Novel Scoring System to Predict Ineligibility for Bridge to Implantable Left Ventricular Assist Device as Destination Therapy Before Extracorporeal Ventricular Assist Device Implantation
– For the Coming Era of Destination Therapy in Japan –

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Background: Although destination therapy (DT) is now expected to be a promising strategy for those who are not suitable for heart transplantation in Japan, there has not been any investigation into ineligibility for bridging to implantable left ventricular assist device (I-LVAD) as DT among patients with extracorporeal LVAD.

Methods and Results: We retrospectively studied 85 patients who had received an extracorporeal LVAD. To assess ineligibility for a bridge to I-LVAD for DT, we defined DT ineligibility (DTI) as BiVAD requirement, death within 6 months, and persistent end-organ dysfunction (medium or high J-VAD risk score) at 6 months after extracorporeal LVAD implantation. DTI was recorded for 32 patients. Uni/multivariate analysis showed that smaller left ventricular diastolic dimension (<64 mm; odds ratio (OR) 4.522), continuous hemodiafiltration (OR 4.862), past history of cardiac surgery (OR 6.522), and low serum albumin level (<3.1 g/dl; OR 10.064) were significant predictors of DTI. By scoring 2, 2, 3, 4 points, respectively, considering each OR, we constructed a novel scoring system for DTI (DTI score), which stratified patients into 3 risk strata: low (0–3 points), medium (4–6 points), and high (7–11 points), from the view point of DTI risk (low 8%, medium 46%, high 93%, respectively).

Conclusions: DTI score is a promising tool for predicting ineligibility for I-LVAD as DT before extracorporeal VAD implantation. (Circ J 2016; 80: 387–394)

Key Words: Advanced heart failure; Bridge to bridge; Destination therapy; Ventricular assist device

Left ventricular assist devices (LVAD) have become a crucial option for advanced heart failure patients as a bridge to transplant (BTT), bridge to recovery, or bridge to decision and destination therapy (DT).1-5 Because of the technological improvement and device miniaturization, the survival and quality of life of patients on DT with implantable LVAD (I-LVAD) has significantly improved.6-9 DT has also become important under the circumstances of donor shortage for heart transplantation. In the USA, DT has been increasingly popular since 2010 after insurance reimbursement for HeartMate II® (Thoratec Corp, Pleasanton, CA, USA) based on the Centers for Medicare and Medicaid Services (CMS) criteria.4,10 On the other hand, DT has not yet been approved in Japan. Contraindications to BTT such as high age, persistent multi-organ dysfunction or pulmonary hypertension sometimes prevent a patient from being listed for heart transplantation even after receiving mechanical circulatory support. In Japan, when a patient with critical cardiogenic shock is refractory to optimal medical treatment and even temporary mechanical circulatory devices, extracorporeal VAD implantation is the only next step available. At present, if the patient proves to be unsuitable for BTT after a certain period of extracorporeal VAD support, there is no further treatment. It is a dismal situation for a patient being dependent on extracorporeal VAD indefinitely within the hospital and the long-term prognosis of such patients is poor owing to the high risk of infection, stroke, or bleeding complication because of the extracorporeal VAD.11

Received September 25, 2015; accepted November 5, 2015; released online December 4, 2015  Time for primary review: 33 days
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VAD implantation and severe cerebral disorder are defined as unsuitable for DT. To assess systemic organ dysfunction, the statement uses the Japan-VAD risk score (J-VAD risk score), which is a modified version of the HeartMate II risk score. The J-VAD risk score is calculated as follows: 0.0274 × age−0.723 × serum albumin (g/dl)+0.74 × serum creatinine (mg/dl)+1.136 × PT-INR+0.807 × (0 or 1) (dependent on the number of I-LVAD cases of the center).

According to the J-VAD risk score, patients are classified as low (<1.58), medium (1.58–2.48) or high risk (>2.48). The statement recommends that the J-VAD risk score should be low or medium in patients <65 years, but should be exclusively low for those ≥65 years to satisfy DT eligibility.

Considering this recommendation, we defined patients who were ineligible for the bridge from extracorporeal VAD to I-LVAD for DT as follows: (1) those who died within 6 months post-LVAD; (2) those requiring BiVAD support; and (3) those with persistent organ dysfunction (medium or high J-VAD risk score) after 6 months’ LVAD support.

Although BiVAD requirement is not an absolute contraindication for BTT, we consider BiVAD patients as DTI because extracorporeal BiVAD patients generally have a poor prognosis unless right ventricular assist device (RVAD) is able to be removed afterward. Moreover, there has not been a definite method of predicting weaning from RVAD at the time of BiVAD implantation. Without knowing who can be successfully weaned from RVAD, we cannot help but hesitate to implant extracorporeal RVAD in transplant-ineligible patients because implantable RVAD system or total artificial heart for DT use is not yet available. Even if a LVAD is converted into an implantable type, the RVAD system remains extracorporeal and the patient is bound to be in hospital indefinitely with miserable quality of life.

We arbitrarily set the time limit of conversion to I-LVAD for DT at 6 months, because complications associated with extracorporeal VAD implantation and severe cerebral disorder are defined as unsuitable for DT. To assess systemic organ dysfunction, the statement uses the Japan-VAD risk score (J-VAD risk score), which is a modified version of the HeartMate II risk score. The J-VAD risk score is calculated as follows: 0.0274 × age−0.723 × serum albumin (g/dl)+0.74 × serum creatinine (mg/dl)+1.136 × PT-INR+0.807 × (0 or 1) (dependent on the number of I-LVAD cases of the center).

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Results

Clinical Outcomes
Among the 85 patients who had received extracorporeal VAD, DTI was recorded for 32 patients: 18 patients (56.3%) required BiVAD support, 15 patients (46.9%) died within 6 months (5 received BiVAD), and 6 patients (18.8%) showed persistent organ dysfunction with medium or high J-VAD risk score at 6 months after extracorporeal VAD implantation (2 received BiVAD).

Among the non-DTI group, 12 patients (22.6%) were successfully bridged to I-LVAD within 6 months; 1 patient (1.9%) underwent heart transplantation and 7 patients (13.2%) were successfully weaned from extracorporeal VAD: 33 patients (62.3%) had low J-VAD risk scores on extracorporeal VAD.
at 6 months (Figure 1). The most common reason why extracorporeal VAD was not converted to I-LVAD in these patients was that I-LVAD had not been approved at the time. In some of them, local cannula site infection was the reason for continuing support on extracorporeal VAD, but we did not include them in the DTI group. In fact, local infection could be successfully managed by appropriate treatment in some cases, and we later converted extracorporeal VAD to I-LVAD.

Preoperative Parameters
The mean age was 37.2±14.1 years and there were 61 (71.8%) males. The DTI group had higher body mass index (BMI), higher incidence of past history of cardiac surgery, CHDF, percutaneous cardiopulmonary support (PCPS) and INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) profile 1 compared with the non-DTI group (Table 1). Hemoglobin and serum albumin were significantly lower (P<0.05, respectively) in the DTI group. Lower pulmonary capillary wedge pressure (PCWP) and smaller left ventricular diastolic dimension (LVDd) were observed in the DTI group (P<0.05) (Table 2).

Univariate Analysis for DTI and Selection of Factors for Multivariate Analysis
Among all baseline variables, 9 factors, comprising INTERMACS profile 1, past history of cardiac surgery, PCPS (+), CHDF (+),
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With a cutoff of 7 points, sensitivity and specificity were 0.406 and 0.981, respectively (Figure 2).

The incidence of DTI was 8% (3/36) in the low-risk group, 46% (16/35) in the medium-risk group and 93% (13/14) in the high-risk group. The number of deaths was 1, 6 and 8 in each group respectively. Kaplan-Meier analysis showed significantly poor survival among those in the high DTI score group within 6 months after extracorporeal VAD implantation (Figure 3).

**Discussion**

Our study demonstrated that LVDd <64 mm, CHDF (+), past history of cardiac surgery and serum albumin <3.1 g/dl were independent predictors for DTI. The DTI score, which was calculated by the existence/absence of these 4 factors, was useful for stratifying patients receiving extracorporeal VAD from the viewpoint of the probability of DTI.
Reason for Stratifying High-Risk Patients for DT Among Extracorporeal VAD Patients

Because prospective trials for DT have not been performed in Japan to date, we retrospectively investigated patients who had received extracorporeal VAD implantation for screening those at high risk for bridge to I-LVAD as DT. Owing to its high cost and limited sources of I-LVAD, it will be necessary to select patients who can receive optimal benefit from DT.

On the other hand, the prognosis and quality of life are extremely poor for those who are destined to live with extracorporeal VAD implantation indefinitely. Therefore, it will also be important to ascertain those who cannot be bridged to heart transplantation or I-LVAD (ie, DTI). In such a population, extracorporeal VAD implantation itself may be potentially contraindicated. Especially in aged (>65 years) patients with INTERMACS profile 1, extracorporeal VAD implantation as a bridge to DT should be cautiously indicated. Because the age is absolutely unmodifiable, there is no chance of using VAD for BTT under the current policy for Japanese heart transplantation listing.

Evaluation for DTI

Because of the high incidence of device-related complications during extracorporeal VAD support,1 bridge to I-LVAD is generally recommended within several months after complications such as infection, thrombosis and bleeding emerge. For the present study, we set the time limit of bridge to I-LVAD for DT at 6 months, and needless to say patients must be alive during this observational period.

Next, persistent systemic organ dysfunction is a substantial barrier for DT. Although there are criteria for DT LVAD eligibility in the CMS criteria, no statements have been made about evaluation for organ dysfunction when selecting DT patients.15 This is not surprising because DT in origin is a therapeutic option for advanced heart failure with irreversible end-organ dysfunction. However, the academic consensus statement for DT eligibility in Japan includes the J-VAD risk score to secure good prognosis of DT, and therefore we applied this score to evaluate patients’ end-organ dysfunction.

Moreover, we defined those who received BiVAD support as ineligible for DT. There is not a systematic tool available for predicting the probability of weaning from RVAD before surgery. Long-term support by RVAD was reported to have a high occurrence of multi-organ failure, sepsis, and thrombosis,17 and was associated with poor prognosis.18 Currently, there is no insurance coverage for implantable RVAD or total artificial heart in Japan, and indefinite support by extracorporeal RVAD is unbearable for anybody.

Significance of Each Parameter of DTI Score

First of all, it is important to determine the characteristics of those who die early (within 6 months in this study) after extracorporeal VAD implantation. The factors for early death after VAD implantation have been reported in several papers, although “early” was variably defined among the studies. We previously reported the TVAD score, which efficiently predicts 1-year survival with LVAD support.19 Our new DTI score included same factors of the TVAD score: lower albumin level and smaller LVDd, indicating that these 2 parameters play a key role in post-LVAD survival.

Preoperative low serum albumin level is known as an independent risk factor for mortality after cardiac surgery.20,21 It was also reported that a low level of serum albumin was associated with postoperative acute renal failure and prolonged hospitalization after LVAD implantation.22 We reported that a perioperative low serum albumin level predicted the recovery of exercise tolerance,2 and was a risk for driveline infection after I-LVAD surgery.24 Low serum albumin may be a mixed consequence of malnutrition,25 congestive hepatopathy,26 or prolonged systemic inflammation.25,27 The causal relationship between albumin level and clinical outcome has long been a matter of debate, but the above-referenced results suggest that low serum albumin is clearly associated with the mortality and morbidity of patients with LVAD implantation. Consequently, most of the scoring systems, including the J-VAD score, to predict post-LVAD survival adopted serum albumin level as a crucial surrogate marker. We have previously reported that postoperative albumin levels significantly correlated with preoperative levels 1 month after VAD implantation.23 Similarly, there was also a significant correlation between preoperative albumin levels and those at 6 months after operation (r=0.261, P=0.036) in the present study. As a result, those who had a lower serum albumin before surgery were likely to have a higher J-VAD score after VAD implantation in this study (r=−0.441, P<0.01).

We previously reported that a smaller LVDd was a risk factor for BiVAD requirement.26 Smaller LVDd was also associated with late-onset RV failure after I-LVAD implantation.29 Because perioperative as well as postoperative RV failure is accompanied by poorer prognosis.30,31 our result that smaller LVDd is a risk factor for post-LVAD survival and is a barrier for bridge to DT among patients with extracorporeal VAD is reasonable.

Renal failure and elevated right atrial pressure are known as significant risk factors for mortality after VAD implantation.5,32 Elevated right atrial pressure itself is reported as a risk factor for renal failure.25 Those who needed CHDF must have had both renal failure and high right atrial pressure, but CHDF by itself was not a risk factor for survival after VAD implantation in our hands.19 However, we reported that CHDF was a significant predictor of BiVAD necessity probably because of the severe RV dysfunction.28 Also, it is not surprising that patients who require CHDF preoperatively are at high risk of post-LVAD prolonged renal dysfunction. Therefore, it is pertinent that CHDF is one of the DTI parameters. We previously demonstrated that post-LVAD recovery of end-organ function was strongly dependent on the patient’s age, although the data were from relatively younger patients.33 Preoperative renal dysfunction may be more difficult to recover in the aged population that would be the main target for DT.

Past history of cardiac surgery has been generally considered as a risk factor for postoperative wound infection or bleeding.34 The 6th INTERMACS annual report stated that a history of cardiac surgery was a significant risk factor for early death after VAD implantation.3 Patents undergoing cardiac reoperation sometimes have complications directly related to sternal reentry, including delayed wound healing, surgical site infection, and sepsis. Besides, past cardiac reoperation is reported as a risk factor for RVAD requirement during LVAD implantation,35 probably because of pericardial constriction, which may result in a high risk for DT.

There have been several scoring systems for assessing postoperative mortality and complications, including the HeartMate II risk score,14 DT risk score,36 the Seattle Heart Failure Model17 or the Model for End Stage Liver Disease score.38 All these scoring systems are for patients with de novo I-LVAD implantation for DT, and there is no scoring system for assessing ineligibility for DT among patients with extracorporeal VAD. Considering that 93% of the high-risk group were clas-
Our novel DTI score was useful for stratifying the possibility of bridge to I-LVAD for DT among patients with extracorporeal VAD implantation itself may not be indicated in such a population because there is little chance of providing any further treatment. In this regard, the DTI score, which consists of objective parameters that can be obtained noninvasively, is useful for screening those high-risk patients. Especially among the aged population with cardiogenic shock, extracorporeal VAD implantation may not be indicated for those with a high DTI score.

Study Limitations
The present study had a small number of subjects at a single center, and may have a potential selection bias. The definitions of DTI we described in the present study are the most essential conditions for DT. Practically, there are other ineligibility factors such as device infection, physical frailty or stroke at a time of bridge to I-LVAD. We could not assess these factors minutely in the present study because they are difficult to quantify appropriately and there would be many confounding factors. In the future, it will be necessary to inspect these factors thoroughly. Perioperative BiVAD implantation would not necessarily be a contraindication for DT. If a patient is over 65 years, there is no chance of using VAD as BTT under the current policy for Japanese heart transplantation listing. In contrast to organ failure, age is absolutely unmodifiable. Of course there may be a chance for RVAD removal in such cases, but as mentioned we do not know yet how to predict the possibility of RVAD removal. We consider it too risky to put BiVAD in older patients who have no likelihood of receiving a transplant in the future, and it is also miserable that older patients with extracorporeal RVAD are destined to stay in hospital indefinitely.

If a patient with multiple organ failure is under the age of 65 years, there may be a chance for BTT after extracorporeal VAD implantation because organ failure is by itself a modifiable issue for transplant listing. That is the usual policy known as “bridge to decision”, and there is nothing new to be discussed. So let us discuss a patient with a recent (<5 years of complete remission) history of cancer going into cardiogenic shock. It may be justified to use extracorporeal VAD (or even BiVAD) in this patient. If the patient is weaned from RVAD support after a certain period of extracorporeal BiVAD treatment, then we will consider bridge for DT. In this context, BiVAD implantation is reasonable as the initial therapy.

Even if RVAD cannot be weaned, the patient can possibly be listed for transplant after keeping the person in the hospital for a couple of years to confirm that cancer does not recur. Therefore, we may not exclude the BiVAD strategy in younger patients, and DT eligibility may be harder to define. However, the story is not easy after successful listing. We have to keep in mind that the patient could wait another 3 years or more after listing before receiving a transplant under the current Japanese policy that does not give a priority for BiVAD patients. In total, the patient will have to wait on BiVAD for 5–6 years. It is definitely a tough decision. We consider the BiVAD option is still challenging, even for younger patients, when they have a recent history of cancer. Finally, although we defined the time limit of conversion to implantable LVAD at 6 months, there may be some cases when the patient can be converted to I-LVAD more than 6 months from extracorporeal VAD implantation.

Conclusions
Our novel DTI score was useful for stratifying the possibility of bridge to I-LVAD for DT among patients with extracorporeal VAD implantation because organ failure is by itself a modifiable issue for transplant listing. That is the usual policy known as “bridge to decision”, and there is nothing new to be discussed. So let us discuss a patient with a recent (<5 years of complete remission) history of cancer going into cardiogenic shock. It may be justified to use extracorporeal VAD (or even BiVAD) in this patient. If the patient is weaned from RVAD support after a certain period of extracorporeal BiVAD treatment, then we will consider bridge for DT. In this context, BiVAD implantation is reasonable as the initial therapy.

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Disclosures
None.

References
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Real VAD. In aged patients who have high DTI scores with cardiogenic shock, the indication for extracorporeal VAD implantation itself should be estimated with caution.