Low Blood Pressure, Low Serum Cholesterol and Anemia Predict Early Necessity of Ventricular Assist Device Implantation in Patients With Advanced Heart Failure at the Time of Referral From Non-Ventricular Assist Device Institutes

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Background: The timing of ventricular assist device (VAD) implantation is always a matter of debate, especially when a patient is referred from a non-VAD institute. We focused on objective noninvasive parameters at the time of admission to a VAD implant center and analyzed the factors predicting the necessity of early VAD.

Methods and Results: We retrospectively analyzed advanced heart failure (HF) patients referred since January 2011, including patients less than 65 years old. They all had a history of hospitalization for HF management in non-VAD institutes within 1 month before referral. We excluded patients transferred with mechanical circulatory support. We enrolled 46 patients (40 males, 39.8 ± 13.4 years old). Among them, 26 patients had a VAD implanted or died within 120 days. By multivariable logistic analysis using admission parameters, systolic blood pressure (BP) <93 mmHg [odds ratio (OR) 13.335], hemoglobin <12.7 g/dl (OR 12.175) and serum total cholesterol <144 mg/dl (OR 8.096) were significant predictors of early VAD requirement. We constructed a scoring system according to the ORs, and the area under the receiver-operating characteristic curve was 0.913.

Conclusions: Low BP, low serum cholesterol and anemia on admission predict early VAD in advanced HF patients who have been treated in non-VAD institutes. Such patients should be promptly referred to a VAD implant center. (*Circ J* 2014; **78**: 2882–2889)

Key Words: INTERMACS profile; Seattle Heart Failure Model; Stage D heart failure

Ventricular assist device (VAD) implantation is an important therapeutic option for advanced heart failure (HF) patients. In the REMATCH trial, the use of VAD significantly improved survival in patients with advanced HF with left ventricular ejection fraction (LVEF) $<25\%$.¹ Furthermore, continuous-flow left VAD (LVAD) is proven to accompany better prognosis and quality of life after implantation.²

In Japan, implantable LVADs have been approved as bridging devices to transplant since April 2011, and consequently the therapeutic strategy for advanced HF has dramatically changed.³ However, in the clinical setting the timing of VAD implantation is always a matter of debate, especially when a

patient is referred from a non-VAD institute. Indeed, some referred patients considered to be candidates for VAD implantation eventually recover with intensive medical therapy in VAD centers. In contrast, others need emergency implantation of paracorporeal VAD because their hemodynamic status has crashed before sufficient evaluation for transplant candidacy.

For the purpose of deciding this timing, profiles defined by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) are useful. Because the prognosis after VAD implantation is worse for patients with profile 1 or 2 than for less sick patients, profile 3 without end-organ dysfunction is the best candidate for VAD implantation.^{3,4} However, the

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Table 1. Baseline Characteristics and Clinical Course of the Enrolled Patients With Advanced HF

	Total (n=46)	Late/no-VAD group (n=20)	Early-VAD group (n=26)	P value
Baseline characteristics				
Age, years	39.8±13.4	43.7±13.0	36.8±12.5	0.084
Male, n (%)	40 (87.0)	18 (90.0)	22 (84.6)	0.468
Body height, cm	168.0±6.9	167.8±6.8	168.2±7.1	0.867
Body weight, kg	62.0±11.2	61.1±9.6	62.8±12.5	0.613
Body mass index	22.0±4.0	21.6±2.7	22.3±4.8	0.584
Body surface area, m ²	1.70±0.15	1.69±0.15	1.71±0.16	0.700
Ischemic etiology n (%)	4 (8.7)	2 (10.0)	2 (7.7)	0.590
History of HF, years	3.3±4.4	2.6±3.8	3.8±4.8	0.361
Family history of HF, n (%)	9 (19.6)	3 (15.0)	6 (23.1)	0.383
CRT/ICD, n (%)	17 (37.0)	4 (20.0)	13 (50.0)	0.036
β-blocker,* mg/day	6.0±5.8	5.6±5.8	6.3±6.0	0.677
ACEI/ARB,** mg/day	4.3±4.1	2.5±2.6	5.7±4.5	0.006
Statin, n (%)	9 (19.6)	6 (30.0)	3 (11.5)	0.117
LVEF <30%, n (%)	42 (91.3)	17 (85.0)	25 (96.2)	0.211
BNP >300 pg/ml, n (%)	42 (91.3)	17 (85.0)	25 (96.2)	0.211
INTERMACS profile	—	—	—	<0.001
Profile 2, n (%)	6 (13.0)	0 (0)	6 (23.1)	—
Profile 3, n (%)	23 (50.0)	6 (30.0)	17 (65.4)	—
Profile 4 or less sick, n (%)	17 (37.0)	14 (70.0)	3 (11.5)	—
Clinical course after admission				
Paracorporeal VAD, n (%)	7 (15.2)	0	7 (26.9)	—
Implantable VAD, n (%)	21 (45.7)	3 (15.0)	18 (69.2)	—
All-cause death, n (%)	4 (8.7)	0	4 (15.4)	—

*Carvedilol equivalent; **enalapril equivalent.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardiac defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; VAD, ventricular assist device.

classification can vary according to the physician's decision, so we consider that objective parameters that can predict the early requirement for VAD in advanced HF patients are essential.

In this study, we focused on objective parameters of advanced HF patients at the time of referral from non-VAD institutes by analyzing the factors related to early necessity for VAD implantation.

Methods

Patient Selection

We retrospectively collected the data for 46 consecutive HF patients who had been referred to the University of Tokyo Hospital from non-VAD institutes for further management of HF between January 2011 and December 2013. The study period was set as described because implantable LVADs were approved in April 2011. The inclusion criteria were defined as follows: <65 years old, and history of hospitalization for HF in a non-VAD institute within 1 month before referral. Patients who were older than 65 years old were excluded because they are ineligible for heart transplantation in Japan and we excluded patients transferred with mechanical circulatory support because they usually need paracorporeal VAD immediately after transfer and thus were not primarily considered as good candidates for implantable LVAD. Patients diagnosed with acute myocarditis, transferred for the purpose of valvular or bypass surgery, or considered ineligible for VAD implantation (ie, social problems) were also excluded.

Variables Evaluated

Patients' demographic data, including vital signs and treatment on admission, were collected. To evaluate the effects of differential doses of β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin II receptor blockers (ARBs), the doses were normalized to approximately equivalent doses of carvedilol and enalapril according to efficacy. We regarded bisoprolol 5 mg as carvedilol 20 mg, and for ACEIs/ARB, the following agents were regarded as enalapril 10 mg: imidapril 10 mg, perindopril 4 mg, losartan 50 mg, valsartan 80 mg, as previously described.⁵ All laboratory data and echocardiographic parameters were obtained within several days of admission. We defined VAD implantation or death as the primary endpoint.

Follow-up After Referral

Before deciding to implant a VAD, all patients received guideline-directed medical therapy consisting of β-blockers, ACEIs/ARB, and aldosterone antagonists as tolerated. Diuretics were also titrated as needed. Cardiac resynchronization therapy (CRT) with a defibrillator was performed if indicated. Intra-aortic balloon pumping (IABP), percutaneous cardiopulmonary support, continuous hemodiafiltration, or mechanical ventilation was executed on the basis of the physician's decision. Timing of VAD implantation was determined by whether the patient developed cardiogenic shock, had progressive decline of end-organ function in spite of maximal treatment, or was considered inotrope-dependent despite optimal medical therapy.

We followed all patients from the date of their referral until

Figure 1. Kaplan-Meier curve for VAD-free survival (A) and survival (B) after admission to referral hospital of all enrolled patients (n=46) with advanced heart failure. VAD, ventricular assist device.

March 2014 or the date of their death. No patient was lost during the follow-up period unless deceased.

Previous Risk Scores

The Seattle Heart Failure Model (SHFM) was developed by Levy et al from the data of New York Heart Association (NYHA) class IIIB or IV patients and calculated from age, vital signs, medications, laboratory measurements and utilization of CRT.⁶ They also updated the SHFM score for LVAD candidates by adding variables such as usage of inotropes, IABP, or mechanical ventilation.⁷ In SHFM, the therapeutic option of LVAD is available if the patients meet ACC/AHA criteria such as (1) NYHA Class IV, (2) LVEF $\leq 25\%$, and (3) mean 2 year survival $\leq 50\%$.⁸ We used their website (<http://depts.washington.edu/shfm>) to estimate the indication for LVAD in the present group of patients.

The INTERMACS profile stratifies patients with advanced HF into 7 categories on the basis of clinical severity.⁹ In this study, patients with profile 1 on admission were not enrolled because we excluded patients transferred with mechanical circulatory support.

Statistical Analysis

Continuous variables of patients who did or did not require early VAD were compared by unpaired t-test or Mann-Whitney test as appropriate. Categorical variables of patients were compared by chi-square test or Fisher's exact test as appropriate. Univariable analyses with a logistic regression model were performed to calculate odds ratio (OR) and 95% confidence interval (CI) to assess the influence of each variable on admission on early requirement for VAD. We chose 3 statistically significant variables from among the baseline characteristics, laboratory measurements and echocardiographic parameters. Cutoff points of the 3 variables were determined by receiver-operating characteristic (ROC) analysis with JMP9 (SAS Institute, Cary,

NC, USA) and entered into the multivariable analysis.

Considering the results of the multivariable analysis, weighted scores were allocated to each selected variable on the basis of each OR, and we defined a summation of scores as a new risk scoring system. We then created a ROC curve for the new score, by which the area under the curve (AUC) for the score was calculated and that AUC was compared with those of previously published risk scores, including SHFM and INTERMACS profile.

Kaplan-Meier survival analysis was also performed to evaluate VAD-free survival after referral on 2 strata of the new score, and VAD-free survival among these strata was compared by log-rank test.

Unless otherwise specified, all data are expressed as mean $\pm$ standard deviation. Probability was 2-tailed, with $P < 0.05$ regarded as statistically significant. All statistical analyses except for the ROC analyses were calculated with PASW Statistics 18 (SPSS, Chicago, IL, USA).

Results

Baseline Characteristics

The baseline characteristics of the 46 enrolled patients are shown in **Table 1**. The mean age was 39.8 ± 13.4 years and 87.0% were male. An ischemic etiology was found in 8.7% of the patients; 6 patients (13.0%) were considered as profile 2 and 23 (50.0%) as profile 3. LVEF was $< 30\%$ in 42 patients (91.3%), and plasma levels of B-type natriuretic peptide (BNP) were > 300 pg/ml in 42 patients (91.3%).

Classification of the Patients

Table 1 shows the clinical course after admission, and **Figure 1** shows the VAD-free survival and overall survival of the patients. As shown in **Figure 1A**, 28 patients (60.9%) eventually needed VAD and of them 25 had the VAD implanted within 4 months

Table 2. Demographic, Physical, Laboratory and Echocardiographic Parameters on Admission and Univariable Analysis for VAD Implantation in 46 Patients With Advanced HF

	Late/no-VAD group (n=20)	Early-VAD group (n=26)	P value	OR	95% CI
Demographic parameters					
Age, years	43.7±13.0	36.8±12.5	0.089	0.959	0.914–1.006
Male, n (%)	18 (90.0)	22 (84.6)	0.593	1.636	0.268–9.980
Body height, cm	167.8±6.8	168.2±7.1	0.863	1.008	0.925–1.097
Body weight, kg	61.1±9.6	62.8±12.5	0.605	1.014	0.962–1.069
Body mass index	21.6±2.7	22.3±4.8	0.577	1.044	0.897–1.216
Body surface area, m ²	1.69±0.15	1.71±0.16	0.693	2.166	0.047–100.583
Ischemic etiology, n (%)	2 (10.0)	2 (7.7)	0.784	0.750	0.096–5.844
History of HF, years	2.6±3.8	3.8±4.8	0.357	1.070	0.926–1.237
Family history of HF, n (%)	3 (15.0)	6 (23.1)	0.496	1.700	0.368–7.845
Physical parameters					
Heart rate, beats/min	88.8±18.0	93.4±19.8	0.413	1.013	0.982–1.046
Systolic BP, mmHg	95.9±12.8	88.0±7.8	0.024	0.924	0.862–0.989
Systolic BP <93 mmHg, n (%)	7 (35.0)	23 (88.5)	0.001	14.238	3.133–64.702
Diastolic BP, mmHg	60.2±8.8	54.6±7.8	0.040	0.916	0.842–0.996
Laboratory parameters					
White blood cell count, ×10 ³ /μl	7.4±2.5	7.2±2.2	0.708	0.953	0.741–1.226
Hemoglobin, g/dl	14.6±2.0	12.4±2.1	0.002	0.585	0.413–0.828
Hemoglobin <12.7 g/dl, n (%)	2 (10.0)	17 (65.4)	0.001	17.000	3.202–90.254
Platelets, ×10 ⁴ /μl	21.2±5.6	22.4±6.8	0.514	1.033	0.937–1.138
Serum sodium, mmol/L	137.1±3.9	135.3±5.4	0.219	0.920	0.805–1.051
Serum potassium, mmol/L	4.4±0.4	4.3±0.5	0.542	0.670	0.185–2.429
Serum chloride, mmol/L	101.6±4.0	99.3±6.0	0.156	0.910	0.798–1.037
Serum blood urea nitrogen, mg/dl	21.0±11.3	23.3±14.6	0.548	1.014	0.968–1.063
Serum creatinine, mg/dl	1.00±0.25	1.12±0.51	0.327	2.150	0.465–9.938
Serum uric acid, mg/dl	7.0±2.2	7.5±3.2	0.525	1.075	0.861–1.341
Serum total protein, g/dl	7.0±0.8	6.7±0.8	0.241	0.634	0.296–1.359
Serum albumin, g/dl	3.9±0.5	3.7±0.6	0.371	0.608	0.204–1.809
Serum lactate dehydrogenase, IU/L	245.3±58.5	276.4±113.5	0.287	1.004	0.996–1.013
Serum aspartate aminotransferase, IU/L	32.2±13.1	36.1±38.8	0.666	1.005	0.983–1.027
Serum alanine aminotransferase, IU/L	36.2±20.2	41.4±52.5	0.670	1.003	0.988–1.019
Serum alkaline phosphatase, IU/L	278.1±75.8	288.5±111.9	0.724	1.001	0.995–1.008
Serum γ-glutamyl transpeptidase, IU/L	117.2±104.7	107.3±88.3	0.724	0.999	0.993–1.005
Serum total bilirubin, mg/dl	1.4±0.7	1.5±0.9	0.663	1.174	0.570–2.418
Serum TC, mg/dl	181.0±43.8	146.2±46.3	0.020	0.983	0.969–0.997
Serum TC <144 mg/dl, n (%)	3 (15.0)	16 (61.5)	0.003	9.067	2.106–39.029
C-reactive protein, mg/dl	0.78±1.30	1.42±2.34	0.289	1.223	0.843–1.774
BNP, log ₁₀ pg/ml	2.84±0.34	2.96±0.25	0.201	3.960	0.480–32.676
Echocardiographic parameters					
LV diastolic diameter, mm	67.5±16.2	73.1±14.3	0.228	1.027	0.984–1.072
LV systolic diameter, mm	63.1±11.6	67.5±14.5	0.263	1.027	0.980–1.077
LVEF, %	21.7±10.5	20.2±6.9	0.545	0.979	0.913–1.049
Interventricular septum thickness, mm	8.3±2.3	7.8±1.8	0.416	0.884	0.657–1.189
Posterior wall thickness, mm	7.9±2.0	8.2±1.3	0.546	1.120	0.775–1.617
LA diameter, mm	50.1±6.7	48.0±7.3	0.341	0.959	0.879–1.045
AR severity	0.50±0.76	0.58±0.70	0.717	1.165	0.510–2.659
MR severity	2.55±0.69	2.31±1.01	0.355	0.725	0.367–1.433
TR severity	1.95±0.69	2.00±0.85	0.826	1.089	0.507–2.340
TR pressure gradient, mmHg	30.3±9.5	37.2±14.6	0.086	1.048	0.993–1.106

AR, aortic regurgitation; BP, blood pressure; CI, confidence interval; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; OR, odds ratio; TC, total cholesterol; TR, tricuspid regurgitation. Other abbreviations as in Table 1.

Table 3. Multivariable Analysis for Early VAD Implantation Among the Variables Measured in 46 Patients With Advanced HF

	P value	OR	95% CI
Systolic BP, <93 mmHg	0.013*	13.335	1.746–101.848
Hemoglobin, <12.7 g/dl	0.013*	12.175	1.698–87.304
Serum TC, <144 mg/dl	0.031*	8.096	1.206–54.340

Abbreviations as in Tables 1,2.

Table 4. AUC of the New Scoring System and Other Scoring Systems for Early-VAD Necessity

	AUC (95% CI)	P value
New score	0.913 (0.798–0.965)	–
INTERMACS profile	0.827 (0.694–0.910)	0.195
SHFM	0.667 (0.553–0.765)	<0.001

AUC, area under the curve; SHFM, Seattle Heart Failure Model. Other abbreviations as in Tables 1,2.

of admission; 1 patient died within the 4 months, before VAD implantation. Next, we classified the patients who had a VAD implanted or died before day 120 into an early-VAD group (n=26), and a late/no-VAD group (n=20). Status on admission and the clinical course of both groups are also shown in **Table 1**. Patients in the early-VAD group tended to be younger than those in the late/no-VAD group, though statistically insignificant (36.8 ± 12.5 vs. 43.7 ± 13.0 years, $P=0.084$). The initial dose of β -blockers on admission was comparable between groups (6.3 ± 6.0 mg/day in early-VAD group vs. 5.6 ± 5.8 mg/day in late/no-VAD group, $P=0.677$) but the doses of ACEIs/ARB were significantly higher in the early-VAD group (5.7 ± 4.5 mg/day vs. 2.5 ± 2.6 mg/day, $P=0.006$). CRT/implantable cardiac defibrillator implantation was performed in 13 patients (50.0%) in the early-VAD group and in 4 patients (20.0%) from the late/no-VAD group ($P=0.036$).

In the early-VAD group, a paracorporeal VAD was implanted in 7 patients as an emergency life-saving procedure in all cases, and an implantable VAD in 18 patients. One patient died before VAD implantation. In the late/no-VAD group, 3 patient had a VAD implanted after day 120. In the follow-up period until March 2014, 3 patients in the early-VAD group died after VAD implantation (all of them had received an implantable VAD), whereas no patients died in the late/no-VAD group.

Univariable Logistic Analysis

We performed univariable logistic analysis to find predictors for early VAD. **Table 2** shows the demographic and physical parameters on admission. Low systolic blood pressure (BP; $P=0.024$, OR 0.924, 95% CI 0.862–0.989) was a significant factor related to the necessity for VAD. Of the laboratory data (**Table 2**), low hemoglobin level ($P=0.002$, OR 0.585, 95% CI 0.413–0.828) and low serum total cholesterol level ($P=0.020$, OR 0.983, 95% CI 0.969–0.997) predicted the early necessity for VAD. Serum bilirubin and creatinine levels, which are the well-known markers of end-organ dysfunction, or the plasma BNP level on admission were not significantly related to early VAD necessity. Of the echocardiographic parameters (**Table 2**), none of the variables, including left ventricular diastolic diameter and LVEF, were significantly related to early VAD necessity.

Multivariable Logistic Analysis

Because 26 primary events were observed in the early-VAD

Figure 2. ROC analysis of the new score, the INTERMACS profile and SHFM for the prediction of VAD necessity within 120 days, with the sensitivity and specificity of each score at the cutoff point. ROC, receiver-operating characteristics; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; SHFM, Seattle Heart Failure Model; VAD, ventricular assist device.

group, we chose all 3 statistically significant variables for the multivariable analysis. Systolic BP <93 mmHg ($P=0.001$, OR 14.238, 95% CI 3.133–64.702), hemoglobin <12.7 g/dl ($P=0.001$, OR 17.000, 95% CI 3.202–90.254) and serum total cholesterol <144 mg/dl ($P=0.003$, OR 9.067, 95% CI 2.106–39.029) were selected (**Table 2**) and entered into the multivariable analysis, which found that all of them were independent predictors for early VAD necessity (**Table 3**).

Scoring System

We created a new scoring system using these 3 factors (**Table 3**). We assigned 2 points to systolic BP <93 mmHg, 2 points to hemoglobin <12.7 g/dl and 1 point to serum total cholesterol <144 mg/dl, based on the ORs in the multivariable analysis. A ROC curve of the score was drawn, and the AUC for the score was 0.913 (**Figure 2**, **Table 4**). With a cutoff of 3 points, the sensitivity for VAD necessity within 120 days was 0.81 and the specificity was 0.85. We also compared the predictability of this score with other risk scores. The AUC of INTERMACS profile was 0.827, and with a cutoff of profile 3 the sensitivity was 0.88 and the specificity was 0.70. The AUC of SHFM was 0.667, and the sensitivity and specificity were 0.38 and 0.95, respectively. Our new scoring had a significantly better predictability for the early necessity of VAD over SHFM (**Table 4**).

We also classified the patients into 2 strata according to the new score (score 0–2 or 3–5), and performed Kaplan-Meier analysis. **Figure 3A** shows that the VAD-free survival was significantly different between the 2 strata ($P<0.001$, by log-rank test). We also compared VAD-free survival after stratification with the INTERMACS profile and SHFM (**Figures 3B,C**). VAD-free survival after admission was also significantly different between the 2 strata according to INTERMACS profile (profile 2–3 and profile 4 or less sick, $P<0.001$) and SHFM (LVAD criteria (+) and (–), $P<0.001$).

Figure 3. Kaplan-Meier analysis of VAD-free survival according to the new score system (A), profile 2 or 3 and profile 4 or less sick in INTERMACS (B), and LVAD criteria (–) and (+) in SHFM (C). VAD-free survival was compared by log-rank test and each P value is shown. INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; SHFM, Seattle Heart Failure Model.

Discussion

This study demonstrated that low systolic BP, and low levels of hemoglobin and low serum total cholesterol on admission were independent predictors of subsequent VAD implantation in the not too distant future for advanced HF patients referred from non-VAD institutes. For the purpose of deciding the timing of VAD implantation, it has been suggested that profiles defined by INTERMACS are useful,^{3,4} but the decision is physician-dependent. We emphasize that the combination of 3 objectively defined parameters was similarly predictive to INTERMACS profile. There have been several risk scores proposed for predicting prognosis after VAD implantation,^{7,10–12} but to our knowledge, this is the first report to focus on the early necessity for VAD using objective parameters. We also underscore that we selected noninvasive variables. Hemodynamic parameters obtained invasively may be useful for determining the timing, but are often unavailable at the time of referral from non-VAD institutes.

In this report, we use the term “at the time of referral”. In reality, we collected the data at the time of admission to the referral hospital, and so to be exact, we use the term “at the time of admission to the referral hospital”. However, we consider it was easier to understand the meaning and importance of this report by using the term “at the time of referral”.

Clinical Course of Advanced HF Patients Referred to Hospital

According to our results, VAD-free survival was only 43.5% at 4 month after admission (Figure 1). Furthermore, the existence of 2 of the 3 factors (systolic BP <93 mmHg, hemoglobin <12.7 g/dl and serum total cholesterol <144 mg/dl) predicted early VAD implantation after admission (Figure 2). Kaplan-

Meier analysis showed these patients had extremely poor VAD-free survival (Figure 3), which was comparable with the VAD-free survival of status 1 patients after being listed for heart transplantation as we reported recently.¹³

Effect of Each Parameter on Patients' Outcomes

It has been previously shown that low BP,^{14,15} anemia^{16,17} and low serum total cholesterol^{18,19} are predictors of higher mortality in HF patients, which is consistent with our results, because patients who needed VAD were expected to have poor prognosis without VAD implantation.

Patients presenting with low systolic BP may have low cardiac output and impaired organ perfusion,²⁰ so it is reasonable that low systolic BP predicts HF severity and the patient's outcome. In this study, the dose of ACEIs/ARB in early-VAD patients was higher than that in late/non-VAD patients (Table 1), which could be related to the duration of HF treatment, and could be a cause of the lower BP in early-VAD patients.

BP is an objective, but fluctuating parameter. We used BP measured noninvasively after admission with the patient in a stable condition and supine position. Although the difference in systolic BP between early-VAD and late/no-VAD patients was small, we consider the cutoff value of 93 mmHg as clinically reasonable, considering that systolic BP <90 mmHg is commonly regarded as a state of shock.

Low serum total cholesterol is a novel predictor of survival in chronic HF, but the mechanism is not fully understood.¹⁸ In our study the dose of statin was not statistically different, but tended to be higher in the patients in the late/no-VAD group than in those in early-VAD group, although the total cholesterol level was significantly lower in the early-VAD group (Tables 1,2). The protective role of lipoproteins in downregu-

lating inflammatory cytokines in HF has been reported.²¹ On the other hand, it is possible that low cholesterol is a marker only for cachexia, a state associated with poor HF mortality, and has no pathophysiologic role. However, in our study low cholesterol was a predictor of early VAD necessity, independent of body mass index or serum albumin, which are also variables associated with poor nutritional condition (data not shown). Therefore, cardiac cachexia may not only be the cause of low serum total cholesterol in our study.

Anemia is common in patients with HF, and patients with both HF and anemia have a lower functional capacity, worse quality of life, and higher rates of hospitalization and death than those without anemia.^{22,23} There are several potential causes of anemia in HF: malnutrition; hemodilution; renal dysfunction and impaired erythropoietin production; usage of ACEIs/ARB; elevated levels of proinflammatory cytokines; and others.²⁴ We found that anemia in the early-VAD group was normocytic and none had undergone blood transfusion prior to referral (data not shown). Renal function was comparable between the early-VAD and late/no-VAD groups (Table 2). We did not have enough data about iron metabolism. Right atrial pressure and pulmonary capillary wedge pressure by cardiac catheterization were significantly higher in the early-VAD group (Table S1). We speculate that hemodilution because of systemic congestion at least partially caused the anemia in the early-VAD group.

Pitfalls of Previous Risk Scores

This study revealed that the INTERMACS profile 3 or greater on admission was another good predictor of early VAD necessity, and the results were consistent with previous recommendations for VAD implantation.^{3,4} However, stratification by these profiles is largely dependent on the physician's decision. In fact, we often suggest that physicians in non-VAD institutes start inotropes before transfer of their patients in order to avoid end-organ dysfunction. Two patients in our study became 'profile 3' just before transfer because of this suggestion. We consider that a scoring system composed of factors that are independent of the decision or intervention by physicians is preferable. In this regard, the scoring system that we newly created is valuable because we selected objective parameters that can be obtained noninvasively.

Is the Current Referral Timing Appropriate?

In Japan, implantable LVADs are available only as a bridge to transplantation, so being listed for heart transplantation is required before implantable LVAD therapy can be performed. Evaluation of eligibility for heart transplant usually takes more than 1 month, and we consider that the current timing of referral is still too late for implantable LVAD therapy. The delay in referral, at least in part, caused the need for life-saving paracorporeal VAD in 7 patients as well as 1 death during evaluation. Although all-cause mortality was not significantly different between the groups stratified by the new scoring system or by INTERMACS profile (data not shown), it is not true that patients are best referred after they have accumulated a high score. We have not yet established the best timing of referral to VAD implant centers, but we would like to emphasize that the referral timing of the patients in early-VAD group was not soon enough for implantable LVAD therapy.

Study Limitations

We acknowledge that our study has several limitations. First, this study was conducted in a single center, and consequently included a limited number of patients. The timing of the decision for VAD implantation may be different in different insti-

tutes. Second, we cannot yet propose appropriate timing of referral for implantable VAD therapy, including preoperative listing for transplant. Because the timing of referral is always a matter of debate, especially for physicians in non-VAD institutes, further investigations such as prospective studies or large-scale surveys are anticipated to establish the best timing of referral. Finally, in this study advanced HF with an ischemic etiology was found in only 4 patients (8.7%), which is a remarkable feature specific to the Japanese population requiring VAD for advanced HF. Other factors may be found in other populations.

Conclusions

Low BP, low serum total cholesterol level and anemia on admission were factors that predicted the early necessity for VAD in advanced HF patients referred from non-VAD institutes. Such patients should be promptly referred for VAD implantation.

Disclosures

Grants: None. We have no conflict of interest to disclosure.

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Supplementary Files

Supplementary File 1

Table S1. Hemodynamic parameters of the 46 enrolled patients with advanced heart failure

Please find supplementary file(s);
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