Table II. Correlation Between Baseline Parameters and Parasympathetic Activity at 6 Months After HTx

Variables	*P*	*r*
Donor parameters		
Age, years	0.898	0.035
Male, *n* (%)	0.585	-0.148
Transplant surgery		
Duration of allograft ischemia, minutes	0.371	-0.240
Cardiopulmonary bypass time, minutes	0.035*	-0.530
Aortic cross-clamp time, minutes	0.639	-0.127
Recipients' pre-HTx parameters		
PF LVAD, *n* (%)	0.320	0.266
CF LVAD, *n* (%)	0.320	0.266
Duration of VAD treatment, days	0.971	-0.010
Etiology of ischemia, *n* (%)	0.787	-0.073
Recipients' demographic parameters		
Age, years	0.293	0.281
Male, *n* (%)	0.408	0.222
Body mass index	0.730	-0.094
Systolic blood pressure, mmHg	0.534	0.123
Diastolic blood pressure, mmHg	0.644	0.154
HbA_{1c} (N), %	0.248	-0.307
Recipients' medications		
Beta-blocker, *n* (%)	0.078	-0.453
ACEI or ARB, *n* (%)	0.154	-0.374
Statin, *n* (%)	0.597	0.143
Cyclosporine, *n* (%)	0.456	-0.201
Tacrolimus, *n* (%)	0.456	0.201
Recipients' laboratory parameters		
White blood cells, $\times 10^3/\mu L$	0.432	0.211
Hemoglobin, g/dL	0.156	0.372
Platelets, $\times 10^3/\mu L$	0.645	-0.125
Serum sodium, mEq/L	0.380	0.236
Serum potassium, mEq/L	0.425	-0.215
Serum BUN, mg/dL	0.712	0.100
Serum creatinine, mg/dL	0.763	0.082
Serum albumin, g/dL	0.372	-0.239
Serum total bilirubin, mg/dL	0.886	0.039
Serum CRP, mg/dL	0.723	0.121
Plasma BNP, pg/mL	0.861	0.048
Recipients' echocardiographic parameters		
LVDd, mm	0.397	0.227
LVDs, mm	0.858	0.049
LVEF, %	0.231	0.317
AR, grade	0.214	0.143
MR, grade	0.793	-0.071
TR, grade	0.541	-0.165
E/e'	0.762	-0.082
Recipients' hemodynamic parameters		
mRAP, mmHg	0.827	-0.059
mPAP, mmHg	0.743	-0.089
PCWP, mmHg	0.935	0.022
CI, L/min/m^2	0.313	-0.269

Abbreviations as in Table I. *$P < 0.05$ by Pearson's product-moment correlation coefficients.

Table III. Clinical Parameters at 6 Months After HTx

Variables	
Recipients' laboratory parameters	
White blood cells, $\times 10^3/\mu L$	6.0 ± 1.8
Hemoglobin, g/dL	10.6 ± 1.5
Platelets, $\times 10^3/\mu L$	25.2 ± 9.1
Serum sodium, mEq/L	137 ± 4
Serum potassium, mEq/L	4.7 ± 0.6
Serum BUN, mg/dL	19 ± 7
Serum creatinine, mg/dL	1.2 ± 0.5
Serum albumin, g/dL	4.0 ± 0.5
Serum total bilirubin, mg/dL	0.5 ± 0.2
Serum CRP, mg/dL	0.3 ± 0.3
Plasma BNP, pg/mL	139 ± 126
Recipients' electrocardiographic parameters	
PQ time, msec	148 ± 17
QRS time, msec	99 ± 19
Heart rate, bpm	80 ± 9
%changes in heart rate, %	-11 ± 10
Recipients' echocardiographic parameters	
LVDd, mm	42 ± 5
LVDs, mm	26 ± 5
LVEF, %	69 ± 8
AR, grade	0.3 ± 0.4
MR, grade	0.3 ± 0.5
TR, grade	0.3 ± 0.5
E/e'	11.4 ± 3.2
Recipients' hemodynamic parameters	
mRAP, mmHg	4 ± 2
mPAP, mmHg	16 ± 4
PCWP, mmHg	9 ± 3
CI, L/min/m^2	3.4 ± 0.5

Abbreviations as in Table I.

pendent on neurotrophins, which are neuronal growth factors produced and released by target tissue.[23] Aging, extensive surgical dissection, and prolonged tissue ischemia may reduce the availability of target-derived neurotrophic factors.[24]

We demonstrated for the first time that a shorter cardiopulmonary time was correlated with more improved parasympathetic reinnervation. A longer cardiopulmonary time indicates complexity of the operation, more injured tissue due to extensive adhesiolysis, or a longer warm ischemic time for the donor heart, which may adversely affect parasympathetic reinnervation in the same manner as that of regeneration of the sympathetic system. Neither diabetes mellitus nor age was associated with parasympathetic reinnervation, most likely because the recipients were all under 60 years-old, and were not complicated with severe diabetes mellitus.

Clinical courses accompanied by reinnervation: Several authors reported a correlation between sympathetic reinnervation and improvement of exercise tolerability demonstrated by improved peak oxygen consumption, recovery time or peak levels of HR, or exercise duration during a cardiopulmonary exercise test.[2,3,8] In contrast, Bengel, *et al* reported that there were no significant differences in hemodynamics between denervated and reinnervated allografts under resting conditions.[12]

No report has discussed the functional outcomes of parasympathetic reinnervation in HTx recipients. We demonstrated that parasympathetic reinnervation was associated with decreased HR at 6 months after HTx. Whether decreased HR by parasympathetic reinnervation improves the prognosis or quality of life of the recipient would be a future concern.

Study limitations: 1. The present study was performed at a single center in a retrospective manner in a small number of recipients under short-term observation. Longer observation of a larger number of recipients would be a future concern, but it may be difficult considering the shortage of donor hearts in Japan. 2. The association between parasympathetic reinnervation and functional outcome under exercise testing or prognostic efficacy should be investigated in the future.

In conclusion, parasympathetic reinnervation occurs along with recovery of tachycardia < 6 months after HTx, es-

Table IV. Relationship Between Clinical Parameters and Parasympathetic Activity at 6 Months After HTx

Variables	*P*	*r*
Recipients' laboratory parameters		
White blood cells, × $10^3/\mu L$	0.600	-0.142
Hemoglobin, g/dL	0.088	0.440
Platelets, × $10^3/\mu L$	0.269	-0.294
Serum sodium, mEq/L	0.802	0.068
Serum potassium, mEq/L	0.448	-0.204
Serum BUN, mg/dL	0.340	-0.255
Serum creatinine, mg/dL	0.874	0.043
Serum albumin, g/dL	0.722	0.097
Serum total bilirubin, mg/dL	0.330	0.261
Serum CRP, mg/dL	0.512	0.143
Plasma BNP, pg/mL	0.313	0.269
Recipients' electrocardiographic parameters		
PQ time, msec	0.441	-0.208
QRS time, msec	0.859	-0.048
Heart rate, bpm	0.035*	-0.514
%changes in heart rate, %	0.007*	-0.644
Recipients' echocardiographic parameters		
LVDd, mm	0.715	0.099
LVDs, mm	0.848	0.052
LVEF, %	0.991	0.003
AR, grade	0.367	-0.242
MR, grade	0.990	-0.003
TR, grade	0.569	0.154
E/e'	0.589	-0.147
Recipients' hemodynamic parameters		
mRAP, mmHg	0.684	-0.110
mPAP, mmHg	0.090	-0.437
PCWP, mmHg	0.288	-0.283
CI, $L/min/m^2$	0.563	-0.156

Abbreviations as in Table I. *$P < 0.05$ by Pearson's product-moment correlation coefficient.

pecially in recipients with a shorter cardiopulmonary bypass time. The clinical benefit of improved parasympathetic reinnervation should be investigated in the future.

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Original article

Midterm outcome of implantable left ventricular assist devices as a bridge to transplantation: Single-center experience in Japan

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ABSTRACT

Background: Two implantable continuous-flow left ventricular assist devices (LVADs), DuraHeart (Terumo Heart, Ann Arbor, MI, USA) and EVAHEART (Sun Medical, Nagano, Japan), were approved in Japan in April 2011. We analyzed the midterm outcome of patients implanted with these implantable LVADs at the University of Tokyo Hospital.

Methods and results: A total of 31 patients who underwent implantation of LVADs (10 DuraHeart, 21 EVAHEART) as a bridge to transplantation at our institution between April 2011 and August 2013 were retrospectively reviewed. All patients were followed up through December 2013. Seven patients underwent conversions from NIPRO paracorporeal LVAD (Nipro, Osaka, Japan) to an implantable LVAD. The mean observation period was 483 ± 239 days (41.0 patient years). Eight patients were transplanted and one patient showed functional recovery with subsequent LVAD explantation. Four patients died due to cerebrovascular accident, empyema, or device malfunction due to pump thrombosis after cerebral bleeding. Kaplan–Meier analysis revealed 6-, 12-, and 24-month survival rates of 93%, 86%, and 86%, respectively. The rates of freedom from cerebrovascular accidents and device-related infections at 1 year after LVAD implantation were 65% and 36%, respectively. Twenty-nine patients were discharged home after LVAD implantation. During the period of this study, there were 59 readmissions (53 urgent, 6 elective) among 22 patients (76%). The overall and urgent readmission rates were 1.66 and 1.49 per patient year, respectively. The common reason for readmission was device-related infection (31%), followed by cerebrovascular accidents (17%). The total out-of-hospital time after the primary discharge was 90%.

Conclusions: Our midterm survival rate after LVAD implantation is satisfactory. However, patients undergoing LVAD support were often readmitted with adverse events.

Introduction

Heart transplantation is a comprehensive solution for patients with end-stage heart failure, but it is available for only a small fraction of these patients because of serious donor shortages [1]. Several types of continuous-flow implantable devices have demonstrated significantly improved clinical results and left ventricular assist devices (LVADs) are increasingly used for destination therapy.

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In Japan, the waiting period for heart transplantation exceeds 2 years [2,3]. Approximately 90% of Japanese recipients currently required LVAD support as a bridge to transplantation. NIPRO LVAD (Nipro, Osaka, Japan), a paracorporeal pneumatic device, was formerly the only choice for patients with end-stage heart failure in Japan [4]. Two implantable centrifugal pumps, DuraHeart (Terumo Heart, Ann Arbor, MI, USA) [5,6] and EVAHEART (Sun Medical, Nagano, Japan) [7,8], were approved by the Japanese Ministry of Health, Labour and Welfare in April 2011 [9]. HeartMate II axial pump (Thoratec Corp., Pleasanton, CA, USA) [10] was also approved in April 2013. These devices are expected to reduce pump-related morbidity and improve quality of life in patients undergoing LVAD support [11].

According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report, which includes data on more than 6000 implants, current 1-year survival rate with a continuous-flow LVAD is 80% [12]. This study included destination therapy as well as bridge to transplant [13], and in which HeartMate II was the most frequently implanted device. Because only centrifugal pumps were available until March 2013 and only for bridge to transplant, an outcome of continuous-flow LVADs in Japan might be different from the INTERMACS report. The Japanese registry for Mechanically Assisted Circulatory Support (J-MACS) database, in which all implantable LVADs treatment facilities participate in Japan, revealed that 1-year survival rate of implantable LVADs was 87% in Japan [14]. Considering an increasing number of patients with LVAD supports, causes and outcomes of readmissions are also of interest [15,16]. However, there are few reports on these outcomes of implanted LVADs in Japan [14,17]. Therefore, in this retrospective study, we analyzed the midterm outcomes of patients implanted with centrifugal pumps at the University of Tokyo Hospital.

Methods

Patients and study design

There were 37 consecutive patients with end-stage heart failure who received implantable LVADs as a bridge to transplantation between April 2011 and August 2013 at the University of Tokyo Hospital. All patients provided written informed consent before LVAD implantation. The study period was divided into 3 periods. Period A was a time between April 2011 and the middle of December 2011, in which both DuraHeart and EVAHEART were available without restriction. Period B was a time between the end of December 2011 and April 2013, in which DuraHeart was not available except for exceptional usage. Period C was a time between May 2013 and August 2013. In our institution, HeartMate II was approved in May 2013. DuraHeart implantation was recommenced from the end of July 2013. Twelve, seventeen, and eight LVAD implantations were performed in Periods A, B, and C, respectively. During Period A, we selected DuraHeart if the patients' body surface area were 1.50 m^2 or less. The patients who underwent LVAD implantation during Period B received EVAHEART except one DuraHeart exceptional usage. During Period C, we selected HeartMate II for the patients with body surface area 1.55 m^2 or less, and the centrifugal pumps for those with right heart failure preoperatively. A total of 6 of the 37 patients with LVAD implantation received HeartMate II device and were excluded from this study because the observation periods were shorter than that for the other devices. We retrospectively evaluated the 31 patients. These 31 patients received either DuraHeart or EVAHEART and were followed up through December 2013. Seven patients underwent conversion from NIPRO paracorporeal LVAD to an implantable LVAD. No patient with an implantable LVAD required a right ventricular assist device perioperatively. Patients with DuraHeart received anticoagulation therapy with warfarin with a target international normalized ratio of prothrombin time (PT-INR) of 2.3–2.8, and patients with EVAHEART received warfarin with a target PT-INR of 2.8–3.5. The patients with an implantable LVAD also received antiplatelet therapy with aspirin 100 mg per day. Dipyridamole 300 mg per day was administered to the patient with a history of embolism. Once critical cerebral bleeding occurred the anticoagulation therapy was reversed fully, and heparin was started at 72 h after the hemorrhage unless active bleeding. After hospital discharge, LVAD recipients were followed up by monthly outpatient visits or, if necessary, more frequently.

Clinical data included demographic profiles, adverse events, readmissions, and outcomes. Definition of adverse events was based on the J-MACS adverse events. Bleeding was categorized as postoperative bleeding requiring re-operation or gastrointestinal bleeding requiring transfusion of red blood cells. Ventricular arrhythmia was defined as a sustained ventricular arrhythmia requiring defibrillation or cardioversion. A cerebrovascular accident was defined as an ischemic or hemorrhagic intracranial event that persisted beyond 24 h or lasted less than 24 h with infarction on an imaging study. A device-related infection was categorized as either (1) a driveline infection, which was localized to the tissue surrounding the driveline accompanied by pain, fever, drainage, or leukocytosis, and treated with nonprophylactic antimicrobial agents, or (2) a pump pocket infection, which involved the tissue surrounding a pump within the body or mediastinal tissue along the inflow or outflow tract, coupled with the need for antimicrobial therapy. Sepsis was defined as systemic infection evidenced by a positive blood culture that was treated with antimicrobial agents with or without a device-related infection. A device malfunction was defined as a failure of one or more of the components of the mechanical cardiac support device system that directly caused or could potentially induce a state of inadequate circulatory support or death.

Statistical analysis

We performed statistical analyses with IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation or mean/median (range). Cumulative survival curves and actuarial freedom from the first event, such as a cerebrovascular accident, device-related infection, or readmission, were computed using the Kaplan–Meier method. Patients were censored in case of transplantation or recovery with device explantation, or on 31 December 2013.

Results

Baseline patient characteristics

The baseline characteristics of 31 patients are listed in Table 1. A total of 10 patients received DuraHeart (32%), and 21 received EVAHEART (68%). Seven patients underwent conversions from NIPRO paracorporeal LVAD to an implantable LVAD. The median interval from a paracorporeal LVAD to an implantable LVAD was 115 days (60–279 days). An LVAD was necessary in 23 patients with idiopathic dilated cardiomyopathy, in 4 patients with ischemic cardiac disease, and in 3 patients with dilated phase hypertrophic cardiomyopathy. All patients who were categorized as preoperative INTERMACS profile 1 underwent NIPRO LVAD implantation and subsequently conversion surgery. A patient who was categorized as INTERMACS profile 4 had suffered from frequent ventricular tachycardia preoperatively.

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Table 1
Baseline patient characteristics.

	Total (N = 31)
Age (years)	39.7 ± 11.7
Male	21 (84%)
Body surface area (m^2)	1.67 ± 0.14
Etiology of heart failure	
Idiopathic dilated cardiomyopathy	23 (74%)
Dilated phase hypertrophic cardiomyopathy	3 (10%)
Ischemic cardiomyopathy	2 (6%)
Cardiogenic shock due to AMI	2 (6%)
Post myocarditis	1 (3%)
Type of LVAD	
DuraHeart	10 (32%)
EVAHEART	21 (68%)
Conversion from NIPRO LVAD	7 (23%)
INTERMACS profile	
Profile 1	6 (19%)
Profile 2	14 (45%)
Profile 3	10 (32%)
Profile 4	1 (3%)

Data given as mean ± SD or n (%).
AMI, acute myocardial infarction; LVAD, left ventricular assist device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Outcome of implanted LVADs

Table 2 summarizes the clinical outcomes after LVAD surgery. The postoperative observation period was 483 ± 239 days (41.0 patient years). Following LVAD implantation, 8 patients were transplanted and 1 patient showed functional recovery with subsequent LVAD explantation [18]. Mean implantable LVADs support time of the 8 patients who underwent heart transplantation was 720 days (453–945 days). Four patients died after LVAD implantation. The causes of death were cerebrovascular accident, empyema, and device malfunction due to pump thrombosis after cerebral bleeding. The details of the four patients are shown in Table 3. The remaining 18 patients underwent ongoing LVAD support. The 6-, 12-, and 24-month survival rates of the patients with implanted LVADs were 93%, 86%, and 86%, respectively (Fig. 1).

The most common adverse events following LVAD implantation are shown in Table 2. During the study period 27 cerebrovascular accidents among 13 patients occurred. A total of 23 of the 27 cerebrovascular events were ischemic and the other 4 were hemorrhagic events. There were 18 cerebral infarctions in patients with EVAHEART. The rates of freedom from cerebrovascular accidents at 1, 6, and 12 months after LVAD implantation were 84%, 77%, and 65%, respectively. Eighteen patients experienced complications of device-related infection. One of these patients developed a pump pocket infection and underwent negative-pressure wound therapy and omental transposition [19]. The rates of freedom from device-related infections at 1, 6, and 12 months after LVAD implantation were 97%, 65%, and 36%, respectively. Freedom curves from cerebrovascular accidents and device-related infections are shown in Fig. 2. Eight patients developed sepsis. The most frequent responsible bacterium was *Staphylococcus aureus*, which was detected in 6 of the 8 sepsis patients. Ventricular arrhythmia was also a major adverse event. The patients with implantable LVADs who developed ventricular arrhythmia and unexperienced loss of consciousness needed defibrillation or cardioversion in the emergency room. No patients developed gastrointestinal bleeding requiring blood transfusion. In 28 patients, von Willebrand factor (vWF) ristocetin cofactor activity (vWF:Rco) was measured at 6–12 months after LVAD implantation, and vWF:Rco was 60% or less in 4 patients.

Table 2
Clinical outcome after left ventricular assist device implantation.

	Total (N = 31)
Outcome	
Transplanted	8 (26%)
Weaned from LVAD support	1 (3%)
Died	4 (13%)
Ongoing LVAD support	18 (58%)
Adverse events	
Postoperative bleeding	2 (6%)
Gastrointestinal bleeding	0 (0%)
Ventricular arrhythmia	5 (16%)
Cerebrovascular accident	13 (42%)
Device-related infection	18 (58%)
Sepsis	8 (26%)

Data given as n (%).
LVAD, left ventricular assist device.

Table 3
Deceased patient characteristics.

Patient no.	1	2	3	4
Age (years)	45	42	53	49
Sex	Male	Female	Male	Male
Body surface area (m^2)	1.72	1.48	1.56	1.55
Etiology of heart failure	DCM	AMI	dHCM	p-carditis
Type of LVAD	EVAHEART	EVAHEART	EVAHEART	EVAHEART
Conversion from NIPRO LVAD	No	Yes	No	No
INTERMACS profile	2	1	3	3
LVAD support time (days)	342	17	265	164
Cause of death	Pump thrombosis	CVA	Empyema	CVA

DCM, idiopathic dilated cardiomyopathy; AMI, acute myocardial infarction; dHCM, dilated phase hypertrophic cardiomyopathy; p-carditis, post myocarditis; LVAD, left ventricular assist device; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; CVA, cerebrovascular accident.

Readmission after discharge

Twenty-nine patients were discharged home after LVAD implantation. Two patients died before discharge. The median

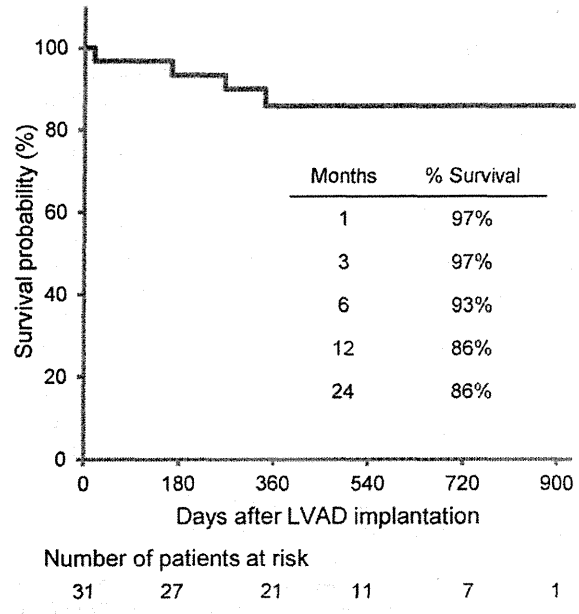

Fig. 1. Kaplan–Meier model of survival after left ventricular assist device (LVAD) implantation.

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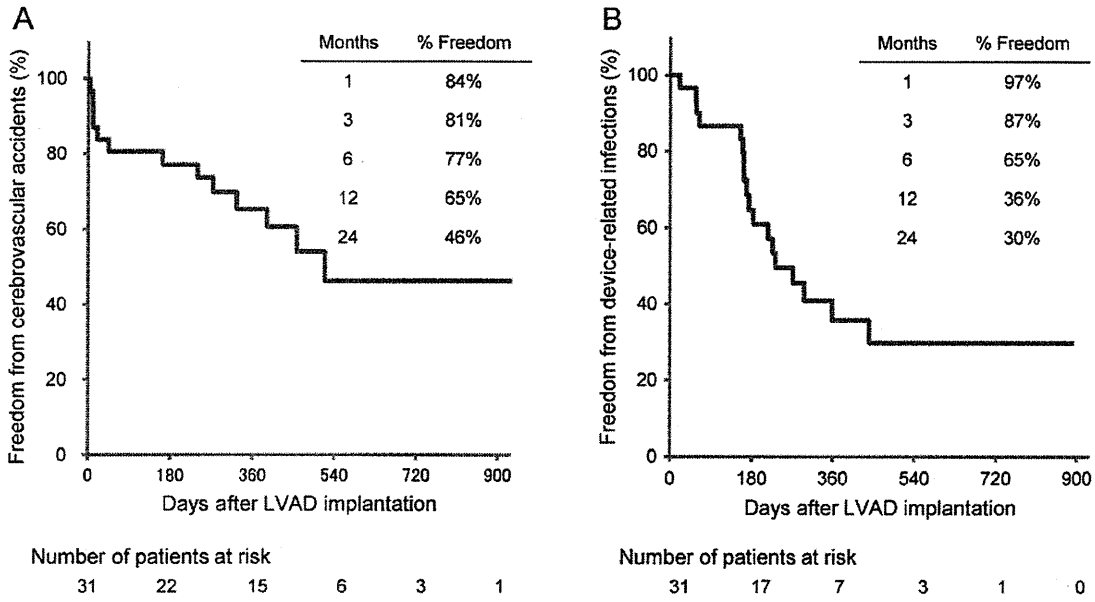

Fig. 2. Actuarial freedom from cerebrovascular accidents (A) and device-related infections (B) in patients who underwent left ventricular assist device (LVAD) implantation.

hospital stay after implantation was 51 days (40–121 days). The observation period after primary discharge was 448 ± 227 days (35.6 patient years). During this time, there were 59 readmissions among 22 patients (76%). The readmissions were categorized as urgent in 53 cases and elective in 6 cases. The overall and urgent readmission rate was 1.66 and 1.49 per patient year, respectively. Freedom curve from urgent readmission appears in Fig. 3. The rates of freedom from urgent readmission at 1, 6, and 12 months after discharge were 86%, 46%, and 29%, respectively. The most common etiology was device-related infection, accounting for 31% of the readmissions, followed by cerebrovascular accidents (17%). Headache and/or dizziness, which were difficult to differentiate from cerebrovascular accidents, were also common reasons for readmission. Two patients were readmitted because of device malfunction. One patient received a controller exchange urgently, and the other accidentally detached bilateral battery at the same time. The most common reason for elective readmissions was cardiac catheterization, which was performed to evaluate the effect of pulmonary vasodilators [20]. The median length of stay after readmission was 14 days (1–168 days) (Fig. 4). The total out-of-hospital time after the primary discharge was 90%.

Discussion

In the present study, we reported our institutional experience with implantable centrifugal pumps in a series of 31 patients after a mean follow-up of 484 days. The 1- and 2-year survival rates after LVAD implantation were 86% and 86%, respectively. Two centrifugal pumps were used in our study. They were the only devices that were approved by the Japanese Ministry of Health, Labour and Welfare until March 2013. The J-MACS reported that 1-year survival rate of implantable LVADs was 87% in Japan [14]. J-MACS report was similar to our study in patients' baselines, device types, indications, and survival rate. According to the INTERMACS report

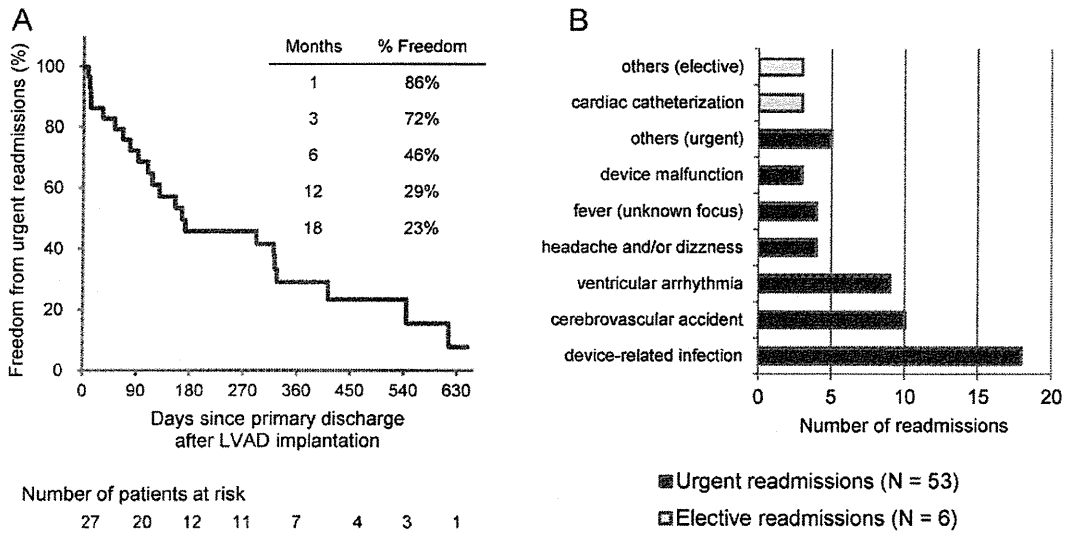

Fig. 3. Actuarial freedom from first readmission after primary hospitalization in patients who underwent left ventricular assist device (LVAD) implantation (A). Reason for readmission (B).

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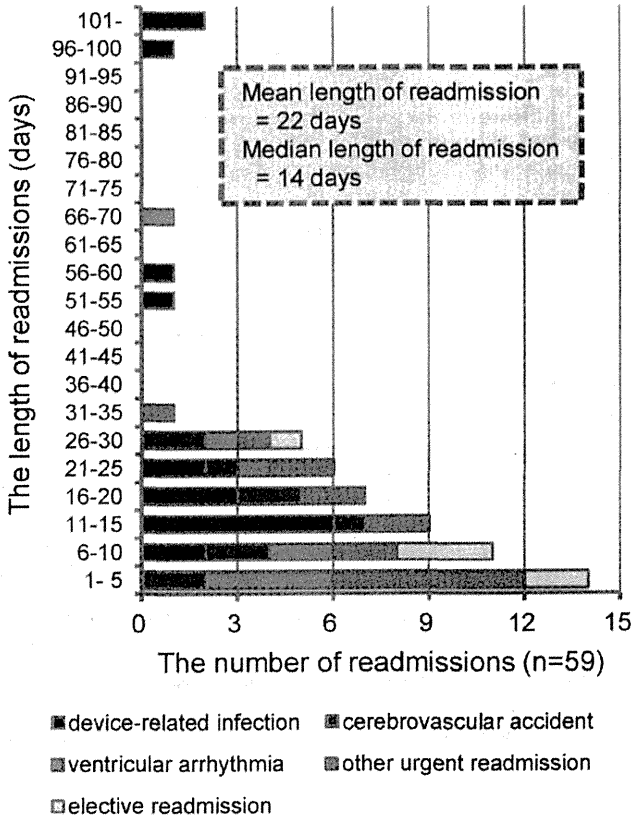

Fig. 4. Length of stay during readmissions for each etiology.

1-year survival rate after continuous-flow LVAD implantation was 80% [12]. European results of continuous-flow LVAD implantation showed 1-year survival rate of 72% [21]. These databases included destination therapy.

Our study included 7 patients who underwent conversion from NIPRO paracorporeal LVAD to an implantable LVAD. The conversion from paracorporeal LVAD to an implantable LVAD is an important strategy for patients who have not yet been approved by the Heart Transplant Recipient Advisory Council at each institution [22,23], because those patients are not currently permitted to use an implantable LVAD in Japan [24]. In the present study, all patients who underwent a conversion procedure experienced a rapid onset of heart failure, and needed LVAD support before listing for heart transplantation. They were categorized as INTERMACS profile 1 or 2. In this study, 3 of the 7 patients with conversion from NIPRO LVAD received DuraHeart, and the others received EVAHEART. In Period A, all patients with conversion procedure received DuraHeart, because the NIPRO apical cuff size was the same as that of DuraHeart [23]. During Period B, we performed conversion to both DuraHeart and EVAHEART. Yoshioka et al. [23] reported that some patients who developed infections of the NIPRO LVAD exit site suffered pump pocket infections after the conversion procedure. Therefore, patients with serious infections of the NIPRO LVAD exit site do not undergo conversion to an implantable LVAD in our institution. In the present study, no patient with conversion surgery had active infection of the exit sites before the procedure. None of them developed pump pocket infections. Prevention of infection at the exit site before the conversion procedure is mandatory for patients who undergo NIPRO LVAD implantation.

In the present study, 42% of the patients who underwent LVAD implantation developed cerebrovascular accidents (0.66 events per patient year). Nakajima et al. [25] reported that 48% of the patients who underwent LVAD implantation developed cerebrovascular accidents. Sakaguchi et al. [17] reported a lower cerebrovascular accident rate of 17%. However, these stroke rates were higher than those in the INTERMACS report. The rates of freedom from stroke at 1 month and 1 year were 97% and 89%, respectively, and only 9% of the patients who underwent continuous-flow LVAD implantation developed stroke according to the INTERMACS report [12]. In the present study, cerebrovascular events included minor symptoms with infarction on head computed tomography according to J-MACS definitions. In Japan, imaging studies are performed relatively many times. They may pick more events up, and our stroke rate may be higher than the USA. In this study, there were 7 patients with permanent damage from a cerebrovascular accident or dying of a cerebrovascular accident. Dell'Aqila et al. [26] reported that the rate of freedom from stroke at 1 month after HeartWare (HeartWare International Inc, Framingham, MA, USA) ventricular assist device implantation was 48% in patients with an INTERMACS profile 1 and 2, and 81% in patients with an INTERMACS profile 3 and 4. The development of cerebrovascular accidents after LVAD implantation may be significantly affected by the device type [27]. There were 18 cerebral infarctions in patients with EVAHEART, and mean PT-INR was 2.83 ± 0.83 at the events. PT-INR values were less than 2.00 at 6 of the 18 events, and more than 3.00 at 6 events. Ischemic events did not always occur during insufficient anticoagulation therapy. In the present study, the first 5 of the 13 cerebrovascular accidents occurred within 1 month after LVAD surgery. Lahpor et al. [21] reported that neurological complications occurred in the first 6 weeks following the implantation in a European multicenter study. Our study also suggests that cerebrovascular accidents are more likely to develop in the early period after LVAD implantation. Starling et al. [28] reported that the risk of pump thrombosis of HeartMate II peaked within 1 month after implantation and then fell after 6–8 months. This result suggested that the risk of embolic disease also peaked in the early period after LVAD implantation.

Infectious complications are also a major problem in patients under LVAD support. Sakaguchi et al. [17] reported that 34% patients developed device-related infections. In the present study, 17 patients (55%) developed device-related infections, and the rate of freedom from device-related infections at 1 year after LVAD implantation was 40%. In 12 of the 17 patients who developed device-related infections, the infections occurred more than 150 days after LVAD implantation. This result was a contrast to cerebrovascular accidents, which were likely to occur in the early postoperative period. Sharma et al. [29] reported that a longer duration of LVAD support significantly increased the risk of driveline infections. Our result was similar to their report. One of the 17 patients developed a pump pocket infection [19], and the other 16 patients developed a driveline infection. Surgical debridement followed by negative pressure wound therapy in a driveline exit site was performed for one patient. Five of the seventeen patients (29%) underwent chronic suppressive antimicrobial therapy. Nienaber et al. [30] reported that 14% of the patients with device-related infections had surgical debridement and 42% of the patients were managed by chronic suppressive antimicrobial therapy.

No patients in the present study developed gastrointestinal bleeding. This result was in contrast to that of US and European multicenter studies [21,31]. In these trials, gastrointestinal bleeding was a major adverse event, and the most common etiology for readmissions [15,16]. The relationship between acquired von Willebrand disease and axial-flow LVADs was pointed out [32]. However, low vWF:Rco was demonstrated in a few patients in our study. All patients in this study were implanted centrifugal pumps, and centrifugal pump may suffer less with acquired von Willebrand disease [7].

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ORIGINAL ARTICLE
Heart Failure

Low Cardiac Output Stimulates Vasopressin Release in Patients With Stage D Heart Failure

– Its Relevance to Poor Prognosis and Reversal by Surgical Treatment –

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Background: Depressed hemodynamics stimulates arginine vasopressin (AVP) release, but the relationship between plasma AVP levels (P-AVP) and cardiac parameters, especially in patients with stage D heart failure (HF) receiving guideline-directed medical therapy, has not examined.

Methods and Results: Data including P-AVP were obtained from 162 in-hospital patients with stage D HF and from 80 patients receiving ventricular assist device (VAD, n=46) or heart transplantation (HTx, n=34) at 3 months after surgery. In the HF group, considerably high P-AVP (5.9±6.1 pg/ml) negatively correlated with serum sodium concentration (S-Na, 135.3±5.8 mEq/L, r=–0.548 [P<0.01]) and cardiac index (CI, 2.2±0.5 L·min^{-1}·m^{-2}, r=–0.458 [P<0.01]). After VAD/HTx treatment, improvement in the CI (2.7±0.5 L·min^{-1}·m^{-2} [P<0.01] vs. HF) was accompanied by normalization of serum sodium concentration (S-Na; 138.2±2.0 mEq/L [P<0.01] vs. HF) and suppressed release of AVP (1.7±3.4 pg/ml [P<0.01] vs. HF). P-AVP positively correlated with only S-Na (r=0.454 [P<0.01]), whereas no correlation was observed with CI after VAD/HTx treatment. P-AVP ≥5.3 pg/ml well predicted poor 2-year survival in HF group (60% [P<0.01] vs. 90%).

Conclusions: Low cardiac output stimulates AVP release via a non-osmotic process that results in hyponatremia and poor prognosis in patients with stage D HF. After sufficient recovery of cardiac output by cardiac replacement therapy, AVP release is suppressed and is mainly regulated by serum osmolality. (*Circ J* 2014; **78:** 2259–2267)

Key Words: Hyponatremia; Osmolality; Survival; Ventricular assist device

Arginine vasopressin (AVP) plays a central role in the regulation of water and electrolyte balance, and is an essential hormone for maintaining homeostasis in humans.[1] AVP is secreted by hypothalamic neurons that project to the posterior pituitary gland in response to changes in plasma osmolality, which are detected by osmoreceptors in the hypothalamus (osmotic pathway).[2,3] AVP is also secreted when arterial underfilling caused by hypotension or volume depletion is detected by baroreceptors (non-osmotic pathway). AVP receptors are classified into V_{1a} (expressed on vascular smooth muscle), V_{1b} (on pituitary), and V_2 (on collecting duct in the kidney). AVP modulates body fluid regulation through water reabsorption in the collecting duct by stimulation of V_2 receptors, and also regulates vascular tone and cardiovascular contractility via V_{1a} receptors.[4]

Editorial p2159

In patients with heart failure (HF), the plasma levels of AVP are inappropriately high despite lower plasma osmolality.[5–10] The elevated AVP increases cardiac preload through water retention in collecting duct via stimulation of the V_2 receptor,[2,11] and also stimulates V_{1a} receptors, which facilitates increasing cardiac afterload by systemic arteriolar vasoconstriction.[12]

Although impaired hemodynamics has been estimated as a key to the inappropriate elevation of AVP levels in patients with HF,[5,7,13] the exact mechanisms and extensive relationship

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between plasma AVP levels and other cardiac parameters have remained unknown thus far. Furthermore, almost all studies of AVP were executed before the establishment of guideline-directed medical therapy (GDMT) for HF including β-blockers, angiotensin-converting enzyme inhibitors (ACEI) and aldosterone antagonists. If hemodynamics really matter in terms of non-osmotic AVP release, stage D HF should be associated with higher AVP levels in comparison with other stages. Dramatic changes in the plasma levels of AVP after ventricular assist device (VAD) implantation or heart transplantation (HTx) should also be expected in those patients. However, stage classification has recently been developed in the guidelines,[14] and AVP levels have not been measured according to the new classification of HF. Therefore, we here examined the relationship between plasma AVP levels and other cardiac parameters in patients with stage D HF before and after VAD/HTx treatment.

Methods

Patient Selection

Of consecutive patients who were hospitalized for stage D HF and followed at the University of Tokyo Hospital between July 2011 and November 2013, 162 patients who were diagnosed as stage D HF by the Framingham Criteria[15] and the guideline of the American Heart Association[14] were retrospectively enrolled in this study (HF group). All patients were refractory to GDMT consisting of β-blocker, ACEI/ARB, and aldosterone antagonist.

VAD group consisted of consecutive 46 stage D HF patients who implanted either type of pulsatile or continuous flow VAD. After LVAD implantation, we followed GDMT to optimize the dosing of medicine as much as tolerated considering each patient's hemodynamics. The setting of pulsatile VAD was adjusted as full-fill full-empty mode for maximum support under non-synchronous mode. The rotation speed of continuous flow VAD was also adjusted appropriately considering patients' hemodynamics and interventricular septum shift observed in transthoracic echocardiography. The HTx group included 34 patients who had once had stage D HF and had been bridged from VAD therapy, but we did not include anyone of HTx group in HF or VAD group because of lack in AVP data during pre-HTx period.

Written informed consent was obtained at admission time from the patients and/or their family members in all cases. The study protocol was approved by the Ethics Committee of Graduate School of Medicine, the University of Tokyo [application no. 779 (1)].

Variables Evaluated

In the HF group, blood samples for AVP measurement were obtained after resting supine for 15 min in the early morning before taking any daily medicine while in a steady state after the treatment of acute exacerbation of HF. Echocardiographic examination was also executed while in a steady state, and cardiac output (CO) was calculated using Doppler-derived aortic flow signals based on the principle that the velocity time integral of blood flow multiplied by the cross-sectional area of the left ventricle outflow estimates CO volume. In patients with VAD support, total CO was calculated as the summation of the CO of the native heart calculated by the Doppler method described above and the estimated VAD flow. There were no patients with moderate or severe aortic regurgitation. In 64 of the HF patients, CO measurement by right heart catheterization was also performed while in the steady state.

In the VAD/HTx groups, echocardiographic examination and hemodynamic study were performed as well as blood sampling for AVP measurement in the same manner as for the HF group at 3 months after the operation. Of them, pairwise data of plasma AVP levels were available for 28 patients between the pre-VAD (ie, stage D HF) and post-VAD periods. No preoperative AVP data were available for patients in the HTx group. Hemodynamic data were obtained for all of the VAD/HTx patients (n=80) before and after operation. All blood samples were centrifuged immediately for 20 min, and the samples were stored at −80°C before the assay. All blood samples for AVP measurements were stored and the AVP levels were determined by a double antibody radioimmunoassay method using AVP RIA Neo from LSI Medicine Corporation available since January 2014.

Statistical Analysis

All statistical analyses were performed using PASW Statistics 18 (SPSS Inc, Chicago, IL, USA). Categorical variables are summarized as frequencies and percentages, and compared using Chi-square test or Fisher's exact test as appropriate. Continuous variables are represented as mean±standard deviation unless otherwise specified, and compared using unpaired t-test or Mann-Whitney test as appropriate. Each variable of the HF, VAD, or HTx group was compared by ad-hoc Tukey's test when analysis of variance confirmed significance among the groups. Pearson product-moment correlation coefficient was used to evaluate the relationship between plasma levels of AVP and other clinical parameters. Each clinical parameter was compared by paired t-test or Wilcoxon signed-rank test as appropriate in the VAD group during the study period. Receiver-operating characteristics (ROC) analysis was performed to obtain a cutoff level of plasma AVP for 2-year survival. To examine the effect of the plasma levels of AVP on prognosis, Kaplan-Meier analysis with log-rank test and Cox proportional-hazard model were adopted. Inter-rater reliability between echocardiography and hemodynamic study for CI was analyzed by calculating intraclass correlation coefficients. All hypothesis tests reported are 2-tailed, and used a P-value <0.05 as significant.

Results

Comparison of Patients' Characteristics Among HF, VAD, and HTx Groups (Table 1)

All patients in the HF group were assigned stage D, and GDMT was introduced and optimized in >80% of patients; inotropes were intravenously infused in >40% of patients. In total, 65 (40.1%) patients were not candidates for VAD/HTx treatment because of their age (>65 years old), 21 patients (13.0%) because of end-organ dysfunction, and 32 patients (19.8%) because of systemic diseases or social problems; 28 patients (17.3%) underwent VAD implantation during the study period. No patients received tolvaptan before enrollment.

Patients who had VAD/HTx showed improved hemodynamics (**Table 2**), together with recovery of end-organ dysfunction and normalization of hyponatremia compared with the HF group (**Figure 1**). There were no significant differences in hemodynamics before (ie, under VAD treatment) and after HTx (**Table 2**). There were no significant differences in cardiac index (CI), plasma levels of BNP or the serum sodium concentration (S-Na) level between the VAD and HTx groups (**Figure 1**). In 64 patients in the HF group and 80 in the VAD/HTx group, CI measured by echocardiography and hemodynamic study had high intraclass correlation coefficients (0.992,

Table 1. Characteristics of the Patients in the HF, VAD, and HTx Groups

	HF group (n=162)	VAD group (n=46)	P value vs. HF	HTx group (n=34)	P value vs. HF	P value vs. VAD
Demographic parameters						
Age, years	58.0±20.1	37.7±13.0	<0.001*	37.4±14.5	<0.001*	1.000
Male, n (%)	115 (71.0)	36 (78.3)	0.579	23 (67.6)	0.684	0.533
Body surface area, m^2	1.68±0.19	1.72±0.18	0.360	1.65±0.23	0.699	0.257
Body mass index	21.9±3.5	20.7±3.5	0.090	20.7±3.4	0.134	0.808
Etiology of ischemia, n (%)	22 (13.6)	7 (15.2)	0.425	8 (23.5)	0.423	0.5313
SBP, mmHg	101.7±13.2	110.0±6.4	<0.001*	128.1±11.2	<0.001*	<0.001*
DBP, mmHg	64.1±6.7	86.4±7.7	<0.001*	72.3±8.2	<0.001*	<0.001*
Heart rate, beats/min	77.3±15.6	81.5±17.3	0.198	84.9±14.7	0.214	0.727
SaO_2, %	96.6±3.4	96.8±3.1	0.512	97.2±3.9	0.166	0.211
Concomitant medication						
Furosemide, mg/day	43.4±26.7	6.3±11.6	<0.001*	2.1±5.3	<0.001*	0.661
Spironolactone, mg/day	22.3±21.3	25.5±19.4	0.553	7.7±15.5	<0.001*	<0.001*
Trichlormethiazide, mg/day	0.2±0.6	0.0±0.2	0.211	0	0.114	0.973
Administration of furosemide, n (%)	162 (100)	13 (28.3)	<0.001†	4 (11.8)	<0.001†	<0.001†
Administration of spironolactone, n (%)	103 (63.6)	33 (71.7)	<0.001†	8 (23.5)	<0.001†	<0.001†
Administration of trichlormethiazide, n (%)	12 (7.4)	0 (0)	0.041†	0 (0)	0.041†	1.000
Administration of β-blocker, n (%)	150 (92.6)	46 (100)	<0.001†	15 (44.1)	<0.001†	<0.001†
Administration of ACEI/ARB, n (%)	134 (82.7)	34 (73.9)	0.034†	23 (67.6)	0.033†	0.123
Administration of statin, n (%)	104 (64.2)	40 (87.0)	<0.001†	34 (100)	<0.001†	0.099
Catecholamine infusion, n (%)	66 (40.7)	0 (0)	<0.001†	0 (0)	<0.001†	1.000
Laboratory parameters						
Plasma AVP, pg/ml	5.9±6.1	2.2±2.8	<0.001*	1.4±1.6	<0.001*	0.694
Hemoglobin, g/dl	11.8±2.3	11.0±1.9	0.062	11.7±2.0	0.952	0.233
Platelets, $\times 10^3/\mu l$	19.7±7.7	23.1±7.0	0.010*	22.4±5.6	0.100	0.872
Serum albumin, g/dl	3.4±0.6	3.7±0.6	0.069	3.9±0.7	<0.001*	0.031*
Serum sodium, mEq/L	135.3±5.8	138.2±1.9	0.001*	138.3±2.0	0.002*	0.997
Serum sodium <136 mEq/L, n (%)	72 (44.4)	0 (0)	<0.001†	2 (5.9)	<0.001†	0.822
Serum potassium, mEq/L	4.3±0.5	4.3±0.4	0.987	4.5±0.5	0.021*	0.096
Serum BUN, mg/dl	26.9±14.3	16.1±5.6	<0.001*	19.4±8.5	0.003*	0.435
Serum creatinine, mg/dl	1.2±0.6	0.9±0.3	<0.001*	1.0±0.4	0.137	0.267
Serum total bilirubin, mg/dl	2.1±10.9	0.8±0.4	0.628	0.6±0.2	0.594	0.997
Plasma BNP, $\log_{10}$ pg/ml	2.68±0.44	1.96±0.33	<0.001*	1.85±0.48	<0.001*	0.089
Echocardiographic parameters						
LV diastolic diameter, mm	62.8±14.2	56.4±12.9	0.042*	43.0±4.7	<0.001*	<0.001*
Ejection fraction, %	36.5±20.1	24.6±12.9	<0.001*	69.3±7.7	<0.001*	<0.001*
E/e'	19.4±7.9	14.2±4.3	<0.001*	12.4±3.8	<0.001*	<0.001*
CI, $L \cdot min^{-1} \cdot m^{-2}$	2.2±0.5	2.6±0.4	<0.001*	2.9±0.6	<0.001*	0.115

*P<0.05 by unpaired t-test or Mann-Whitney test as appropriate. †P<0.05 by Chi-square test or Fisher's exact test as appropriate.
ACEI, angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; AVP, arginine vasopressin; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; CI, cardiac index; DBP, diastolic blood pressure; E/e', ratio of the mitral velocity to the early-diastolic velocity of the mitral annulus; HF, heart failure; HTx, heart transplantation; LV, left ventricle; SaO_2, oxygen saturation; SBP, systolic blood pressure; VAD, ventricular assist device.

Table 2. Hemodynamic Study Before and After VAD/HTx Treatment

	VAD (n=46)			HTx (n=34)		
	Pre-VAD	Post-VAD	P value	Pre-HTx (all VAD support)	Post-HTx	P value
Mean RAP, mmHg	12.3±6.8	7.2±4.5	0.008*	4.6±2.0	4.2±2.2	0.269
Systolic PAP, mmHg	43.8±13.9	21.1±5.2	<0.001*	20.0±4.2	18.7±2.6	0.069
Diastolic PAP, mmHg	24.9±7.6	9.1±3.6	<0.001*	8.3±3.8	7.6±3.0	0.322
Mean PAP, mmHg	32.5±9.5	15.6±6.1	<0.001*	14.0±3.5	12.6±3.4	0.089
PCWP, mmHg	23.9±8.3	7.7±3.7	<0.001*	7.8±3.4	7.3±2.5	0.148
CI, $L \cdot min^{-1} \cdot m^{-2}$	1.7±0.3	2.7±0.4	<0.001*	2.6±0.3	2.8±0.4	0.121

*P<0.05 by paired t-test. PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure. Other abbreviations as in Table 1.

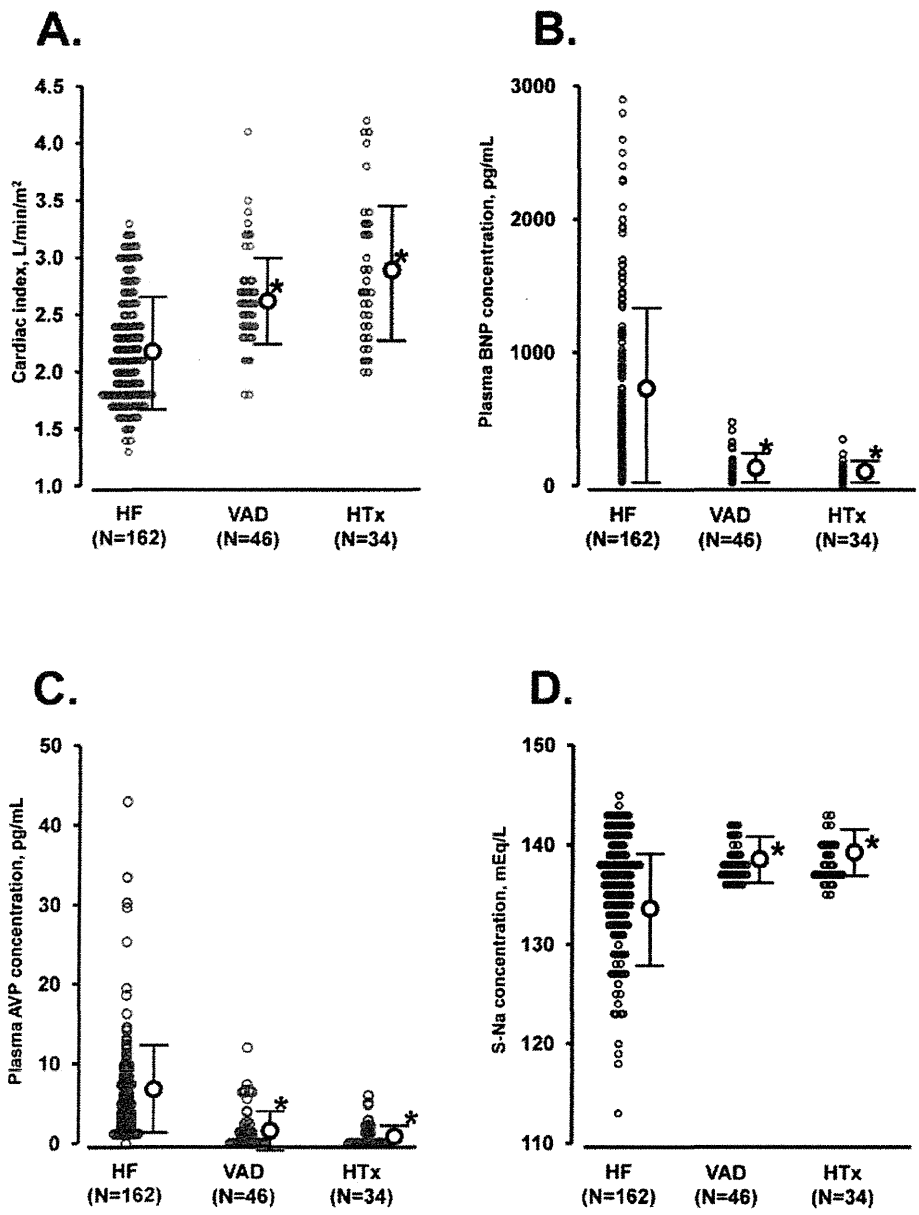

Figure 1. Comparison of CI (**A**), plasma levels of BNP (**B**) and AVP (**C**), and S-Na (**D**) in HF (n=162), VAD (n=46), and HTx groups (n=36). *P<0.05 by ad-hoc Tukey's test compared with HF group when analysis of variance proved to be significant. AVP, arginine vasopressin; BNP, B-type natriuretic peptide; CI, cardiac index; HF, heart failure; HTx, heart transplantation; S-Na, serum sodium concentration; VAD, ventricular assist device.

P<0.001).

Relationship Between Plasma Levels of AVP and Other Clinical Parameters in HF and VAD/HTx Groups

Plasma AVP levels had a non-normal distribution in the HF and VAD/HTx groups (P<0.05 by Shapiro-Wilk's test). Unlike the plasma BNP levels, plasma AVP levels were not log-normally distributed. Plasma AVP levels were significantly lower in the VAD/HTx group (n=80) than in the HF group (n=162), whereas plasma AVP levels were not different between the VAD and HTx groups (**Table 1**, **Figure 1**). In 28 patients who had VAD implantation, pairwise measurement of plasma AVP levels confirmed that marked decreases in AVP levels were associated with improvement of CI and normalization of plasma BNP levels and S-Na (all P<0.01; **Figure 2**).

In the HF group (n=162), plasma AVP levels significantly correlated with CI, ejection fraction, plasma BNP levels, and S-Na (**Table 3**). Higher plasma levels of AVP were associated with lower CI (**Figure 3A**), higher plasma levels of BNP (**Figure 3B**), and lower S-Na (**Figure 3C**). There were 5 pa-

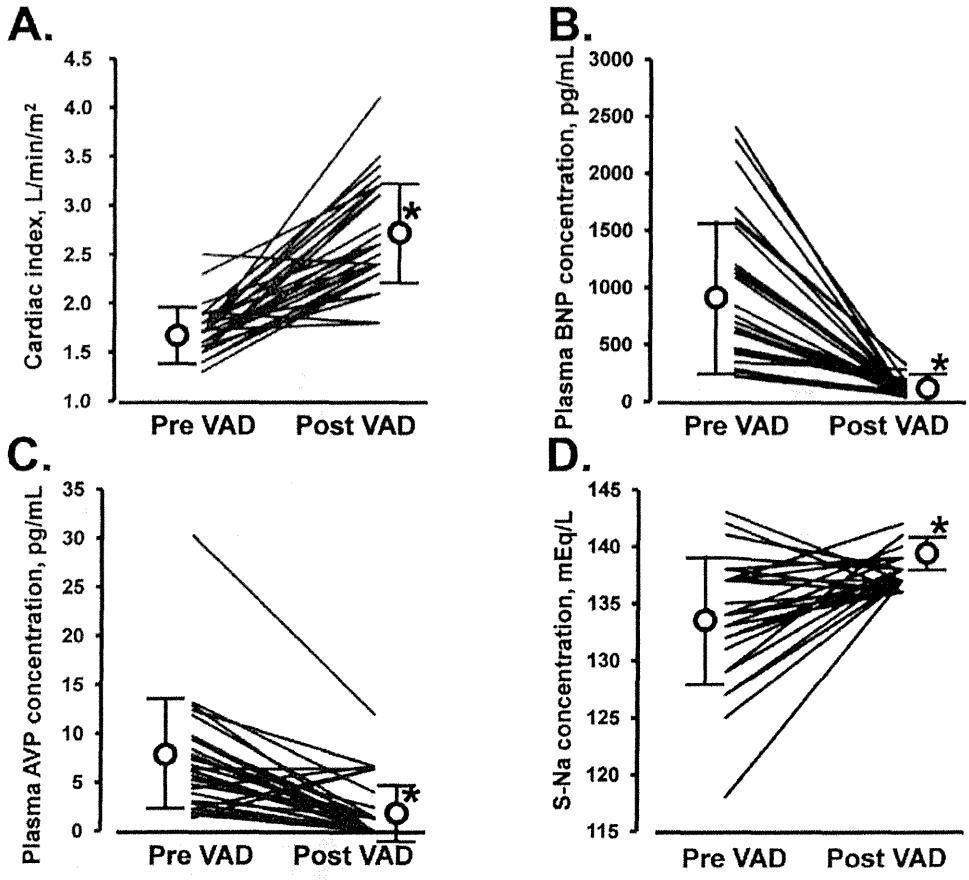

Figure 2. Changes in CI (**A**), plasma levels of BNP (**B**) and AVP (**C**), and S-Na (**D**) in patients who had VAD implantation during the study period (n=28). *P<0.05 by paired t-test or Wilcoxon signed-rank test compared with preoperative parameters as appropriate. AVP, arginine vasopressin; BNP, B-type natriuretic peptide; CI, cardiac index; S-Na, serum sodium concentration; VAD, ventricular assist device.

tients with extremely high plasma AVP levels (>20 pg/ml), whose CI were <2.0 L·min^{-1}·m^{-2}, plasma BNP >1,500 pg/ml, and S-Na <130 mEq/L. Although all hemodynamic parameters were improved after VAD implantation (all P<0.05; **Table 2**), only CI negatively correlated with the plasma level of AVP among the hemodynamic parameters (P=0.008, r=–0.516) (**Table 4**) in the stage D HF patients in whom a hemodynamic study was performed before VAD implantation (n=64).

In the VAD/HTx group (n=80), plasma AVP levels had no correlation with CI (**Figure 3D**) or plasma BNP levels (**Figure 3E**). None of hemodynamic parameters correlated with plasma AVP levels in the VAD/HTx group (**Table 4**). The only significant correlation was between the plasma AVP level and S-Na (**Table 3**), but in sharp contrast to the HF patients, higher AVP levels were accompanied by higher S-Na in the VAD/HTx group (**Figure 3F**).

Clinical Prognosis Stratified by Plasma AVP Levels in Patients With Stage D HF (Figure 4)

In the HF group, 24 patients (14.8%) died during the study period. ROC analyses demonstrated that a cutoff level of plasma AVP for all-cause survival over 2 years was identically 5.3 pg/ml (area under curve, 0.681; sensitivity, 0.708; specificity, 0.674). According to the cutoff level of plasma AVP, patients were stratified into 2 groups, and Kaplan-Meier analyses showed significant differences between them in terms of all-cause survival over 2 years (P<0.001). Cox regression analysis demonstrated that higher plasma levels of AVP were significantly associated with decreased survival (hazard ratio, 4.803; 95% confidence interval, 2.045–11.28; P<0.001). In contrast, plasma levels of AVP had no significant effect on mortality in the VAD/HTx group (P=0.254 by Cox regression analysis).

Discussion

In this study, we demonstrated that a lower CO had a significant correlation with increased secretion of AVP, and that elevated plasma levels of AVP were significantly associated with hyponatremia and poor prognosis in patients with stage D HF. Plasma AVP levels normalized along with the improvement of CO after VAD/HTx treatment, and positively correlated with S-Na, in contrast to the HF group. VAD treatment was as efficient at improving hemodynamics and reducing plasma levels of AVP as HTx.

Table 3. Correlation Between Plasma AVP Concentration and Other Characteristic Parameters in the HF and VAD/HTx Groups

vs. Plasma AVP	HF (n=162)		VAD/HTx (n=80)	
	P value	R value	P value	R value
Demographic parameters				
Age, years	0.862	0.014	0.114	0.131
Body surface area, m^2	0.304	−0.081	0.161	0.089
SBP, mmHg	0.058	−0.175	0.631	−0.053
DBP, mmHg	0.053	−0.153	0.117	0.131
Heart rate, beats/min	0.068	0.183	0.165	−0.159
SaO_2, %	0.438	0.053	0.721	0.079
Concomitant medication				
Furosemide, mg/day	0.128	0.120	0.119	0.151
Spironolactone, mg/day	0.910	0.009	0.978	0.003
Trichlormethiazide, mg/day	0.856	−0.014	0.092	0.179
Catecholamine infusion, n (%)	0.755	0.025	–	–
Laboratory parameters				
Hemoglobin, g/dl	0.379	−0.07	0.085	0.188
Platelets, $\times 10^3/\mu l$	0.290	−0.084	0.895	0.023
Serum albumin, g/dl	0.187	−0.105	0.452	0.088
Serum sodium, mEq/L	<0.001*	−0.548	<0.001*	0.464
Serum potassium, mEq/L	0.676	0.033	0.364	0.105
Serum BUN, mg/dl	0.089	0.132	0.234	0.141
Serum creatinine, mg/dl	0.074	0.164	0.664	0.049
Serum total bilirubin, mg/dl	0.802	0.020	0.359	0.103
Plasma BNP, pg/ml	<0.001*	0.633	0.334	0.109
Echocardiographic parameters				
LV diastolic diameter, mm	0.083	0.137	0.215	0.134
Ejection fraction, %	0.018*	−0.230	0.521	−0.071
E/e'	0.118	0.231	0.367	0.096
CI, $L \cdot min^{-1} \cdot m^{-2}$	<0.001*	−0.458	0.810	−0.026

*P<0.05 by Pearson's product-moment correlation coefficient. Abbreviations as in Table 1.

Non-Osmotic Regulation of AVP in Stage D HF

AVP secretion is regulated by a non-osmotic pathway that is responsive to such stimuli as decreased circulation, hypoxia, intravenous inotropic infusion, activation of renin-angiotensin-aldosterone, and sympathetic nerve system stimulation.[5,16–18] The non-osmotic pathway has been considered a dominant modulator of plasma AVP levels in hemodynamically sick conditions, including HF, although no quantitative studies have been reported thus far, especially in patients with stage D HF.

This study is a novel quantitative study that demonstrated a significant negative correlation between CO and plasma AVP levels in patients with stage D HF. Other hemodynamic parameters including right atrial pressure and pulmonary capillary wedge pressure did not correlate with plasma AVP levels. As a non-osmotic trigger, arterial underfilling caused by low CO rather than congestion contributes to the secretion of AVP.

Interestingly, improvement of CO by VAD treatment was as sufficient to normalize the plasma levels of AVP as HTx. Hemodynamic parameters in the VAD group were consistently indistinguishable from those of the HTx group. In other words, not only HTx but also VAD treatment can be a cardiac replacement therapy from the viewpoint of sufficient reduction of plasma AVP levels. Our observation was consistent with the fact that the non-osmotic trigger of impaired hemodynamics may be a key to stimulating AVP secretion in patients with advanced HF, as several authors have previously speculated.[5,13] Uretsky et al's data that demonstrated a significant negative correlation between changes in systemic blood pressure and plasma AVP levels after intravenous infusion of vasodilator accompanied by non-significant increases in CO would support our result,[7] although the correlation between blood pressure and AVP levels barely reached statistical significance in our analysis.

Neurohumoral activation, which contributes to the malignant cycle of HF,[19] results in higher levels of AVP (6.5–9.5 pg/ml) according to previous studies,[5,10,20,21] but all those studies were executed before the current GDMT was established. Relatively lower plasma levels of AVP in our study (average 5.9±6.1 pg/ml) may be attributable to the effective suppression of neurohumoral activity by the application of GDMT including β-blocker, ACEI, and aldosterone blocker at high rates (92.6%, 82.7%, and 63.6%, respectively). The recently reported subanalysis of the EVEREST study consistently included 78% of patients with plasma AVP levels ≤8 pg/ml receiving high rates of β-blocker and ACEI (83% and 74%, respectively) therapy.[6]

In this study, S-Na negatively correlated with plasma AVP levels in patients with stage D HF. Secreted AVP binds V_2 receptor located in collecting duct, and activates the signaling cascade including aquaporin 2, which facilitates water reabsorption and often causes dilution hyponatremia.[2,11,22] Only a few authors have previously reported such a correlation among

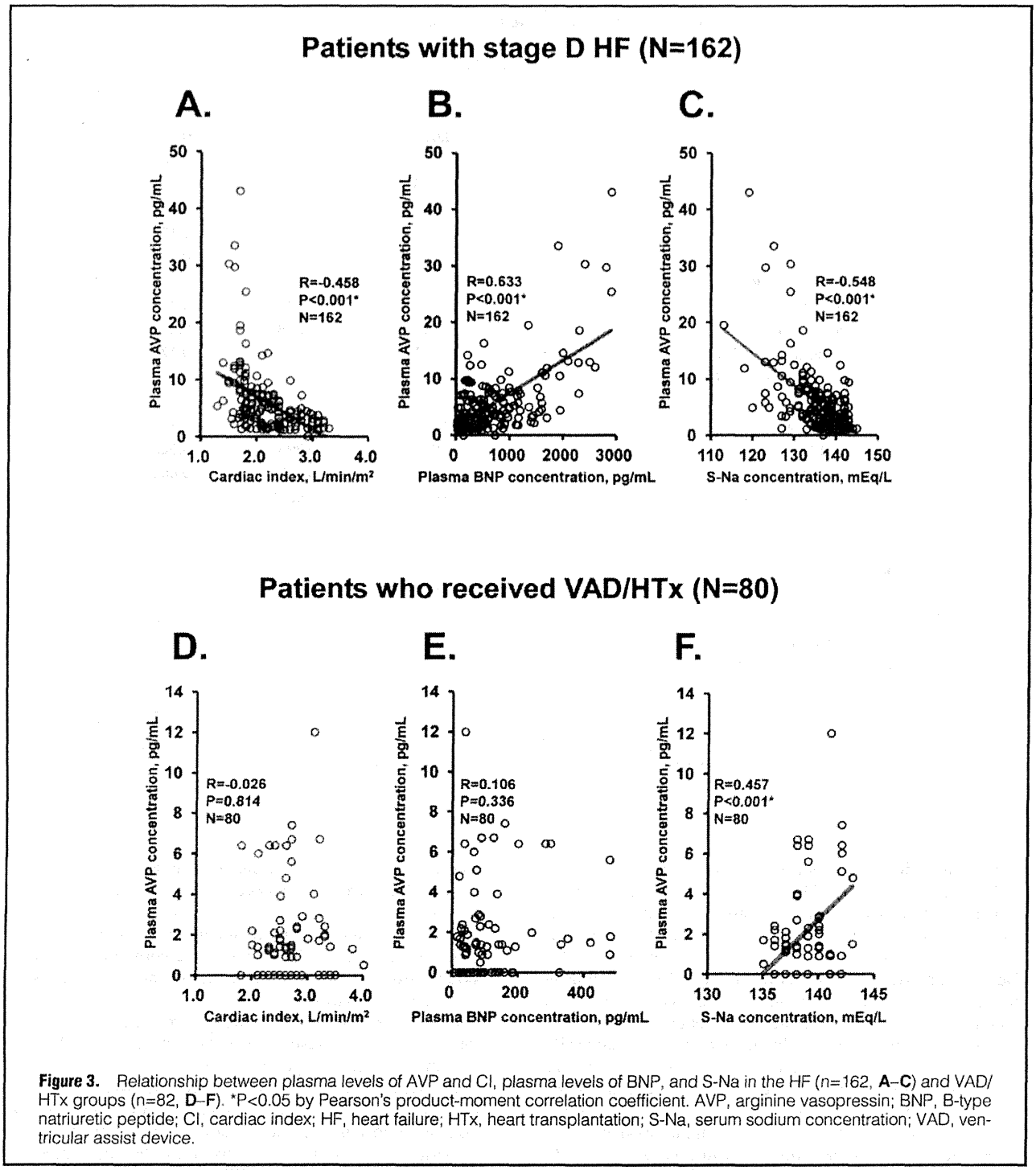

Figure 3. Relationship between plasma levels of AVP and CI, plasma levels of BNP, and S-Na in the HF (n=162, **A–C**) and VAD/HTx groups (n=82, **D–F**). *P<0.05 by Pearson's product-moment correlation coefficient. AVP, arginine vasopressin; BNP, B-type natriuretic peptide; CI, cardiac index; HF, heart failure; HTx, heart transplantation; S-Na, serum sodium concentration; VAD, ventricular assist device.

small numbers of HF patients or those with acute myocardial infarction.[8,23] We believe that ours is a noteworthy report showing the close relationship of low CO, increased AVP and hyponatremia in advanced HF.

Osmotic Regulation of Plasma AVP After Improvement of Hemodynamics

The osmotic control of AVP release is one of 2 modulators of homeostasis,[2] and individual variation, genetic, environmental, species differences, circadian rhythm, or the nature of solute providing the osmotic stimuli can significantly affect the release of AVP by altering the threshold and/or the sensitivity of osmoreceptors.[4,24,25] Consistently, plasma levels of AVP had a positive correlation with S-Na but not with CO or plasma BNP levels in our VAD/HTx group whose hemodynamics appeared to be almost normal. In other words, AVP secretion was mainly regulated by S-Na in an osmotic manner after VAD/HTx treatment under hemodynamically stable con-

Table 4. Correlation Between Plasma AVP Concentration and Hemodynamic Parameters in the HF and VAD/HTx Groups

vs. Plasma AVP	HF (n=64)		VAD/HTx (n=80)	
	P value	R value	P value	R value
Mean RAP, mmHg	0.964	0.028	0.366	0.178
Systolic PAP, mmHg	0.984	0.014	0.387	0.157
Diastolic PAP, mmHg	0.497	0.152	0.570	0.116
Mean PAP, mmHg	0.587	0.143	0.437	0.188
PCWP, mmHg	0.524	0.217	0.564	0.114
CI, $L \cdot min^{-1} \cdot m^{-2}$	0.008*	−0.516	0.791	0.052

*P<0.05 by Pearson's product-moment correlation coefficient. Abbreviations as in Tables 1,2.

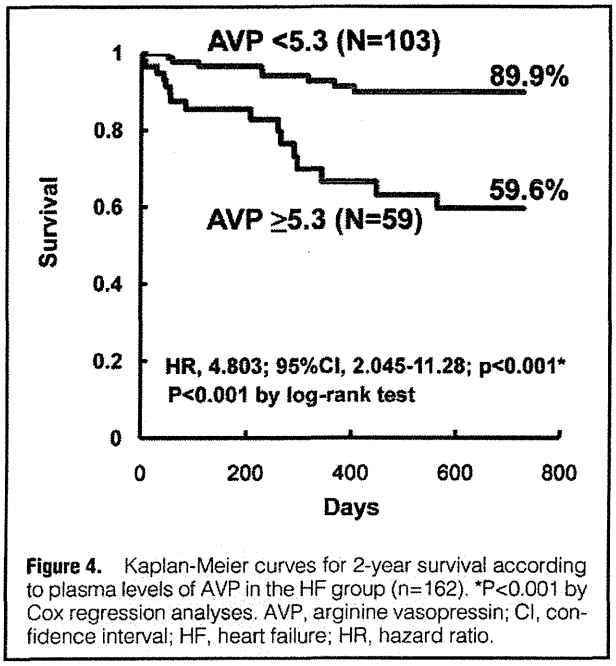

Figure 4. Kaplan-Meier curves for 2-year survival according to plasma levels of AVP in the HF group (n=162). *P<0.001 by Cox regression analyses. AVP, arginine vasopressin; CI, confidence interval; HF, heart failure; HR, hazard ratio.

ditions. Not only HTx but also VAD treatment could reverse the dominant mechanism of AVP secretion from a non-osmotic pathway to an osmotic pathway by improving hemodynamics.

Plasma Levels of AVP and Prognosis

There have been no studies demonstrating increased plasma levels of AVP as a significant predictor for prognosis except for the recent subanalysis of the EVEREST study.[6] Their cutoff value of plasma AVP was almost consistent with our result (8.0 vs. 5.2 pg/ml). They adopted the upper limit of the healthy population (ie, 8.0 pg/ml) as the cutoff value, whereas we derived our cutoff value of 5.2 pg/ml by ROC analysis. Elevated AVP may have a crucial role in the vicious cycle of worsening HF, because it results from hemodynamic decline, and facilitates worsening of HF including hyponatremia and increased preload and afterload to the heart.[26] Consistently, elevated AVP levels were associated with lower CI and S-Na in the present study (**Figure 3**). Goldsmith et al experimentally demonstrated that intravenous infusion of AVP caused adverse circulatory effects, including decreases in CO and increases in systemic vascular resistance and pulmonary capillary wedge pressure, in patients with HF.[5] We recently reported that a V_2 receptor antagonist improved congestion and hyponatremia especially in HF patients with preserved function of collecting duct during short-term clinical course.[27,28] It would be a future concern whether a V_2 receptor antagonist improves long-term prognosis in patients with stage D HF.

Study Limitations

All data were analyzed in a retrospective manner, and our result was derived only from the observational analyses. Our result should be tested in a prospective manner. Data for the HF, VAD, and HTx groups were unpaired except for 28 patients who received VAD implantation during the study period. Consecutive observation during HF duration and VAD/HTx treatment in larger populations would strengthen our results. CO was estimated by echocardiography in most of the HF patients, although data were validated by hemodynamic study in 64 of the HF group as well as 80 of the VAD/HTx group. Because we included only patients with stage D HF as the HF group, our results may not be adopted in cases of mild to moderate HF. We evaluated AVP levels in patients with VAD/HTx at 3 months after operation, considering hemodynamic stability. However, future studies are needed to clarify whether osmotic AVP regulation is maintained for longer after surgery.

Conclusions

In patients with stage D HF, low CO stimulates AVP release via a non-osmotic pathway, and elevated AVP results in hyponatremia and poor prognosis. After sufficient recovery of hemodynamics by VAD/HTx therapy, AVP release is suppressed and is mainly regulated by serum osmolality. VAD treatment was as sufficient to improve hemodynamics and reduce plasma AVP levels as HTx.

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Disclosures

The authors have no conflicts of interest.

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ORIGINAL ARTICLE
Heart Failure

Increased Urine Aquaporin-2 Relative to Plasma Arginine Vasopressin Is a Novel Marker of Response to Tolvaptan in Patients With Decompensated Heart Failure

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Background: Preserved function of the renal collecting duct may be essential for response to the vasopressin V_2 receptor antagonist, tolvaptan (TLV), but the predictors of response to TLV are unknown.

Methods and Results: Sixty consecutive patients with stage D decompensated heart failure (HF) who had received TLV on a de novo basis were retrospectively enrolled (TLV(+) group). Among them, 41 patients were responders defined according to urine volume (UV) increase after TLV initiation. In the UV-defined responders, plasma arginine vasopressin (P-AVP) had a close correlation with urine aquaporin-2 (U-AQP2; 5.42±3.54 ng/ml; r=0.843, P<0.001). In contrast, 19 were UV-defined non-responders, and they had extremely low U-AQP2 (0.76±0.59 ng/ml, P<0.001 vs. responders) regardless of P-AVP level. On receiver operating characteristic analysis, U-AQP2/P-AVP ≥0.5×10^3 clearly separated the UV-defined responders from the non-responders. We then identified AQP-defined responders as having U-AQP2/P-AVP ≥0.5×10^3. Sixty propensity score-matched HF patients without TLV treatment were examined, and exactly the same number of patients as that of the AQP-defined responders (n=41) was selected. These patients had a poorer survival without TLV than the TLV-treated responders during a 2-year observation period (73.8% vs. 94.8%, P=0.034).

Conclusions: U-AQP2/P-AVP is a novel predictor of response to TLV in patients with decompensated HF. AQP-defined responders may have a better prognosis on TLV treatment. (*Circ J* 2014; **78:** 2240–2249)

Key Words: Chronic kidney disease; Congestive heart failure; Diabetes insipidus; Diuretics

Low cardiac output stimulates secretion of arginine vasopressin (AVP) via a non-osmotic pathway,[1] and its plasma level (P-AVP) is inappropriately elevated despite low serum osmolality in heart failure (HF).[2] AVP exacerbates myocardial fibrosis/hypertrophy and induces vasoconstriction due to stimulation of V_{1a} receptors,[3] as well as facilitating fluid retention accompanied by hypervolemic hyponatremia by activating V_2 receptors in the renal collecting duct.[4] Elevated P-AVP is one of the risk factors for poor prognosis in patients with HF.[2]

Editorial p2157

Tolvaptan (TLV), a vasopressin V_2 receptor antagonist, has recently been developed to treat patients with decompensated HF refractory to diuretics. Many authors including us demonstrated that TLV improved symptomatic congestion and normalized hyponatremia by excretion of free water into urine, maintaining hemodynamics and renal function even in patients with stage D HF.[5–12] This promising outcome, however, may not be expected in non-responders, whose urine volume (UV) does not increase at all after TLV initiation.[5] We hypothesized that the residual potential of the renal collecting duct may be essential for the response to TLV, but there have been no definitive predictors for response to TLV before TLV treatment thus far.[13,14]

Recently, aquaporin-2 (AQP2), a protein that forms vasopressin-regulated water channels and is located in the renal collecting ducts, was characterized, and its excretion into urine has been considered as a functional marker of the collecting duct.[15] We here analyzed the relationship between urine concentration of AQP2 (U-AQP2) and other laboratory parameters including P-AVP in patients with stage D HF who had received TLV, in order to identify a novel marker to predict response to TLV before TLV initiation.

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Methods

Study Design and Patients

Among the patients who were hospitalized for decompensated HF at the University of Tokyo Hospital between February 2011 and October 2013, 60 consecutive patients who had received 3.75–15 mg/day TLV on a de novo basis were retrospectively enrolled (TLV(+) group). All patients were treated with guideline-directed medical therapy for HF, including β-blocker, aldosterone antagonist, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), and doses of these medications had been titrated as tolerated. They had also been treated with conventional diuretics including loop diuretics and/or thiazides in addition to appropriate restriction of sodium and water intake, but they had symptomatic congestion, as evidenced by either lower limb edema, pulmonary congestion or jugular venous distension. As a result, all patients had New York Heart Association (NYHA) class III/IV symptoms. Attending physicians determined the initial dose of TLV and adjusted the dosage during the study period according to patient hemodynamics and degree of congestion. Patients with any of the following characteristics were excluded and did not receive TLV: severe stenotic valvular disease, severe systemic infection or inflammation, end-stage renal failure or on hemodialysis, acute coronary syndrome within 1 month, use of any mechanical support, hypovolemia, impaired consciousness with lack of thirst, or hypernatremia (>145 mEq/L).

Of 120 consecutive patients who were hospitalized for decompensated HF with NYHA class III/IV symptoms at the University of Tokyo Hospital between February 2011 and October 2013, 60 patients were selected as a propensity-matched control group on the basis of patient background (TLV(–) group). They had also received guideline-directed medical therapy but had never been treated with TLV before enrollment or during the observation period.[16]

The present study complied with the Declaration of Helsinki, and the institutional review board of University of Tokyo approved the research protocol (application no. 779(1)). Informed consent was obtained from all patients (including both the TLV(+) and TLV(–) groups) before enrollment.

Measures

Data on demographic characteristics and concomitant medication were obtained during hospitalization in the TLV(–) group or within 24 h before TLV initiation in the TLV(+) group. Blood samples including those for AVP measurement were obtained after the patients had rested for 15 min in the supine position in the early morning before taking any daily medicine during hospitalization in TLV(–) group, or on the day of TLV initiation (day 1) in the TLV(+) group. All blood samples were centrifuged immediately for 20 min, and the samples were stored at –80°C before the assay. Urine samples including those for the measurement of U-AQP2 were obtained in the early morning immediately before any medication including diuretics during hospitalization in the TLV(–) group or on day 1 in the TLV(+) group. All urine samples were stored immediately at –80°C until assayed. U-AQP2 was measured using sandwich enzyme-linked immunosorbent assay,[17,18] and normalized by urine creatinine (U-Cre) concentration for quantitative comparison. In some patients, U-APQ2 was measured at 4–6 h after TLV treatment on day 1.

UV during 24 h before TLV (day 0) was compared with that of the next 24 h after treatment (day 1) in each patient. If there was any increase in UV after TLV treatment, the patient was defined as a responder to TLV (UV-defined responder), and the reverse was a UV-defined non-responder.[5]

On the basis of the Minnesota Living with Heart Failure Questionnaire, one of the most widely used questionnaires to evaluate HF-specific quality of life,[19,20] we calculated "HF symptom score"[5] at baseline and at 1 month after enrollment in all candidates. The score was the sum of the following symptoms due to HF: (1) pitting edema in lower extremities (1 point); (2) pulmonary congestion (1 point); (3) jugular venous distention (1 point); (4) dyspnea (1 point); and (5) NYHA class (1–4 points according to class, eg, 4 points for NYHA class IV). The internal consistency among each item was sufficient (Cronbach's α, 0.795).

To analyze prognostic impact of TLV treatment, we examined the rate of re-hospitalization due to worsening of HF in addition to all-cause mortality. Patients were censored at the time of cessation of TLV, such as at ventricular assist device implantation.

Statistical Analysis

Data analysis was performed using PASW Statistics 18 (SPSS, Chicago, IL, USA). Categorical parameters are presented as frequencies and percentages unless otherwise described. For continuous variables, mean±SD is given. Patient characteristics were compared using unpaired t-test or Mann-Whitney test for continuous variables, and chi-squared test or Fisher's exact test for categorical variables as appropriate. Pearson's product-moment correlation coefficient was calculated to assess the relationship between P-AVP, U-AQP2, and %changes in UV after TLV. P-AVP and U-AQP2 obtained after TLV initiation were compared with those of the pretreatment period on paired t-test. A cut-off of U-AQP2/P-AVP for any increase in UV after TLV initiation was calculated using receiver operating characteristic (ROC) analysis. Propensity score-matching analysis was performed to adjust patient background HF severity of TLV(–) group to those of TLV(+) group on the basis of age, serum sodium, creatinine, and plasma B-type natriuretic peptide level.[21] Baseline variables among the 4 groups stratified according to response to TLV and use of TLV were compared using ad-hoc Tukey analysis when analysis of variance was significant. Logistic regression analysis was performed for the AQP-defined non-responders using the baseline variables of all patients. Categorical variables were created from continuous variables with $P<0.05$ on univariate analysis, using the cut-off calculated on ROC analysis. Variables with $P<0.05$ on univariate analysis were used in multivariate analysis. Kaplan-Meier analysis was performed to assess all-cause mortality and re-hospitalization rate due to worsening of HF in patients with/without TLV over 2 years, and each survival curve was compared with the log-rank test. All statistical tests were 2-tailed, with $P<0.05$ regarded as statistically significant.

Results

Baseline Characteristics

The TLV(+) group consisted of 60 patients who received TLV, and the TLV(–) group consisted of 60 propensity score-matched patients without TLV treatment (Table 1). Mean age was 55.0±19.3 years, and 18 patients (15.0%) had ischemic etiology. All patients had received guideline-directed medical therapy for HF including β-blockers (91.7%), ACEI or ARB (85.0%), and aldosterone antagonists (74.2%) at the maximum dose tolerated. Fifty-seven patients (47.5%) were dependent on i.v. infusion of inotropes. All patients had been dependent on diuretics, including furosemide (50.2±27.5 mg/day on av-

Table 1. Baseline Characteristics vs. Presence of TLV

	Total (n=120)	TLV(–) (n=60)	TLV(+) (n=60)	P-value
Demographic parameters				
Age (years)	55.0±19.3	55.1±18.7	54.8±20.0	0.933
Male	93 (77.5)	52 (86.7)	41 (68.3)	0.068
Body weight (kg)	57.2±11.3	58.1±10.6	56.3±12.0	0.400
BSA (m^2)	1.68±0.18	1.70±0.17	1.66±0.20	0.209
Etiology of ischemia	18 (15.0)	9 (15.0)	9 (15.0)	1.000
SBP (mmHg)	101.3±12.8	102.7±12.7	98.0±12.4	0.087
DBP (mmHg)	64.5±8.1	65.3±8.1	63.7±8.2	0.293
HR (beats/min)	79.9±16.2	77.0±15.4	81.7±16.2	0.072
Concomitant medication				
Furosemide (mg daily)	50.2±27.5	46.2±18.7	54.2±33.8	0.064
Aldosterone antagonist (mg daily)	28.4±22.2	24.6±20.3	32.1±23.5	0.065
Trichlormethiazide (mg daily)	0.2±0.7	0.1±0.4	0.3±0.9	0.058
β-blocker (mg daily)	6.5±6.5	6.3±5.6	6.7±7.4	0.728
ACEI/ARB (mg daily)	3.2±2.8	3.6±3.3	2.8±2.1	0.114
Furosemide	117 (97.5)	57 (95.0)	60 (100)	0.244
Aldosterone antagonist	89 (74.2)	41 (68.3)	49 (81.7)	0.144
Trichlormethiazide	10 (8.3)	3 (5.0)	7 (11.7)	0.186
β-blocker	110 (91.7)	57 (95.0)	53 (88.3)	0.186
ACEI/ARB	102 (85.0)	53 (88.3)	49 (81.7)	0.306
I.v. inotropes	57 (47.5)	22 (36.7)	35 (58.3)	0.017*
Laboratory parameters				
Plasma AVP (pg/ml)	5.8±5.7	5.5±5.6	6.0±5.8	0.606
Hemoglobin (g/dl)	11.7±2.3	11.5±2.5	11.8±2.1	0.481
Platelets ($\times 10^3/\mu l$)	19.2±2.3	19.6±9.0	18.7±6.5	0.527
Serum albumin (g/dl)	3.5±0.6	3.4±0.6	3.5±0.7	0.329
Serum sodium (mEq/L)	135.1±5.2	135.7±4.2	133.5±6.4	0.088
Serum potassium (mEq/L)	4.3±0.5	4.3±0.5	4.2±0.4	0.586
Serum BUN (mg/dl)	28.3±14.8	25.7±14.3	30.9±14.8	0.064
Serum creatinine (mg/dl)	1.3±0.7	1.3±0.7	1.4±0.6	0.776
Serum total bilirubin (mg/dl)	1.3±1.0	1.1±0.7	1.4±1.2	0.068
Serum AST (IU/L)	32.5±26.4	35.4±33.3	29.7±16.7	0.244
Serum ALT (IU/L)	30.5±31.7	34.3±38.6	26.7±22.4	0.189
Plasma BNP ($\log_{10}$ pg/ml)	2.68±0.44	2.68±0.47	2.68±0.42	0.997
Urine AQP2 (ng/ml)	3.89±3.86	3.84±4.10	3.94±3.66	0.888
Urine AQP2/plasma AVP ($\times 10^3$)	1.08±1.63	1.28±2.15	0.88±0.80	0.175
Echocardiographic parameters				
LV diastolic diameter (mm)	61.3±14.6	60.5±13.2	62.1±15.9	0.554
LV systolic diameter (mm)	51.8±16.6	50.8±15.8	52.8±17.4	0.507
Ejection fraction (%)	32.6±19.0	33.8±19.0	31.5±19.1	0.510
Ejection fraction ≥50%	22 (18.3)	11 (18.3)	11 (18.3)	1.000
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.1±0.4	2.2±0.5	2.1±0.4	0.273
HF symptom score	6.2±1.1	6.3±1.2	6.1±1.1	0.712

Data given as mean±SD or n (%). *P<0.05 (unpaired t-test or Mann-Whitney test).
ACEI, angiotensin-converting enzyme II inhibitor; ALT, alanine aminotransferase; AQP2, aquaporin-2; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; AVP, arginine vasopressin; BNP, B-type natriuretic peptide; BSA, body surface area; BUN, blood urine nitrogen; DBP, diastolic blood pressure; HF, heart failure; HR, heart rate; LV, left ventricular; SBP, systolic blood pressure; TLV, tolvaptan.

erage; range, 20–200 mg/day), aldosterone antagonist (28.4±22.2 mg/day on average; range, 0–100 mg/day), and trichlormethiazide (0.2±0.7 mg/day on average; range, 0–4 mg/day). Many enrolled patients had mild end-organ dysfunction: that is, serum creatinine and total bilirubin 1.3±0.7 mg/dl and 1.3±1.0 mg/dl, respectively. Fifty patients (41.7%) had hyponatremia (<135 mEq/L), whereas no patients had serum sodium >145 mEq/L. P-AVP was detectable in all patients (5.8±5.7 pg/ml on average; range, 0.9–43.0 pg/ml).

There were no statistically significant differences between the TLV(+) group and TLV(–) group in demographic, medication, laboratory, or echocardiographic parameters, except for rate of inotrope infusion (58.3% in the TLV(+) group vs. 36.7% in the TLV(–) group, P=0.017).