular assist device support. (**A**) Thinning of the cusp due to collagen depletion (Masson's trichrome stain). (**B**) Fused commissure showing proliferation of collagen fibres and a microthrombus (Masson's trichrome stain). (**C**) No inflammatory reaction was observed in the aortic valve (haematoxylin and eosin stain).

Another possible factor of AI progression is commissural fusion. It has attracted attention as one of the remodelling responses. Aortic valve fusion was first reported in association with pulsatile implantable LVADs and vented-electric (VE) and implantable-pneumatic (IP) HeartMates [8–10, 12, 16]. Connelly *et al.* and Letsou *et al.* from the Texas Heart Institute reported that commissural fusion was found in 17 of 33 hearts supported by VE and IP HeartMates, and it was more common in patients with VE than IP HeartMates [8, 16]. They commented that such fusion could necessitate an increased level of LVAD support. They also mentioned strategies to minimize the occurrence of commissural fusion, including careful control of blood pressure, periodic decreases in the LVAD pump rate and discontinuation of left ventricular assistance for short periods of time; the HeartMate IP originally required venting every 24 h [16].

The exact mechanism of aortic valve commissural fusion is still unclear, but is hypothesized to result from prolonged leaflet coaptation due to poor or no antegrade flow through the valve [8, 13]. Such fusion was also reported in patients with severe chronic heart failure [8], and we indeed observed commissural fusion in patients with heart failure without LVAD support. Conceivable mechanisms include morphological remodelling of valvular endothelial cells during altered shear stresses or an absolutely static environment that promotes local fibrosis [13, 22]. Another possible mechanism may be local inflammatory changes, including thrombus formation [4, 23]. However, no cases of cellular inflammatory infiltration or thrombus were recognized on the aortic valve leaflet in our study.

Recently, as implantable LVADs with continuous flow have become more common, aortic commissural fusion has been reported with the use of non-pulsatile LVADs. Mudd *et al.* [13] demonstrated a higher prevalence of aortic commissural fusion in patients with the HeartMate II than with pulsatile LVADs and an increasing prevalence of mild-to-moderate AI during LVAD support, suggesting a correlation between the two. However, there are also some studies in the literature reporting AI without commissural fusion or no AI with commissural fusion in LVAD patients [9, 11, 16, 21]. In our study, there was no correlation between commissural fusion and late AI. It is still unclear whether commissural fusion is responsible for the development of AI.

Few reports have demonstrated the detailed histological changes in the aortic valve with or without commissural fusion after long-term LVAD support. In this study, we analysed the pathological changes in the aortic valve and root after prolonged LVAD support and their correlation with the clinical course as assessed by echocardiography. After ~3 years of LVAD support, some degenerative changes, including shortening and thinning of the aortic leaflets and commissural fusion, and aortic root remodelling were certainly observed in the majority of patients. Although there was no close correlation between these pathological findings and the development of AI independently, such degenerative changes might multiply contribute to the progression of AI. We also found that less frequent aortic valve opening was the predictor of mild or mild-to-moderate AI after long-term LVAD support.

Given the improved mechanical durability and feasibility, more patients may be able to receive mechanical support for a longer period. More patients may develop aortic valve lesions during long-term support. Because progression of AI can lead to poor haemodynamics, an optimal strategy to prevent AI development has to be determined. Taking account of potential factors of AI development mentioned above, it is important to keep the native aortic valve (sometimes) open. We recommend adjusting the

pump flow as low as possible unless symptoms of low output syndrome do not appear. Appropriate anticoagulation therapy is also essential, and periodic close echocardiographic examination is mandatory. Moreover, we believe that mild or more AI at the time of LVAD implantation or symptomatic AI during LVAD support should be actively treated surgically [24, 25].

This study has several limitations. First, most of the LVADs enrolled in this study were the extracorporeal pulsatile Nipro-Toyobo VAD, which is the characteristic VAD of Japan, because implantable non-pulsatile VADs became commonly available only a few years ago in Japan. It is still the most commonly implanted VAD in Japan, but is rarely used in other countries. Moreover, due to the vastly unequal size of samples, a valid comparison between pulsatile and non-pulsatile devices as well as the comparison of influence of outflow graft size and flow rate was not possible. Secondly, the duration of LVAD support was relatively long in this study, although it was almost average in Japan. We did not analyse the short-term heart support, and thus could not discuss when and how the degenerative changes in the aortic valve began.

In conclusion, some degenerative changes in the aortic valve were observed after long-term LVAD support. There was also an increasing prevalence of mild and mild-to-moderate AI, which may have been associated with continuous aortic valve closure. An optimal strategy to prevent AI development should be determined and careful periodic echocardiographic follow-up is essential.

Conflict of interest: none declared.

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ORIGINAL ARTICLE

Artificial Heart (Clinical)

Paracorporeal ventricular assist device as a bridge to transplant candidacy in the era of implantable continuous-flow ventricular assist device

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Abstract Ventricular assist devices (VADs) have long been used as bridge to transplant therapy (BTT). Nipro-Toyobo paracorporeal pulsatile-flow VAD (nt-VAD) was the only device available until April 2011, when implantable continuous-flow VADs (cf-VADs) became available. Although cf-VADs are central to BTT, nt-VAD remains a necessary option. We aimed to clarify the role of nt-VAD in an era of increasing cf-VAD use. We retrospectively reviewed patients who underwent VAD implantation at the National Cerebral and Cardiovascular Center from May 2011 to March 2013. Characteristics were compared between the nt-VAD and cf-VAD groups. Twenty-nine patients (mean age 37.7 ± 11.1 years, 23 males) underwent VAD implantation. Fifteen patients initially received nt-VADs, although 4 were converted to cf-VADs. Of these 15 patients, 3 were too small for cf-VADs and 2 needed bilateral ventricular support. The remaining 10 patients received nt-VADs (7 patients at INTERMACS level 1 and 3 at level 2). The nt-VAD group patients had significantly more preoperative mechanical circulatory support and were in a more critical condition before VAD implantation than the cf-VAD group. The 2-year survival rate was not significantly different. Despite the critical conditions of nt-VAD patients, their overall survival is not statistically inferior to that of cf-VAD patients. nt-VAD is a good option as a BTC for the patient with urgent and critical condition.

Keywords Ventricular assist device · Bridge to transplant candidacy · Implantable continuous-flow ventricular assist device · Paracorporeal pulsatile-flow ventricular assist device

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Introduction

The ventricular assist device (VAD) is an alternative therapy for the patient with advanced heart failure who does not respond to conventional pharmacological and non-pharmacological treatments, whereas VAD was basically allowed to use only for patients deemed eligible for candidates of heart transplant in Japan [1–3]. Until April 2011, Nipro-Toyobo-paracorporeal pulsatile-flow ventricular assist device (nt-VAD, Nipro, Osaka, Japan) has been long used as only device for bridge to transplant therapy (BTT) in Japan and almost 90 % of the candidates for heart transplant received VAD. Therefore, over 90 % of heart transplant candidate had to wait at least for a couple of years with nt-VAD under hospitalization before receiving heart transplant so far [4]. On the other hand, 2 implantable continuous-flow ventricular assist device [cf-VAD, EVAHEART (Sun Medical, Nagano, Japan) and DuraHeart (Terumo Heart, Ann Arbor, MI, USA)] which has been long awaited was approved for health insurance coverage

from April 2011 and it has become a central player in BTT since then [5]. cf-VAD has been expected to bring in more safe and fulfilling lives for heart transplant candidates at their home. With these circumstances, demands for nt-VAD, a former central player of BTT in Japan, has reduced and its role in clinical practice has changed.

This study aimed to clarify renewed roles of nt-VAD in the era of cf-VAD and to review the underlying problems of current VAD therapy by analyzing the 2-year experience of VAD usage in National Cerebral and Cardiovascular Center.

Methods

Patient population

We retrospectively analyzed 29 consecutive patients with advanced heart failure who received VADs from May 2011 to March 2013 at the National Cerebral and Cardiovascular Center. Although cf-VAD was approved for health insurance coverage in April 2011 in Japan, our institute only employed it from May 2011, after 1 month preparation. All patients received VAD implantation for BTT or bridge to transplant candidacy (BTC) after approval for transplant candidates by institutional committee. Patients' characteristics were compared between nt-VAD group and cf-VAD group. VAD implantation was performed as previously reported [6]. Administration of heart failure medications such as angiotensin-converting enzyme inhibitors and β-adrenergic blockades after device implantation was encouraged same as patients with heart failure without mechanical supports. All subjects enrolled in this research have given their informed consent. Data collection, analysis, and reporting were approved by the National Cerebral and Cardiovascular Center Institutional Review Board.

Clinical parameters

We retrospectively obtained baseline clinical parameters from patients' medical records, including demographics, blood examinations, and echocardiographic parameters [left ventricular diastolic dimension (LVDd), left ventricular systolic dimension (LVDs), ejection fraction (EF), left atrial dimension (LAD), interventricular septal thickness (IVST), posterior wall thickness (PWT)]. Severity of each patient was stratified based on The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patient profile [7].

Clinical events

VAD-related cerebrovascular events included transient ischemic attack (TIA) and clinical strokes (ischemic or hemorrhagic) including subarachnoid hemorrhage. A TIA was defined as an episode of neurological disorder (lasting < 24 h) resulting from focal cerebral ischemia and not associated with evidence of cerebral infarction on imaging. Clinical strokes were defined as acute neurological disorder that lasted more than 24 h with evidence of infarction or hemorrhage on computed tomography. Event of VAD-related infection included infection caused by drive-line of cf-VAD or inflow and outflow cannulas of nt-VAD requiring hospitalization for receiving intravenous antibiotics. Drive-line and cannula infection was defined as the presence of purulent discharge from exit-site of drive-line and cannula. Administration of oral antibiotics at outpatient clinic was not considered an event of VAD-related infection.

Statistical analysis

Statistical analysis was performed using JMP software (version 9, SAS institute Inc. USA). Continuous variables with normal distribution are expressed as mean ± standard deviation (SD). The Chi square test was used for categorical variables, and analysis of variance (ANOVA) test was used for continuous variables. A values of $P < 0.05$ was considered significant. Kaplan–Meier analysis was used to evaluate overall survival and event-free survival for device-related cerebrovascular disease and infection of nt-VAD and cf-VAD group.

Results

Preoperative patient characteristics

The preoperative characteristics of both nt-VAD and cf-VAD group are listed in Table 1. A total of 29 patients underwent VAD implantation from May 2011 to March 2013 at our institute. Of these, 14 patients (48.2 %) initially received cf-VAD, while 15 patients (51.8 %) initially received nt-VAD. Comparison between the 2 groups revealed that female sex, patients with small BSA, and patients with critical conditions including more severe INTERMACS levels requiring more temporary mechanical circulatory support prior to VAD implantation were found in nt-VAD group. Lower rate of β-adrenergic blockades and angiotensin-converting enzyme inhibitors administration were also demonstrated. There were no differences in the baseline data of blood examinations and echocardiographic findings.

Clinical course

The clinical course of enrolled patient is summarized in Fig. 1. The cf-VAD group consist of 12 EVAHEARTs and

Table 1 Baseline characteristics of the patients according to the types of ventricular assist device implanted

	cf-VAD ($n = 14$)	nt-VAD ($n = 15$)	*P* value
Age at VAD implantation, years	42.4 ± 7.4	35.1 ± 9.9	0.05
Male sex, *n* (%)	14 (100)	9 (60)	0.01
BSA at the time of VAD surgery, m^2	1.73 ± 0.08	1.56 ± 0.18	0.02
Duration of heart failure, day	2892 ± 1404	2283 ± 2175	0.3
Etiology, *n* (%)			
DCM	11 (78.7)	10 (66.8)	–
d-HCM	1 (7.1)	2 (13.4)	–
ICM	1 (7.1)	1 (6.6)	–
PPCM	0 (0)	1 (6.6)	–
Others	1 (7.1)	1 (6.6)	–
INTERMACS patient profile, *n* (%)			
Level 1	0 (0)	9 (60)	–
Level 2	3 (21.4)	6 (40)	–
Level 3	11 (78.6)	0 (0)	–
Pre-VAD MCS, *n* (%)			
ECMO	0 (0)	6 (40)	0.01
IABP	3 (21.4)	13 (86.6)	0.001
Intravenous inotropic agents, μg/kg/min			
(DOA, μg/kg/min + DOB, μg/kg/min)	5.04 ± 1.04	7.39 ± 2.63	0.04
Medication, *n* (%)			
β-blocker	14 (100)	9 (60)	0.01
ACE inhibitor or Ang-II antagonist	13 (76.9)	7 (46.6)	0.01
Aldosterone antagonist	13 (76.9)	6 (40)	0.05
Laboratory examinations			
WBC, /μL	6321.4 ± 1144.8	7586.7 ± 2079.1	0.21
Hb, mg/dL	12.3 ± 1.2	11.4 ± 1.6	0.14
T-Bil, mg/dL	1.29 ± 0.43	2.07 ± 1.18	0.08
Cre, mg/dL	1.17 ± 0.34	1.01 ± 0.36	0.51
Na, mEq/L	136.4 ± 2.6	135.2 ± 5.2	0.53
CRP	1.49 ± 1.38	5.25 ± 5.02	0.08
BNP, pg/dL	812.6 ± 458.2	933.9 ± 494.2	0.1
Echocardiographic parameters			
LVEDD, mm	74.6 ± 7.7	71.7 ± 9.7	0.77
LVESD, mm	67.4 ± 9.9	65.8 ± 10.5	0.95
LVEF, %	16.5 ± 6.9	16.8 ± 7.4	0.76
AR, grade 1–4			
1	1	1	0.87
2–4	0	0	–

cf-VAD implantable continuous-flow ventricular assist device, *nt-VAD* Nipro-Toyobo paracorporeal pulsatile-flow ventricular assist device, *VAD* ventricular assist device, *BSA* body surface area, *DCM* dilated cardiomyopathy, *d-HCM* dilated-phase hypertrophic cardiomyopathy, *ICM* ischemic cardiomyopathy, *PPCM* peripartum cardiomyopathy, *INTERMACS* the interagency Registry for Mechanical Assisted Circulatory Support, *Pre VAD MCS* mechanical circulatory support prior to VAD implantation, *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump, *DOA* dopamine, *DOB* dobutamine, *ACE* angiotensin converting enzyme, *Ang-II* angiotensin II, *WBC* white blood cell, *Hb* hemoglobin, *T-Bil* total bilirubin, *Cre* creatinine, *Na* sodium, *CRP* C-reactive protein, *BNP* brain natriuretic peptide, *LVEDD* left ventricular end-diastolic dimension, *LVESD* left ventricular systolic dimension, *LVEF* left ventricular ejection fraction, *AR* aortic regurgitation

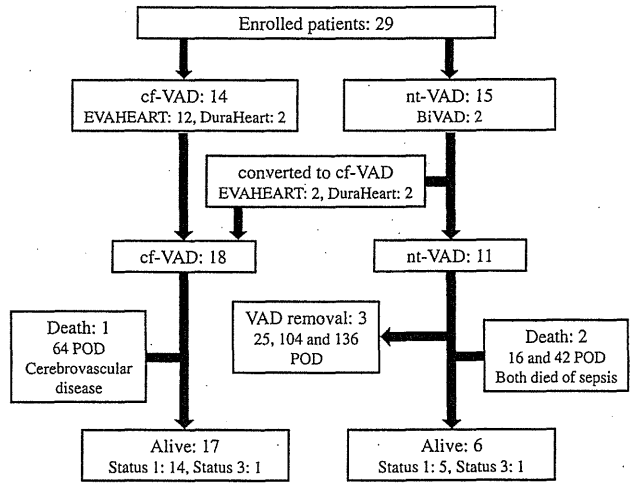

Fig. 1 Clinical course of all study patients. This flowchart shows the clinical course of patients who initially received nt-VAD or cf-VAD

2 DuraHearts. In the nt-VAD group, 2 patients needed biventricular support and 4 were converted to cf-VADs. In the 2 cases needing biventricular support, both nt-VAD and extracorporeal membrane oxygenation (ECMO) were used for right ventricular support, respectively. In the 4 conversion cases, 2 EVAHEARTs and 2 DureHearts were used. One patient receiving cf-VAD and 2 patients receiving nt-VAD died due to cerebrovascular disease and sepsis, respectively. Furthermore, 3 patients implanted with nt-VAD were weaned from VAD because of recovery of native cardiac function, while no patient with cf-VAD demonstrated sufficient recovery of native cardiac function enough to be weaned from VAD. By the end of the study period, 17 of original patients were supported by cf-VAD and 6 were supported by nt-VAD. The overall survival curves of both cf-VAD and nt-VAD were shown in Fig. 2. Whereas, the cf-VAD and nt-VAD group demonstrated

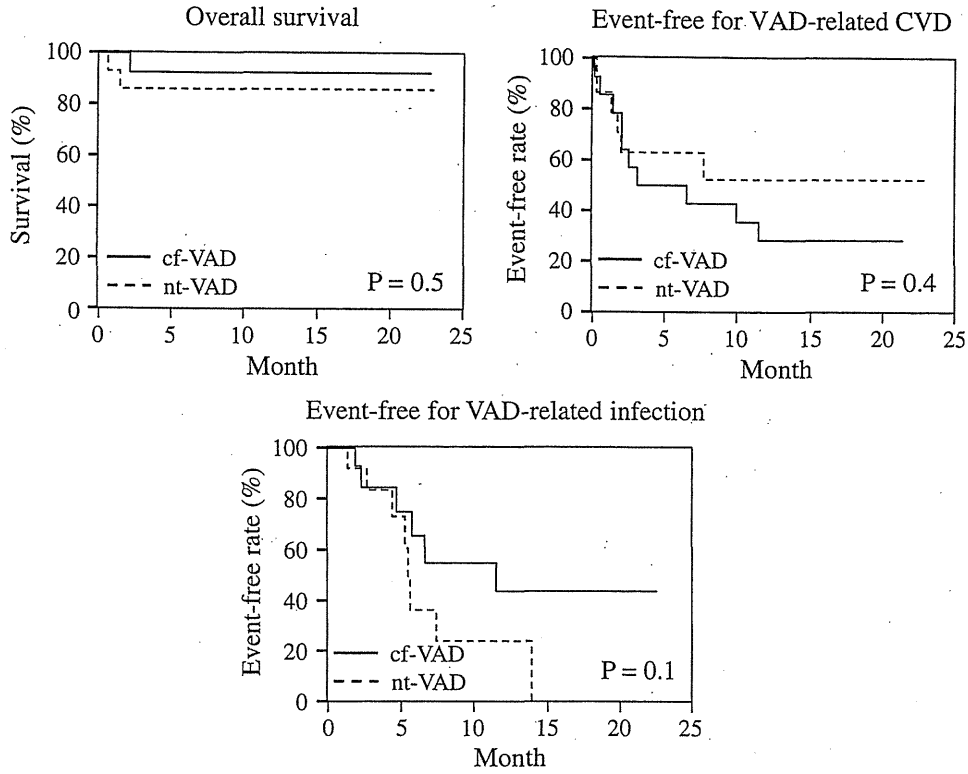

Fig. 2 Kaplan–Meier curves for overall survival and freedom from device-related complications. There were no significant differences between patients who initially received cf-VAD or nt-VAD in terms of overall survival, VAD-related infection, or VAD-related cerebrovascular disease (CVD) ($P = 0.5$, $P = 0.4$, and $P = 0.1$, respectively)

comparatively favorable 2-year survival rates of 92.8 and 86.6 %, respectively; there was no statistically significant difference in survival between them. The event-free curves for VAD-related complications such as VAD-related infection and VAD-related cerebrovascular disease are displayed in Fig. 2. There were no statistically significant differences between the patient who initially received cf-VAD and nt-VAD in terms of either VAD-related infection or VAD-related cerebrovascular disease.

Individual demographics of the patient receiving nt-VADs

The individual demographics for patients who initially received nt-VADs are shown in Table 2. nt-VADs were implanted in 3 patients (1 male and 2 females) because of their less body surface area (BSA; lower than 1.4 m^2) and in 2 patients because of severe heart failure requiring a biventricular assist device (BiVAD). One case requiring BiVAD was diagnosed as peripartum cardiomyopathy and was weaned from VAD when native cardiac function was recovered, whereas the other BiVAD case had a diagnosis of d-HCM with hypoplastic right ventricle and died due to sepsis. BTC was the main indication for nt-VAD implantation in 10 patients (7 patients were INTERMACS level 1 while 3 patients were INTERMACS levels 2). Preoperatively, of 7 INTERMACS level 1 patients, 4 were supported by both ECMO and the intra-aortic balloon pump (IABP) and 3 were supported with IABP alone. Two patients with INTERMACS level 2 were also supported with IABP before surgery. Among the 10 BTC patients, 4 were converted to cf-VAD and of these 4 patients, case 1 who had been converted to cf-VAD 108 days after nt-VAD implantation suffered from VAD pocket infection requiring repetitive lavage of infected pocket with long-term administration of antibiotics after conversion. Remaining 3 patients were converted within 15 days after nt-VAD implantation and they had uneventful postoperative outcome. In total, 5 patients were now on nt-VAD support for BTT and 1 patient who had complicated by repetitive cerebrovascular disease following nt-VAD implantation still on nt-VAD support for BTC.

Discussion

VAD therapy is currently the most established therapy for advanced heart failure that is unresponsive to conventional treatments, and its use is increasing annually. For a long time, nt-VAD was the only consistently used device approved for use in BTT in Japan. However, in April 2011, the EVAHEART and DuraHeart cf-VADs were introduced and approved for health insurance coverage for BTT [8–10], with the expectation that patients would have an improved quality of life in their homes and that nt-VAD would be used in fewer cases. However, after analyzing the

Table 2 Patient demographics for the Nipro-Toyobo ventricular assist device

Patient number	Sex	Age (y. o)	BSA (m^2)	Etiology	pre VAD MCS	INTERMACS profile	Reason for nt-VAD	Conversion or weaning of VAD	Duration of nt-VAD (days)	VAD-related complications	Current status
Case 1	M	28	1.63	DCM	IABP	1	BTC	Conversion to cf-VAD	108	Pocket and drive-line infection	BTT at outpatient
Case 2	M	16	1.6	DCM	IABP	1	BTC	Conversion to cf-VAD	15	Drive-line infection	BTT at outpatient
Case 3	M	26	1.87	DCM	IABP, ECMO	1	BTC	Conversion to cf-VAD	15	CVD and drive-line infection	BTT at outpatient
Case 4	M	55	1.73	ICM	IABP	1	BTC	Conversion to cf-VAD	7	CVD	BTT at outpatient
Case 5	M	43	1.85	DCM	None	2	BTC	Weaned from VAD	136		Stable at outpatient
Case 6	M	33	1.69	DCM	IABP	2	BTC	Weaned from VAD	104		Stable
Case 7	F	22	1.41	d-HCM	IABP, ECMO	1	BTC		16		Death (sepsis)
Case 8	F	21	1.44	DCM	IABP, ECMO	1	BTC		262	Cannula infection	BTT with nt-VAD
Case 9	M	38	1.83	DCM	IABP	2	BTC		226	CVD and cannula infection	BTT with nt-VAD
Case 10	M	37	1.67	DCM	IABP, ECMO	1	BTC		206	CVD and cannula infection	BTT with nt-VAD
Case 11	F	27	1.31	d-HCM	None	2	BSA < 1.4 m^2		625	CVD	BTT with nt-VAD
Case 12	M	26	1.34	DCM	IABP	2	BSA < 1.4 m^2		470	Cannula infection	BTT with nt-VAD
Case 13	F	57	1.33	DCM	IABP	3	BSA < 1.4 m^2		115	CVD	BTC with nt-VAD
Case 14	F	31	1.33	PPCM	IABP, ECMO	1	BiVAD	Weaned from VAD	25		Stable at outpatient
Case 15	F	49	1.4	Others	IABP, ECMO	1	BiVAD		42		Death (sepsis)

BSA body surface area, *pre VAD MCS* mechanical circulatory support prior to VAD implantation, *INTERMACS* the interagency Registry for Mechanical Assisted Circulatory Support, *DCM* dilated cardiomyopathy, *IABP* intra-aortic balloon pump, *BTC* bridge to candidacy, *cf-VAD* implantable continuous-flow ventricular assist device, *BTT* bridge to transplant, *ECMO* extracorporeal cardiopulmonary membrane oxygenation, *CVD* cerebrovascular disease, *ICM* ischemic cardiomyopathy, *d-HCM* dilated-phase hypertrophic cardiomyopathy, *nt-VAD* Nipro-Toyobo extracorporeal pulsatile-flow ventricular assist device, *PPCM* peripartum cardiomyopathy, *BiVAD* biventricular assist device

2-year experience of VAD therapy in the National Cerebral and Cardiovascular Center, we found that since the introduction of cf-VAD, nt-VADs were still initially implanted in 15 (51.7 %) of the 29 patients studied. The indications for nt-VAD implantation were the necessity of bilateral ventricular support (2 cases), less BSA for cf-VAD (3 cases), and BTC (10 cases) in patients at lower INTERMACS patient profiles (levels 1 and 2).

The INTERMACS annual report recently revealed that VAD implantation was associated with a poor prognosis in patients at INTERMACS levels 1 and 2. As a result, the proportion of patients at INTERMACS level 1 undergoing VAD implantation gradually decreased from 44.2 % in the first annual report to 19.7 % in the fifth annual report [7, 11–14]. In response to these reports, use of nt-VADs has become a reasonable strategy for INTERMACS level 1 patients as BTC in order to avoid use of expensive implantable devices in high-risk patients and to allow more time to assess their transplant candidacy. Our study further disclosed that there were no statistically significant difference between nt-VAD and cf-VAD in terms of their overall survival and VAD-related complications such as drive-line or cannula infection, and cerebrovascular disease despite much sicker patients were included for nt-VAD patients. Furthermore, there was always the possibility of these nt-VAD patients converting to cf-VAD later if they stabilized and were deemed eligible for heart transplant. In our patient series, 4 cases of nt-VAD were converted to cf-VAD, and all continue to be well in outpatient clinic reviews.

Of course, there still remain several problems in operating nt-VAD for BTC device. First, not all the patients can afford to be converted from nt-VAD to cf-VAD. Continuous infection associated with both surgical procedure of nt-VAD implantation and nt-VAD itself (e.g., cannulas infection) are potential obstacles to VAD conversion. Indeed, nt-VAD has been reported to be an independent risk factor for VAD-related infection over time; therefore, conversion of nt-VAD to cf-VAD always carries a risk of post-conversion infection such as pump pocket infection [15]. In fact, case 1 of our series, who had been converted to cf-VAD over 3 months after initial nt-VAD implantation, developed pocket infection from the cannula exit-site infection of nt-VAD. Furthermore, case 8, 9 and 10 could not be converted to cf-VAD because of clinically evident cannula exit-site infection of nt-VAD. Yoshioka et al. [16] also reported their experience of 8 conversions from nt-VAD to DureHeart in which 3 cases were complicated by pocket infection. Considering that the incidence of device-related infection is known to increase over time, VAD conversion was performed as soon as possible after the patients' condition stabilized and their suitability for transplant was determined [15]. In fact, Case 2, 3 and 4 received VAD conversion within 15 days after nt-VAD implantation, and they did not develop pocket infections. The second problem is that use of nt-VADs for BTC may force patients with critical conditions to undergo a second invasive surgical procedure in a relatively short period of time when they undergo VAD conversion. The third problem is that if candidacy for transplant is not approved, since nt-VAD has been shown to be a durable device, patients receiving nt-VADs have to be hospitalized for the rest of their lives with nt-VAD support and no hope for heart transplant. In fact, our case 13 who had repeated cerebrovascular events after nt-VAD implantation still could not apply for the transplant waiting list due to residual neurological defects.

To resolve these issues, we propose the followings. Both approval of destination therapy (DT) for health insurance coverage and introduction of other easy-to-use and short-term devices that can be implanted by low-invasive procedures may be helpful. However, DT is currently under consideration in Japan and it should be considered carefully in terms of both ethical perspective and its cost effectiveness. Short-term VADs have been used as BTC so far [17, 18]. John et al. [19] reported their experience with the Levitronix CentriMag circulatory support system as bridge to decision in patient with refractory acute cardiogenic shock with multi-system organ failure. In this study, 12 critical patients were enrolled for analysis, of whom 8 were successfully bridged to implantable VAD (HeartMate XVE); 5 were successfully bridged to heart transplant and only 1 died before heart transplant despite extreme critical conditions of the patient (1-month survival of 75 % and 1-year survival of 62.5 %). Therefore, temporary devices such as the Levitronix CentriMag circulatory support system may play a role in BTC. However, since there is no big difference in terms of invasiveness between nt-VAD and Levitronix CentriMag circulatory support system, development and introduction of less-invasive, short-term VADs are essential for improvement of current VAD therapy.

In addition, it would be useful to encourage close communication with primary care physicians and general cardiologists of other facility with no VAD programs about the importance of VAD therapy for advance heart failure patients before they deteriorate to lower INTERMACS level.

Conclusion

At present, cf-VADs are the first-line mechanical circulatory device for patients with advanced heart failure who meet the indications for both heart transplant and VAD implantation. However, not all patients are suitable for cf-VAD, and a prominent reason for nt-VAD implantation is use as BTC in critically ill INTERMACS level 1 or 2 patients. In our case series, nt-VAD could be subsequently

converted to cf-VAD and there were no significant differences in overall survival or the development of VAD-related complications. Therefore, nt-VAD is potentially a good option for BTC in critically ill patients even in the era of cf-VAD. However, VAD therapy is still in transition, and we are currently seeking better ways to use VADs in advanced heart failure patients. Other new VADs are scheduled to be available in the near future, and they will further impact the current role of the nt-VAD.

Study limitations

This study had several limitations. First, this study was a retrospective study in a single center with a relatively small sample size. Second, device strategy of VAD differs somewhat by each institution. Nevertheless, our device strategy in this study basically stands on current health insurance regulation so that we believe that our report can be a general applicable reference for current device strategy.

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Conflict of interest All the authors have declared no conflict of interests.

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