ELSEVIER

Importance of Early Appropriate Intervention Including Antibiotics and Wound Care for Device-Related Infection in Patients With Left Ventricular Assist Device

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ABSTRACT

Introduction. A left ventricular assist device (LVAD) is essential for treating patients with advanced heart failure. However, LVAD-related infection is a significant cause of mortality and morbidity, with bloodstream infection (BSI) especially associated with high mortality. We investigated the incidence of infectious complications in patients who received an LVAD and evaluated the effects of early and appropriate intervention for LVAD-related infection.

Method. We retrospectively reviewed 27 consecutive patients who underwent continuous-flow LVAD (CF-LVAD; n = 16) or pulsatile-flow LVAD (PF-LVAD; n = 11) implantation at the National Cerebral and Cardiovascular Center between April 2011 and March 2013. Incidences of LVAD-related infections, such as drive-line infection in patients with CF-LVAD, cannula infection in patients with PF-LVAD, and BSI in patients with both types, were examined (follow-up period, 342 ± 229 days). The mandatory antibiotic prophylaxis protocol at our institution includes teicoplanin (400 mg) 2 days before LVAD implantation and doripenem (1000 mg) within 1 hour of skin incision. In addition, the driveline exit sites undergo sterile cleansing with diluted hydrogen peroxide and placement of an antimicrobial occlusive dressing for wound care, with dressing changes performed 2–3 times per day.

Results. More than 90% of all patients suffered from a drive-line infection within 12 months after LVAD implantation. However, BSI developed in only 12.5% of CF-LVAD and 10% of PF-LVAD patients within 12 months (log-rank test; $P = .875$).

Conclusions. LVAD-related infections, such as drive-line and cannula infections, were common, whereas the incidence of BSI was low in our LVAD-implanted patients. Our results highlight the importance of early and appropriate intervention including antibiotics and wound care for device-related infections for reducing the incidence of potentially fatal BSI.

A LEFT ventricular assist device (LVAD) has become an essential therapeutic option for management of advanced heart failure. However, several important clinical issues remain to be resolved. LVAD-related infection can be a serious clinical issue for LVAD patients, with bloodstream infection (BSI) showing the highest incidence of mortality [1,2]. Findings from the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial revealed that BSI was the leading cause of death in LVAD patients and accounted for 41% of all deaths [3]. Also, in the HeartMate II bridge-to-transplant study, BSI affected 20% of patients with a continuous-flow device and accounted for 20% of deaths occurring within 6 months [4]. The etiology of device-related infection is multi-factorial. In addition to drive-line surface characteristics, patient comorbidities, nature of the infecting micro-organism (virulence and ability to form biofilm), and perioperative and postoperative care (eg, administration of appropriate antibiotics and wound care) play important roles [5].

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0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.11.106

A device-related infection is a common complication that can affect heart transplantation and is also a major cause of death. In the present study, we investigated the incidence of infectious complications in patients who received a continuous-flow implantable LVAD (CF-LVAD) or pulsatile-flow extra-corporeal LVAD (PF-LVAD) as a bridge to heart transplantation. In addition, we evaluated the effects of early and appropriate intervention, including antibiotics and wound care, on LVAD-related infection.

METHODS

Study Design

We retrospectively reviewed 27 consecutive patients who received implantation of a PF-LVAD (n = 11) or CF-LVAD (n = 16) at the National Cerebral and Cardiovascular Center between April 2011 and March 2013. Variables examined included demographics (age and gender) and the etiology of heart failure, whereas the incidences of BSI and drive-line infection were also investigated (follow-up period, 342 ± 229 days), with organisms obtained from bloodstream samples used to assess drive-line infections in more detail. The study protocol was approved by the Ethics Committee of our institution.

Outcome Definitions

The criteria used for infection were clinical infection accompanied by pain, fever, drainage, and/or leukocytosis treated using antimicrobial agents. A positive culture from the infected site, organ, or blood was required unless strong clinical evidence indicated the need for treatment despite negative culture findings.

We referred to the criteria of the American College of Chest Physicians and Society of Critical Care Medicine (ACCP/SCCM) for treating BSIs, which state that the following 2 or more conditions be found: (1) temperature > 38°C or < 36°C, (2) heart rate > 90 beats/min, (3) respiratory rate > 20 breaths/min or $PaCO_2$ < 32 mm Hg, and (4) white blood cell count 12,000 cells/mm^3, 4000 cells/mm^3, or 10% immature bands resulting from a confirmed infectious process [6]. In addition, using the Hospital Infection Control Practices Advisory Committee (HICPAC) surgical site infection criteria template, drive-line (and LVAD pocket) infections were defined as either: (1) purulent drainage from the drive-line exit site (or device pocket), (2) organisms isolated from an aseptically obtained culture of fluid or tissue from the drive-line exit site (or device pocket), or (3) abscess or other evidence of infection involving the drive-line tract (or device pocket) found on direct examination, during reoperation, or in a histopathologic or radiological examination [7].

Statistical Analysis

Baseline clinical characteristics were assessed using Wilcoxon test for continuous variables, with a chi-square test used for categorical variables. Kaplan-Meier estimates of freedom from infectious complications were performed for first analyzing bloodstream and drive-line infections in the overall cohort by device type. Then those results were compared using a log-rank test. For all analyses, $P < .05$ was considered to indicate statistical significance. Analyses were conducted using JMP software, version 10 (SAS Institute Inc., Cary, North Carolina, United States).

Culture Protocol and Wound Care

The mandatory antibiotic prophylaxis protocol at our institution includes teicoplanin (400 mg) 2 days before LVAD implantation and doripenem (1000 mg) within 1 hour of skin incision. Antibiotic drugs are redosed based on their pharmacokinetic properties in the operation room. Doripenem (1000 mg, 3 times daily) is administered until extubation after sterna closure, whereas teicoplanin (400 mg, once daily) and micafungin (150 mg, once daily) are administered until healing of the wound. Furthermore, routine cultures are performed within 1 week from the day of LVAD implantation, with additional cultures done where there is clinical suspicion of infection, pain in the exit site, acute neutropenia or leukocytosis, or temperature <36°C or >38°C.

Naturally, we consider that careful sterile management of the exit site is important. The drive-line exit sites receive sterile cleansing with diluted hydrogen peroxide and placement of an antimicrobial occlusive dressing for wound care, with dressing changes performed 2–3 times per day. All LVAD-related infections are treated with adequate systemic antibiotics including teicoplanin, vancomycin and linezolid as soon as possible and for the proper dosing periods. Early de-escalation of antimicrobials, based on Gram staining of an exit site sample and blood culture results, is performed. Antibiotics are dosed according to renal function when appropriate.

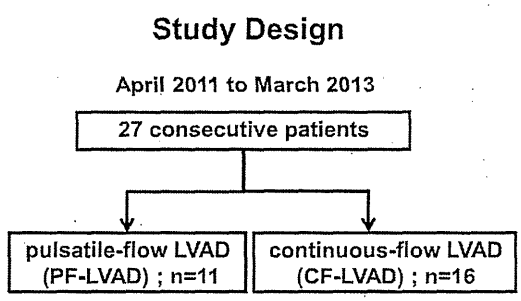

Fig 1. Study design.

RESULTS

Infectious Outcomes

Sixteen patients received a CF-LVAD and 11 a PF-LVAD during the study period (Fig 1). The follow-up period for the present patients was 342 ± 229 days. Baseline clinical characteristics were similar between the groups (Table 1).

Infectious event-free days stratified by device type were reviewed for BSI and drive-line–related infection (Fig 2). Although nearly all patients in both groups suffered from an

Table 1. Baseline Characteristics of Patients Stratified by LVAD Type

	PF-LVAD (n = 11)	CF-LVAD (n = 16)	*P*
Age (y)	34.6 ± 9.6	37.5 ± 11.9	.51
Gender	Male: 7 (63.6%)	Male: 16 (100%)	.0188
DCM	6 (54.5%)	9 (56.3%)	.93
dHCM	2 (18.2%)	1 (6.3%)	.35
ICM	1 (9.1%)	3 (18.8%)	.51
2nd CM	1 (9.1%)	3 (18.8%)	.51
PPCM	1 (9.1%)	0 (0%)	.23
Follow-up (d)	277 ± 182	387 ± 228	.23

Note: Comparisons between 2 groups were done using Wilcoxon test or a chi-square test, with $P < .05$ considered to be significant.

Abbreviations: DCM, dilated cardiomyopathy; dHCM, dilated-phase hypertrophic cardiomyopathy; ICM, ischemic cardiomyopathy; 2nd CM, secondary cardiomyopathy; PPCM, peripartum cardiomyopathy.

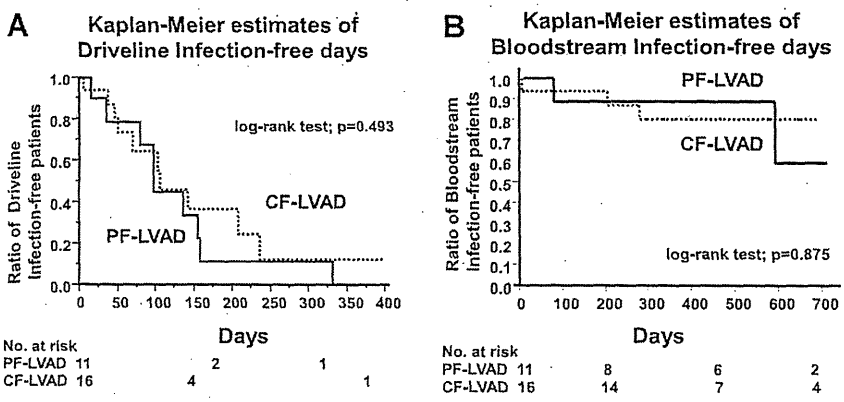

Fig 2. (A) Kaplan-Meier estimates of freedom from drive-line infection stratified by device type. (B) Kaplan-Meier estimates of freedom from BSI stratified by device type.

exit site infection within 12 months after LVAD implantation, BSI developed in only 12.5% of the CF-LVAD and 10% of the PF-LVAD cases within 12 months (log-rank test; $P = .875$). Overall, a total of 5 (18.5%) patients developed BSI. Furthermore, 2 (40%) had sepsis develop to severe sepsis, although none of those cases was fatal.

Cultured Organisms

Bacterial profiles were generated from the results of examinations of both blood cultures and cultures of discharge obtained from the drive-line or cannula exit sites (Table 2). Bacterial organisms cultured from blood samples were found to be methicillin-resistant *Staphylococcus aureus*

Table 2. Organisms Detected From Sites of Drive-line Infection

	PF-LVAD			CF-LVAD	
	n	%		n	%
GPC			GPC		
MRSA	14	4.3	MRSA	48	11.9
MSSA	43	13.1	MSSA	39	9.7
S anginosus	0	0.0	*S anginosus*	5	1.2
S capitis	36	11.0	*S capitis*	10	2.5
S caprae	1	0.3	*S caprae*	5	1.2
S epidermidis	19	5.8	*S epidermidis*	45	11.1
S haemolyticus	0	0.0	*S haemolyticus*	4	1.0
S lagunensis	32	9.8	*S lagunensis*	26	6.4
S schleiferi	8	2.4	*S schleiferi*	0	0.0
α-Streptococcus	4	1.2	*α-Streptococcus*	9	2.2
Staphylococcus species	3	0.9	*Staphylococcus* species	14	3.5
GPR			GPR		
Corynebacterium	32	9.8	*Corynebacterium*	28	6.9
GNR			GNR		
P aeruginosa	37	11.3	*P aeruginosa*	0	0.0
K pneumonia	23	7.0	*K pneumonia*	39	9.7
K oxytoca	11	3.4	*K oxytoca*	0	0.0
E coli	28	8.6	*E coli*	38	9.4
Enterobacter aerogenes	0	0.0	*Enterobacter aerogenes*	16	4.0
Enterobacter cloacae	8	2.4	*Stenotrophomonas maltophilia*	7	1.7
Enterococcus faecalis	8	2.4	*Enterococcus faecalis*	22	5.4
Morganella morganii	0	0.0	*Morganella morganii*	18	4.5
Citrobacter freundii	0	0.0	*Citrobacter freundii*	18	4.5
C koseri (ESBL)	11	3.4	*C koseri (ESBL)*	0	0.0
P fluorescens	0	0.0	*P fluorescens*	4	1.0
Serratia marcescens	9	2.8	*Serratia marcescens*	9	2.2
Fungi			Fungi		
Fungi	0	0.0	Fungi	0	0.0

Abbreviations: GPC, gram positive cocci; MSSA, methicillin-sensitive Staphylococcus aureus; MRSA, methicillin-resistant Staphylococcus aureus; GPR, gram positive rod; GNR, gram negative rod; ESBL, extended spectrum beta lactamase.

(MRSA; n = 1), *Pseudomonas aeruginosa* (n = 1), *Staphylococcus bovis* (n = 1), and *Staphylococcus epidermidis* (n = 2). More than 60% of the BSI and drive-line–related infections were due to Gram-positive cocci (GPC), such as *Staphylococcus* species. In contrast, gram-negative rods such as *Pseudomonas*, *Escherichia*, and *Klebsiella* species were rarely isolated from blood and exit site samples.

DISCUSSION

We reviewed device-related infectious complications that occurred in 27 LVAD patients treated at our institute. Our results showed that exit site infections developed as early as 30 days postoperatively and more than 90% of all patients suffered from an infection within 12 months after LVAD implantation. However, despite the high frequency of exit site infections, only a small percentage of these patients developed BSI (CF-LVAD 12.5% and PF-LVAD 10% at 12 months postoperatively). In addition, drive-line and cannula exit site culture profiles disclosed that most of the bacterial organisms were GPC, such as *Staphylococcus* species, which are resident flora of the skin. These results suggest that exit site infections in patients with an LVAD are nearly inevitable, because the source of infection in our cases was mainly GPC from resident flora that cannot be completely eradicated. Exit site infections are thought to gradually progress over time, resulting in BSI, which is related to high mortality in patients with an LVAD. However, we found that the rate of BSI incidence in our patients was significantly lower as compared with that of exit site infection within 12 months after surgery, indicating that not all exit site infections worsen to become BSI and can often be treated by various clinical means. At our institution, antibiotic prophylaxis including teicoplanin (400 mg) before LVAD implantation and doripenem (1000 mg) within 1 hour of skin incision is mandatory. Furthermore, doripenem (1000 mg, 3 times daily) is administered until extubation after sterna closure, and teicoplanin (400 mg, once daily) and micafungin (150 mg, once daily) until healing of the wound. Our strategy is not only prevention of infection during the perioperative period, but also strict wound site control including surveillance cultures, wound care, and proper use of antibiotics. Our LVAD care team, which consists of surgeons, cardiologists, advanced practice nurses, dieticians, and pharmacists, make great effort in regard to exit site wound care from a variety of perspectives, which may contribute to lowering the development of systemic BSI from localized exit site infections.

In conclusion, LVAD-related infections including drive-line infection are common in LVAD-implanted patients, with GPC, especially staphylococci species, the representative pathogens and the drive-line exit site the major gate of entry. Our findings highlight the importance of early and appropriate intervention including antibiotics and wound care for device-related infections to decrease possibly fatal BSI cases.

Limitations

Our study had some limitations, including its retrospective nature, which may also be associated with data collection bias, the single-center analysis, which may have influenced outcomes, and the nonrandomized small sample size.

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実地医家による心不全診療実践の具体的ポイントとコツ

補助人工心臓治療と心臓移植

—現状と展望—

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はじめに

従来の治療抵抗性の末期心不全に対して選択しうる治療手段として，補助人工心臓（VAD）と心臓移植があり，心臓移植は欧米を中心に，年間3,700～3,800例に施行されている．また，VADでは近年非拍動流植込型補助人工心臓が臨床応用されるようになり，心臓移植へのブリッジ（BTT）のみならず，心臓移植の適応のない患者に対していわゆるdestination therapy（DT）としても積極的に用いられるようになっている．わが国においては，1997年10月に臓器の移植に関する法律が施行され，この法律に基づく心臓移植が1999年2月に行われ，徐々に施行数は増加したが，年間施行10例前後であった．2009年に家族同意により脳死者からの臓器提供を可能とする改正臓器移植法が制定され，2010年7月から施行された．この結果，年間30例程度の施行状況となっているが，心臓移植希望者数も増加しているのが現状である．わが国におけるVADおよび心臓移植の現状と展望について概説する．

わが国における心臓移植[1～5]

1999年2月臓器移植法に基づく心臓移植が行われてから2013年9月までに175名の心臓移植が施行された．そのなかで，2013年8月16日までに施行された170例で検討すると，臓器移植法が改正される2010年7月までは，年間11例までであったが，改正後施行数は年間30例前後と著明に増加し，改正後3年1ヵ月で法改正前69例を超える101例となった（図1）．施行例の性別は，男性75%，女性25%で，年齢は10歳未満から62（平均37.5）歳で，20歳

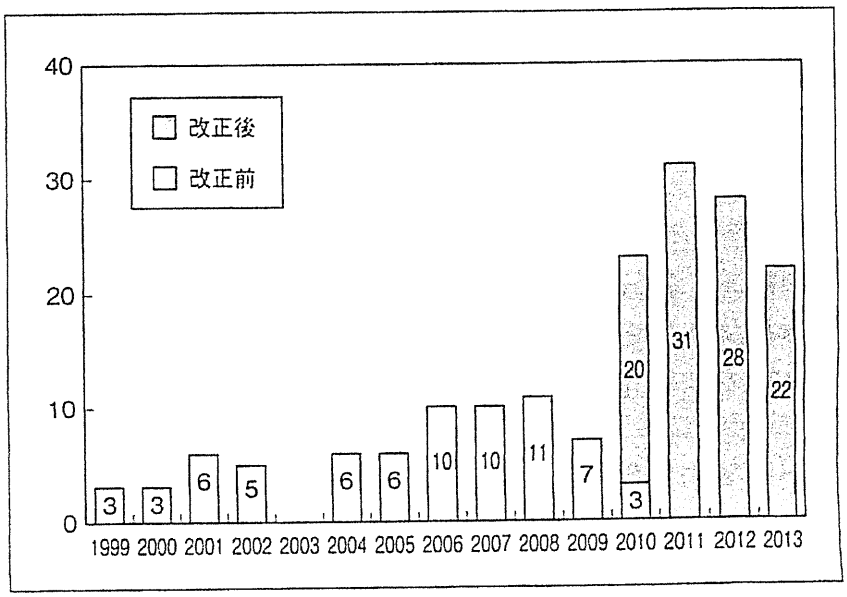

図1　わが国における心臓移植の推移

- 従来の治療抵抗性の末期心不全に対して選択しうる治療手段として，補助人工心臓（VAD）と心臓移植がある．
- わが国の心臓移植は，臓器移植法改正後施行数が増加しているが，現状では年間30例前後である．
- 近年非拍動流植込型VADが臨床応用され，欧米では心臓移植へのブリッジ（BTT）のみならず，いわゆるdestination therapy（DT）としても用いられている．

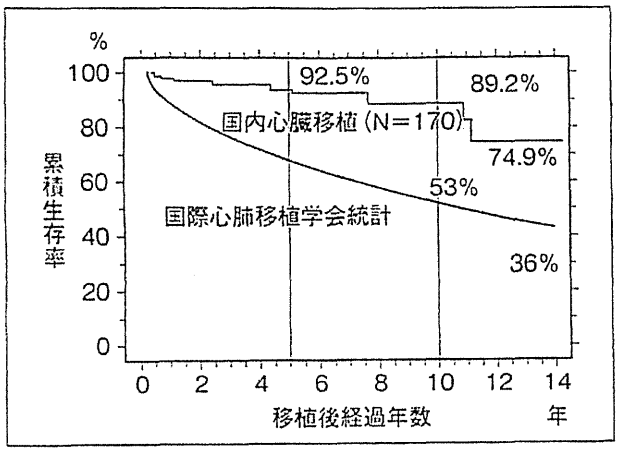

図2　わが国における心臓移植の累積生存率
（文献3）より引用）

代から50歳代がそれぞれ20%前後であった．また，原因疾患は，特発性拡張型心筋症が69%と最も多く，虚血性心筋症は8%のみであった．

待機状況は，10歳未満の1例のみStatus 2で，ほかはすべてStatus 1であった．また，Status 1の状況をみると，強心剤によるものは9%のみで，91%は各種の補助人工心臓によるブリッジ例であった．用いられた補助人工心臓の55%はニプロ-東洋紡左室脱血型であるが，改正臓器移植法施行後は無拍動流植込型左心補助人工心臓が増加している．また，Status 1での待機期間は29～1,707（平均855）日で，1年以内は8%のみで2～3年の待機症例が50%を占めている．また，法改正後も待機日数は短縮していない．ブリッジ例155例の補助期間は21～1,738（平均861）日で，2～3年の補助が41%と最も多く，4年以上も5%となっている．多くの移植手術において，術式はModified-Bicaval法が，心筋保護液はCelsior液が用いられている．免疫抑制療法としては，全例カルシニューリンインヒビター（最近ではタクロリムスが多い），代謝拮抗薬（主としてミコフェノール酸モフェチル）およびステロイドを用いる三者併用療法が行われ，最近保険承認されたエベロリムス移植後冠動脈病変，腎機能障害，悪性腫瘍などへの対応として用いられている．心臓移植例の10年の生存率は89.2%と国際心肺移植学会レジストリーより良好である（図2）．また，2例が14年以上生存し，100例以上が社会復帰（主婦，パートなどを含む）している．死亡は11例で，死因は感染症，多臓器不全，移植後冠動脈病変，胃癌，腎不全などである．

わが国における補助人工心臓治療

心臓ポンプ機能を代行する人工心臓には，自己心を切除し血液ポンプを埋め込む全置換型人工心臓total artificial heart（TAH）と，自己心を温存し血液ポンプを自己心近傍に設置する補助人工心臓ventricular assist system（VAS）があり，血液ポンプとしては拍動流型と連続流型がある．また，VASには血液ポンプの設置部位から体外設置型と植込型に分けられる．

現在わが国では体外設置型VASとしてニプロ-東洋紡VAS（図3）が用いられている．左心補助では主として左室脱血方式が主に用いられ，高度右心不全例では，右房/右室—主肺動脈間の右心補助人工心臓（RVAS）の装着が必要となる．植込型LVASは在宅治療が可能であり，第一世代として拍動型のNovacorとHeart-

- わが国における心臓移植の原因疾患は，特発性拡張型心筋症が多く，虚血性心筋症は少数である
- わが国の心臓移植の施行数は少ないが，10年の生存率は89.2%と国際心肺移植学会レジストリーより良好である．
- わが国の心臓移植は長期待機を必要とするため，補助人工心臓によるブリッジ例が大部分を占めている．

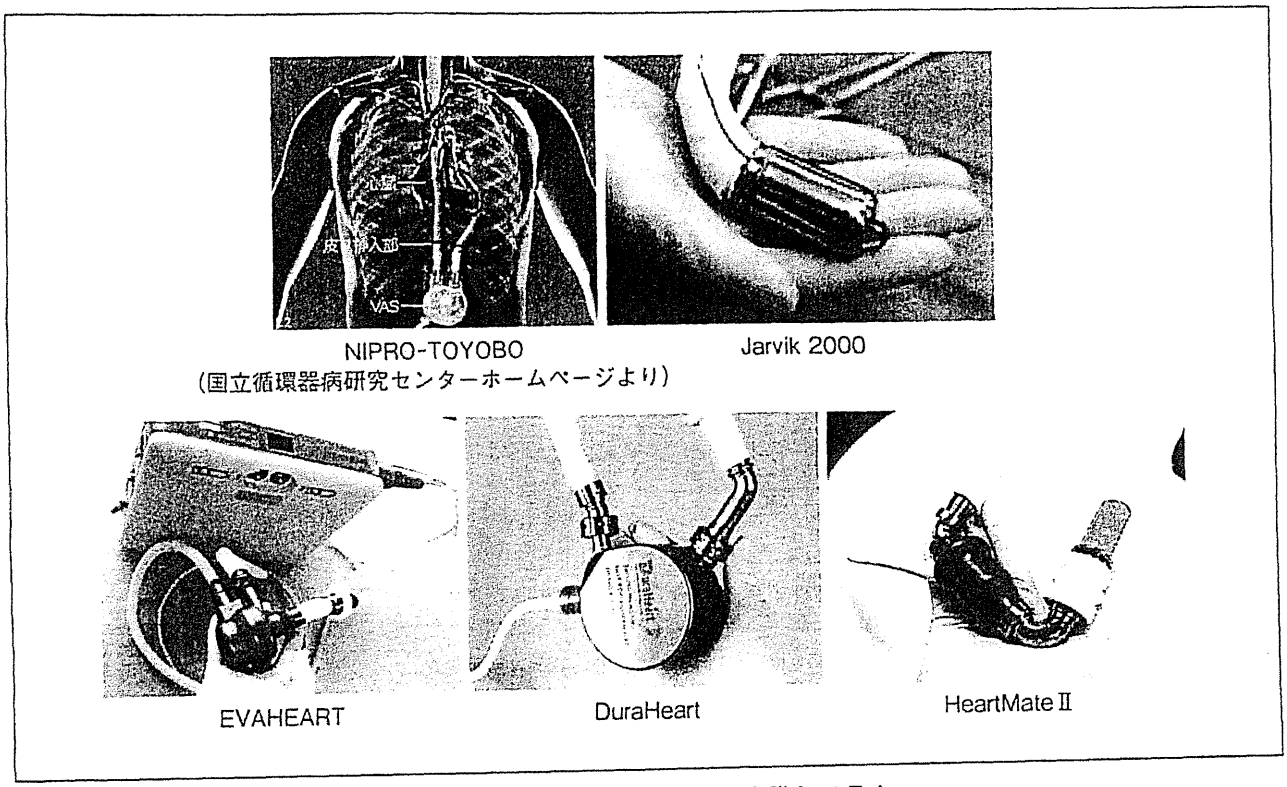

図3　わが国における補助人工心臓システム

Mate-Iが臨床応用された．その後，次世代型として，長期使用可能で体格の小さな人への適応を考慮した連続流血液ポンプを用いたシステムの開発・臨床応用が行われるようになった．2011年4月には，わが国で開発された遠心ポンプを用いたシステム(EVAHEART，DuraHeart)が心臓移植へのブリッジとして保険償還された(図3)．その後，米国で開発された軸流ポンプを用いたシステムのHeartMate Ⅱが2013年4月に保険償還され，2014年1月にはJarvik 2000が保険償還される予定である(図3)．

補助人工心臓の適応は，高度重症心不全が対象となるが，従来急性発症の症例に対して，体外設置型の適応が行われてきた．しかし，心臓移植が定着するにつれ，慢性心不全の急性増悪例など心臓移植へのブリッジとして多く用いられるようになってきた．適応判定においては血行動態指標に加え重要臓器など全身状態への配慮が重要で，不可逆性の腎・肝障害，敗血症，中枢神経疾患，高度の出血傾向を伴う症例は除外される(表1)．また，現状の植込型補助人工心臓の適応は心臓移植へのブリッジであり，心臓移植の適応検討が必須である．さらに，本人および家族へのインフォームドコンセントが重要である．さらに，適応のタイミングも重要である．最近では，INTERMACS Profile(表2)

表1　植込型補助人工心臓適応基準

1. 対象疾患・病態	
心臓移植適応基準に準じた末期的重症心不全で，対象となる基礎疾患は，拡張型および拡張相肥大型心筋症，虚血性心筋疾患，弁膜症，先天性心疾患，心筋炎後心筋症などが含まれる	
2. 選択基準	
1) 心機能	NYHA：クラスⅢ～Ⅳ(Ⅳの既往あり)
2) ステージ	D (重症の構造的疾患があり，最大限の内科治療にもかかわらず，安静でも明らかな心不全症状がある患者)
3) 薬物治療	ジギタリス・利尿薬・ACE 阻害薬・ARB・硝酸塩・β遮断薬などの最大限の治療が試みられている
4) 強心薬・補助循環	ドブタミン・ドーパミン・エピネフリン・ノルエピネフリン・PDE Ⅲ阻害薬などに依存，または IABP，体外設置型補助人工心臓などに依存
5) 年齢	65 歳以下が望ましい(身体能力によっては 65 歳以上も考慮する)
6) BSA	システムにより個別に規定
7) 血行動態	stage D, NYHA クラスⅣの既往
8) 条件	ほかの治療では延命が望めず，また著しく QOL が障害された患者で，治療に参加することで高い QOL が得られ，長期在宅治療が行え，社会復帰が期待できる患者
9) 治療の理解	補助人工心臓の限界や併発症を理解し，家族の理解と支援が得られる
3. 除外基準	
1) 感染症	重症感染症
2) 呼吸器疾患	重度の COPD 高度の肺高血圧症 30 日以内に発症した肺動脈塞栓症
3) 循環器疾患	開心術後早期(2 週間程度) 治療不可能な腹部動脈瘤や重度の末梢血管疾患 胸部大動脈瘤，心室瘤，心室中隔破裂 中等度以上の大動脈弁閉鎖不全症 胸部大動脈に重篤な石灰化
4) 神経障害	重度の中枢神経障害 薬物中毒またはアルコール依存の既往 プロトコールに従えない，あるいは理解不能と判断されるほどの精神神経障害
5) その他の臓器不全	重度の肝臓疾患 重度の出血傾向，高度慢性腎不全，慢性腎不全による透析症例，癌などの生命予後不良な悪性疾患，膠原病などの全身性疾患，インスリン依存性重症糖尿病
6) 妊娠	妊娠中
7) その他	著しい肥満，輸血拒否など施設内適応委員会が不適当と判断した症例
4. 在宅治療安全管理基準	
(1) 在宅治療体制	補助人工心臓を扱う病院医療チームをはじめ患者自宅復帰の実現に向けて体制を整え，在宅経過観察基準を整えること.
(2) 患者・介護者の遵守事項	患者および介護者の遵守事項を定めること.
(3) 退院許可基準	住宅条件を含めた退院許可基準を定めること.
(4) 緊急時の対応	在宅時における緊急時の患者，介護者および病院の対応方法を明らかにするとともに，必要な機関(消防など)への協力要請を行うこと．24 時間対応が可能であること.
(5) 機器モニタリング	在宅時の患者および機器のモニタリング方法を整えること.
(6) 機器保守点検	機器の保守点検法を整えること.
(7) トラッキング	治療成績評価のためレジストリーを構築すること.

- 長期間の補助を行うために，在宅治療可能な植込型補助人工心臓が望まれてきた．
- 2011年4月より，非拍動流植込型補助人工心臓が心臓移植へのブリッジとして保険償還された．
- 植込型補助人工心臓実施施設の認定制度が発足し，認定された移植施設以外でも実施されるようになった．
- 2013年から心臓移植の年齢条項は65歳未満が望ましいとなった．

表2 INTERMACS Level of Limitation at Time of Implant

INTERMACS Profile Description	
1. Critical cardiogenic Shock (Crash and burn)	Definitive intervention needed within hours [重度の心原性ショック]
2. Progressive decline (Sliding on inotopes)	Definitive intervention needed within few days [進行性の悪化]
3. Stable but inotrope dependent (Dependent stability)	Definitive intervention elective over a period of weeks to few months [安定した強心剤依存]
4. Resting symptoms	Definitive intervention elective over period of weeks to few months [安静時症状]
5. Exertion intolerant	Variable urgency, depends upon maintenance of nutrition, organ function and activity [運動不耐容]
6. Exertion limited	Variable, depends upon maintenance of nutrition, organ function and activity [軽労作可能状態]
7. Advanced NYHA Ⅲ	Transplantantion or circulatory support may not currently be indicated [安定状態]

(Stevenson, L.W. et al.：JHLT 28：535-541, 2009より引用)

により適応のタイミングが検討されるが，わが国ではこれまでProfile 1から3の状態で補助人工心臓の装着が行われてきた．心臓移植へのブリッジとして長期補助を必要とする症例に対しては，可能な限り植込型を選択するのが望ましい．しかし，INTERMACS Profileからの検討では，Crash and Burnと呼ばれるProfile 1の成績は不良であることが示されるようになった．また，わが国ではこのような症例の多くはPCPS装着例であり，現状では植込型の適応タイミングとしてはProfile 2ないし3である．Profile 1の症例においては，まず体外設置型を装着し，状態が安定し心臓移植適応と判定される場合に，植込型への移行が検討されることとなる．

VAS装着後の管理としては，装着後早期では循環動態および全身状態の安定化を図る．その後，積極的にリハビリを行い，自己心の回復を試み，自己心機能が良好である場合，VASからの離脱を考慮する．回復不良な場合には心臓移植へと待機を続けることとなる．長期の補助における管理においては，抗血栓療法と感染予防が重要となり，精神状態への配慮も必要で，精神科医を含めた医療チームでの対応が重要となる．さらに，在宅治療を行う場合には，介護者への配慮も重要である．

わが国での臨床応用の現状は，2013年度の日本臨床補助人工心臓研究会レジストリーでは，1,627例にVASが適応され，うち840例が心筋症例であった．施行日数は平均404(最長2,266)日で，181例において心臓移植が施行された．

- 現在のわが国における植込型補助人工心臓の適応は，心臓移植へのブリッジのみである．
- 植込型補助人工心臓の適応判定においては，心臓移植の適応検討が必須である．
- 植込型補助人工心臓の適応検討においては，本人および家族へのインフォームドコンセントが重要である．

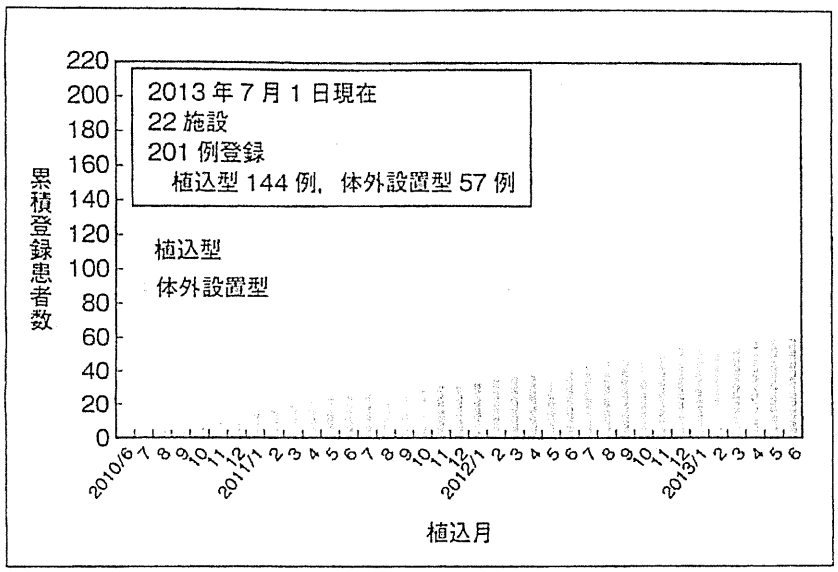

図4　J-MACS登録患者数の推移
PMDAホームページより
(http://www.info.pmda.go.jp/kyoten_kiki/track.html)

第一世代の拍動流植込型LVASによる心臓移植へのブリッジ例の適応は，心臓移植施設に限定されていた．第二世代の連続流植込型の承認にあたっては，心臓移植実施施設以外でも装着ができる体制を構築することとし，補助人工心臓治療関連学会協議会による実施施設および実施医の認定制度が設立された．2011年4月からは，心臓移植実施施設以外でも，ブリッジ使用としての植込型LVASの装着が開始されている．また，わが国における補助人工心臓に関連した市販後のデータ収集を行うために，Japanese registry for Mechanically Assisted Circulatory Support (J-MACS)が，医薬品医療機器総合機構，関連学会，医療機関，関連企業により設立され，2010年6月から症例登録が開始されている．連続流植込型LVAS装着例は全例登録することとなっており，2013年6月までに201例が登録され，うち144例が植込型である(図4)．わが国での連続流植込型補助人工心臓の実態が明らかになり，今後のわが国での補助人工心臓治療への貢献が期待されている．

今後の展望

末期心不全に対する治療選択として心臓移植および補助人工心臓がわが国においても受け入れられ，体制整備も進められている．また，施行数も増加し，その成績は良好である．また，臓器移植法の改正により，施行数の増加のみならず小児での心臓移植が施行できるようになり，小児例でのブリッジ用の補助人工心臓が望まれている．さらに心臓移植の適応年齢は60歳未満が望ましいから65歳未満が望ましいに変更され，補助人工心臓によるブリッジの対象

- 植込型補助人工心臓の適応のタイミングも重要であり，最近では，INTERMACS Profileにより検討される．
- 植込型補助人工心臓による在宅治療を行う場合には，患者のみならず介護者への配慮も重要である．
- わが国における補助人工心臓に関連した市販後のデータ収集を行うために，Japanese registry for Mechanically Assisted Circulatory Support (J-MACS)が設立されている．
- 今後，小児例でのブリッジ用の補助人工心臓が望まれる．
- 植込型補助人工心臓装着例における終末期対応は今後の検討課題である．

症例も増加している．また，心臓移植施設以外でも植込型補助人工心臓の使用が行える体制となり，その管理体制の整備が検討されている．諸外国では補助人工心臓治療として，心臓移植の適応とならない症例に対するいわゆるdestination therapyとして植込型補助人工心臓の装着が行われており，わが国においても，植込型補助人工心臓による長期在宅治療として，検討が開始されている．植込型補助人工心臓装着例における長期補助例が増加するにつれ，心臓移植へブリッジされない例などにおける終末期における対応も今後の検討課題である[6]．

末期心不全治療における心臓移植および補助人工心臓治療の位置づけは大きく変貌しようとしており，わが国に適した治療体系の構築を進める必要がある．

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Post-approval study of a highly pulsed, low-shear-rate, continuous-flow, left ventricular assist device, EVAHEART: A Japanese multicenter study using J-MACS

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KEYWORDS:
EVAHEART LVAS;
J-MACS;
heart failure;
survival;
ventricular assist device;
continuous flow;
bridge to transplantation

BACKGROUND: The EVAHEART left ventricular assist device was approved in 2010 by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for bridge to heart transplantation (BTT). However, its effectiveness has not been evaluated since approval. In this study we evaluated the EVAHEART device in a commercial setting in Japan.

METHODS: Ninety-six consecutive patients enrolled in the Japanese Registry for Mechanically Assisted Circulatory Support (J-MACS), who were listed for transplant or likely to be listed and who received an EVAHEART device, were enrolled from 2011 to 2013 at 14 Japanese centers. Patients' survival rates, adverse events and quality-of-life data were obtained from the J-MACS Registry.

RESULTS: Patients' median age was 43 years (85% male). The Interagency Registry for Mechanically Assisted Circulatory Support profiles revealed 12 patients in Level 1, 45 in Level 2, 37 in Level 3 and 1 in Level 4. The mean support duration was 384.7 days, with a cumulative duration of 101.2 years. The Kaplan–Meier survival rate during support was 93.4% at 6 months, 87.4% at 1 year and 87.4% at 2 years. Seventy-seven patients (80.2%) currently remain on support, 7 received a transplant and 10 died during support. Major adverse events included drive-line infection (14.6%) and neurologic events such as ischemic stroke (17.7%), hemorrhage (13.5%), transient ischemic attack (3.1%), pump thrombosis (1%) and hemolysis (1%). There was no gastrointestinal (GI) bleeding or right heart failure requiring right ventricular assist device (RVAD). There was no pump exchange due to mechanical failure.

CONCLUSIONS: The EVAHEART device provides safe, reliable and long-term circulatory support with improved survival in commercial settings of BTT in Japan, where the transplant waiting period is much

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http://dx.doi.org/10.1016/j.healun.2014.02.015

longer. Incidences of GI bleeding, hemolysis, right ventricular failure, device thrombosis and mechanical failure were extremely rare in patients on EVAHEART devices.
J Heart Lung Transplant 2014;33:599–608

Left ventricular assist device (LVAD) utilization is an indispensable treatment that provides a bridge to transplantation as well as a final therapy when hearts are not available due to donor shortage.[1–3] Continuous-flow LVADs are the predominant devices used for advanced heart failure patients awaiting transplantation and also for patients not eligible for transplant and refractory to medical management.[1,2]

In Japan, donor shortage is a critical problem in the treatment of severe end-stage heart failure. Donor organs are scarce due to social and ethical reasons, although legislation allowing for organ transplantation in Japan was passed in 1997.[3,4] The EVAHEART LVAS (Figure 1), an implantable, continuous-flow LVAD, was developed by Sun Medical Technology Research Corporation (Nagano, Japan), and the EVAHEART LVAS study was the first clinical trial for an implantable, continuous-flow LVAD in Japan.[5,6]

After completion of a prospective, multicenter clinical trial, the EVAHEART LVAS system was approved by the Japanese Pharmaceutical and Medical Device Agency (PMDA) for bridge-to-transplant (BTT) indications in April 2010. Post-approval studies were required by the PMDA to monitor the device in a commercial setting for safety, and also to compare its performance with other available devices for the same indication. We report here primary and secondary end-points from BTT post-approval study patients who completed at least 6 months of follow-up.

Methods

Device description

The EVAHEART LVAS blood pump is made of pure titanium and weighs 420 g (Figure 1). A 40-mm-diameter impeller is directly driven by a sensorless, brushless, direct current motor. The pump draws the blood from the left ventricle through the apical inflow cannula and propels it into the ascending aorta via the outflow vascular graft. The hydrodynamically levitated bearing rotates in a non-contact manner, allowing an unlimited bearing lifespan. To achieve relatively high flow as well as flow pulsatility, large-diameter inflow and outflow conduits (16-mm inner diameter) were chosen, along with wide cross-sectional areas of the entire flow pathway within the pump.[6,7]

The EVAHEART has very flat-slope pressure–flow setting. At lower pressure areas, pump flow reaches a higher flow rate of 15 to 20 liters/min. This pressure–flow characteristic enables it to provide a significant flow difference between systole and diastole, resulting in highly pulsed flow circulatory support with a pulse pressure of 15 to 30 mm Hg (Figure 2). The EVAHEART LVAS was designed for low shear rates (<1500 N/m^2) and has a wide clearance between the housing and impeller to provide pulsatile, high-flow circulatory support.

The normal operating speed of the pump is 1,800 to 2,400 rpm, providing a maximum flow rate of 10 to 15 liters/min. The pump is connected to the external controls by a drive-line and exits through the patient's abdominal wall. The controller operates the pump, regulates power, monitors system performance, and displays alarm notifications, speed and power. A pair of rechargeable lithium-ion batteries can provide power for at least 12 hours.

Patients

This study was a prospective evaluation of the first EVAHEART patients consecutively enrolled after the PMDA had approved the device and was listed in the Japanese Registry for Mechanically Assisted Circulatory Support (J-MACS; accessed at: http://www.pmda.go.jp/english/service/j-macs.html). All patients who were identified in the J-MACS Registry as BTT before implant (listed for transplant or BTT), and likely to be eligible for transplant, were enrolled in the study. Patients who received the EVAHEART from March 2011 through May 2013 at 14 Japanese centers were enrolled.

The data from the self-reporting centers were adjudicated by an unbiased party. All patients were followed for at least 6 months after implant or until an outcome occurred. The primary end-point was survival while waiting for transplantation. Secondary end-points included adverse events and functional status as determined by the 6-minute walk test at baseline and at 3, 6 and 12 months after implant.

Anti-coagulation was individualized among the different centers. The recommended international normalized ratio (INR) range was 2.5 to 3.5, and aspirin (at least 100 mg/day) was started during patients' transition from heparin. Platelet functional assays were performed at some centers, using various methods.

This was a registry-based study using the J-MACS database. Self-reporting was provided by each center according to the specified J-MACS definitions, and time-points were used that facilitated a PMDA-stipulated post-market outcomes analysis. Information regarding J-MACS variables, definitions, reporting time-points and data analysis is available at the J-MACS website. This report represents the first post-market approval study using the J-MACS Registry.

The studies were conducted in compliance with PMDA regulations for good clinical practice, and were approved by each site's institutional review board. All patients or their authorized representatives provided informed consent.

Statistical analysis

Descriptive statistics were used to evaluate baseline demographics, incidence rates and changes from baseline. Continuous data are expressed as mean ± standard deviation. Survival is reported descriptively through Kaplan–Meier analyses, with follow-up censored at the time of heart transplantation, device explant for recovery, and withdrawal of consent, or for patients lost to follow-up.

All adverse events meeting the J-MACS definition were evaluated with respect to classification and device-relatedness. Adverse events are reported as percentage of patients with events, and as event rate in events per patient-year, calculated as the number of events divided by the cumulative support durations for all patients. All statistical comparisons were 2-sided, and the level of significance was set at $p < 0.05$. All biochemical and hemodynamic data are presented as mean ± standard deviation (SD) or as median and range when appropriate. Discrete variables are presented as percentages. Adverse events are presented as both percentage of all patients and as events per patient-year.

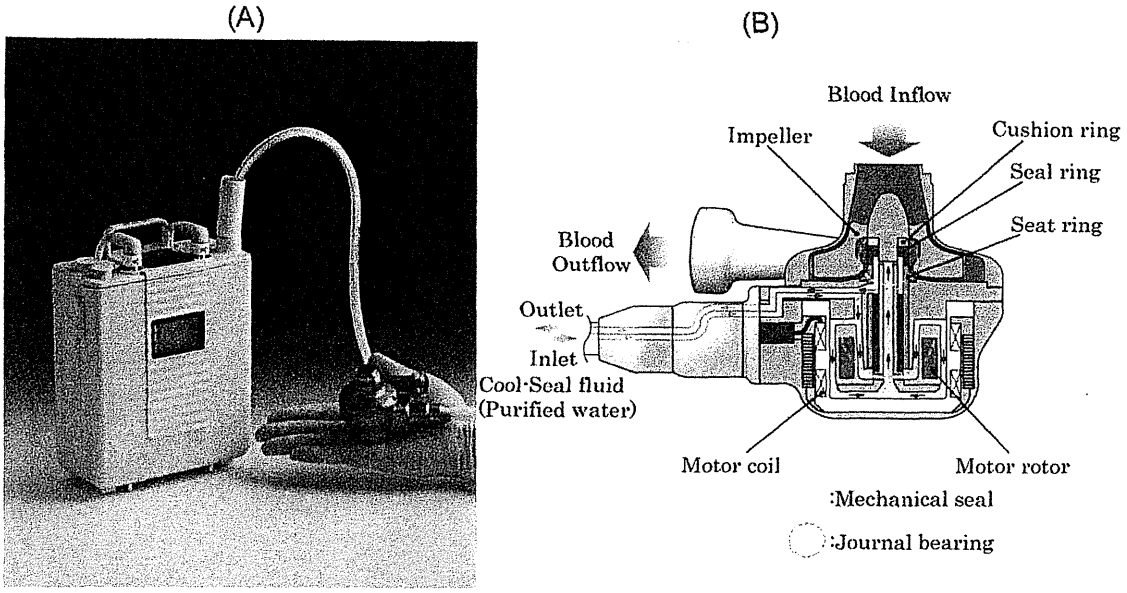

Figure 1 EVAHEART LVAS. (A) The pump and controller. (B) A cross-section of the EVAHEART LVAS. The device has a wide flow pathway and hydrodynamic journal bearing, which rotates without any contact to enable an unlimited bearing life.

Results

Baseline characteristics

Between March 2011 and May 2013, 96 patients (88.5% men) were enrolled at 14 centers throughout Japan. Baseline demographics are presented in Table 1. Patients had a mean age of 41.9 ± 11.7 years and a mean body surface area of 1.7 ± 0.2 m^2. Heart failure due to ischemic heart disease was present in 6.3% of patients. Thirteen patients (13.5%) had an extracorporeal device pre-operatively, and had undergone a conversion procedure to an EVAHEART device. The earlier extracorporeal devices included 10 Nipro paracorporeal pneumatic pumps (Nipro, Osaka, Japan),

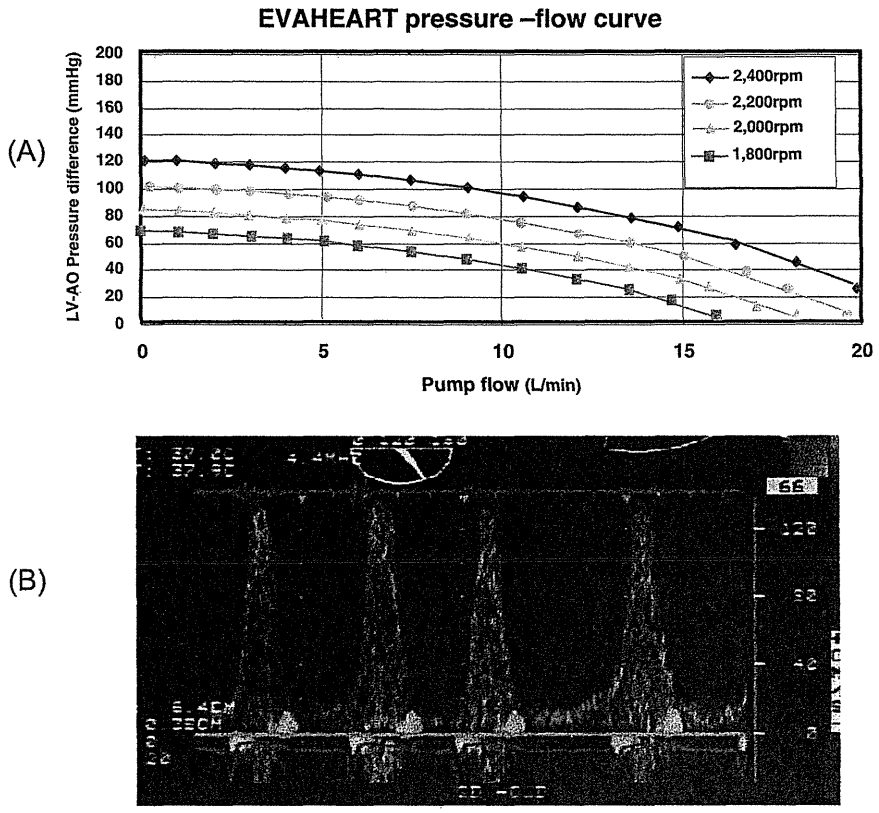

Figure 2 (A) Pressure–flow curves of EVAHEART LVAS. At low pressure, the pump flow reaches a high flow rate of 15 to 20 liters/min. (B) Typical flow pattern of an outflow graft in a patient with an EVAHEART device. The pump provides high-pulsed flow with a constant pump speed of 1,900 rpm.

Table 1 Baseline Characteristics ($N = 96$)

Age (years)	41.9 ± 11.7
Male gender (%)	85.5
Body surface area (m^2)	1.7 ± 0.2
Ischemic cause of heart failure (%)	6.3
Conversion from extracorporeal device	13 (13.5%)
Left ventricular ejection fraction (%)	17.2 ± 8.4
Inotrope-dependent	82 (85%)
Pulmonary artery pressure (mm Hg)	
Systolic	45.4 ± 14.9
Diastolic	24.2 ± 8.1
Arterial blood pressure (mm Hg)	
Systolic	86.4 ± 12.1
Diastolic	56.9 ± 9.9
Mean	66.9 ± 9.6
Cardiac index (liters/min/m^2)	2.0 ± 0.5
Creatinine (mg/dl)	1.2 ± 0.5
Total bilirubin (mg/dl)	1.4 ± 1.0
Brain natriuretic peptide (pg/ml)	863 ± 753.2
New York Heart Association class (%)	
I	3[a]
II	8
III	17
IV	67
NA	1
INTERMACS (%)	
1	12
2	45
3	37
4–7	1
Not available	1
Central venous pressure (mm Hg)	9.63 ± 5.61
Tricuspid regurgitation	
Moderate (%)Moderate	21
Severe (%)	9
RV dysfunction (more than moderately impaired) (%)	64

[a]All 3 patients underwent LVAD conversion from the extracorporeal device.

1 AB5000 pump (Abiomed, Danvers, MA) and 2 temporary left ventricular assist device (LVAD)-utilizing Gyro pumps (Medtronic, Minneapolis, MN). Among these 13 patients, 2 were New York Heart Association (NYHA) Class II, 2 were Class III and 9 were Class IV. Five patients had an INTERMACS Profile 1, 2 had Profile 2 and 6 had Profile 3.

The mean left ventricular ejection fraction was 17.2 ± 8.4%, and the mean cardiac index was 2.0 ± 0.5 liters/min/m^2. NYHA Functional Class IV was recorded for 69.8% of the patients. An INTERMACS classification of 4 to 7 was reported for 1% of the patients, whereas 38.5% were INTERMACS 3, 46.9% INTERMACS 2 and 12.5% INTERMACS 1.

Mean central venous pressure was 9.63 ± 5.61 mm Hg, and 30% of the patients had moderate or severe tricuspid regurgitation. Moderate or severe right ventricular dysfunction was observed in 64% of the patients. Eighty-two patients were inotrope-dependent, and 21 required balloon pump support pre-operatively.

Support duration

The average support duration for the EVAHEART was 384.7 (median 372) days. The cumulative follow-up duration was 101.2 patient-years of support.

Survival rate, transplantation rate and cause of death

Patients were monitored for at least 180 days or until transplant or death. Kaplan–Meier survival analysis for BTT patients revealed that survival at 6 months, 1 year and 2 years was 93.4%, 87.4% and 87.4%, respectively (Figure 3). Seventy-seven patients (80.2%) currently remain on the EVAHEART device, 10 patients (10.4%) died during support, and only 7 patients (7.3%) were transplanted (Figure 4). The causes of death of the 10 patients were neurologic events

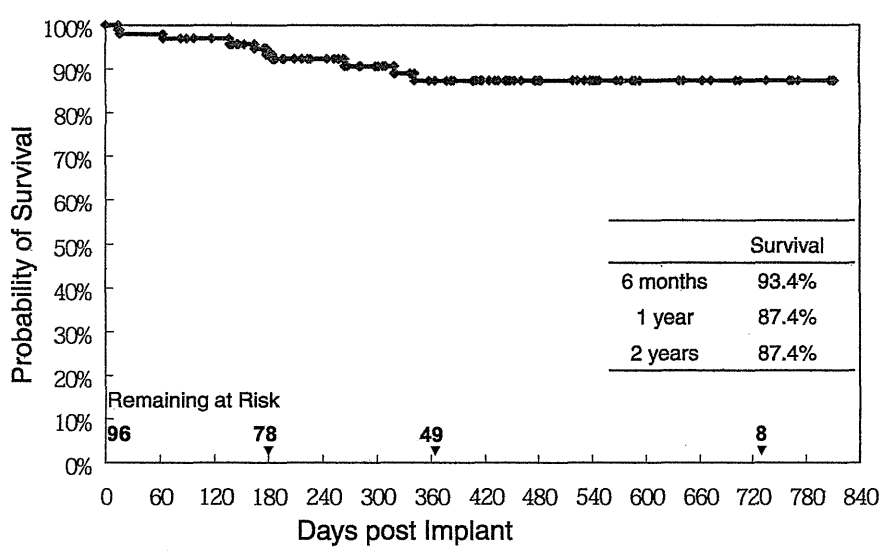

Figure 3 Survival analysis of the EVAHEART LVAS as bridge to transplant (BTT).

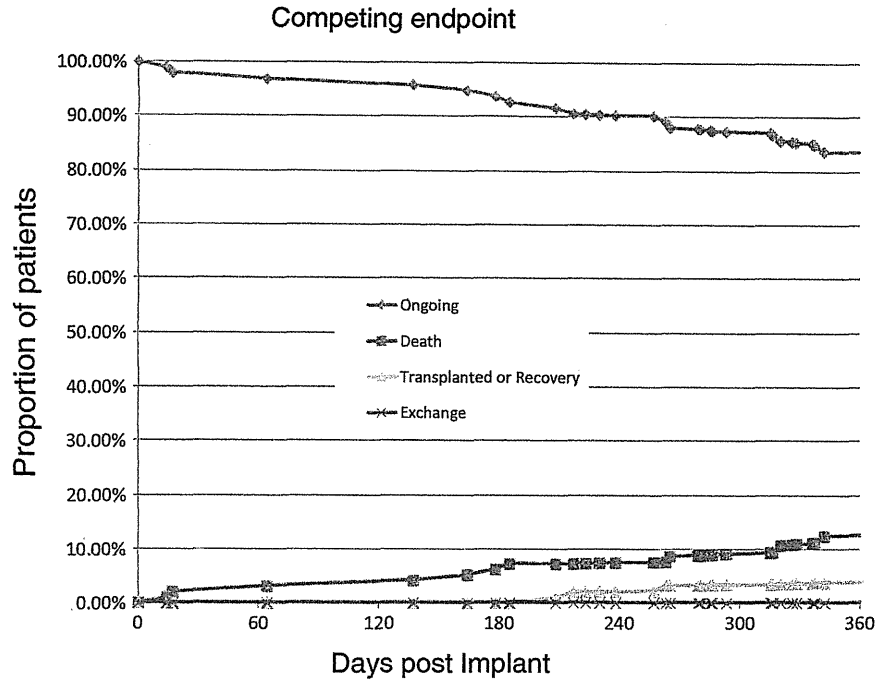

Figure 4 Competing end-point. Only 7.3% of patients were transplanted, and 80.2% of patients remained on the EVAHEART device at 1 year.

(4 patients), multisystem organ failure (4 patients), infection (1 patient) and device thrombosis (1 patient).

Seventy-four patients were discharged home after a mean of 108.2 days of hospitalization.

Cardiac index

The average cardiac index at baseline ($n = 76$) was 2.0 ± 0.5 liters/min/m^2. Average cardiac index according to the Swan–Ganz catheter was measured post-operatively at 1 week in 10 patients (2.7 ± 0.7 liters/min/m^2), 1 month in 28 patients (2.6 ± 0.6 liters/min/m^2) and 3 months in 8 patients (2.8 ± 0.5 liters/min/m^2). There was a significant improvement in cardiac index at every time-point up to 3 months post-operatively, as compared with before implantation (Figure 5).

Brain natriuretic peptide

Brain natriuretic peptide (BNP) values measured at baseline and post-operatively at 1 week, 1 month, 3 months, 6 months and 12 months were 863 ± 753, 584 ± 671, 442 ± 484, 281 ± 332, 239 ± 207 and 258 ± 175 pg/ml, respectively. This value decreased significantly compared with pre-implant at every time-point after implant (Figure 6).

Six-minute walk test

Six-minute walk test (6MWT) was assessed in all patients at baseline (pre-implant) and at 3, 6 and 12 months after implant. The percentages of all patients able to complete the 6MWT at these time-points were 6%, 47%, 50% and 25%, respectively. The percentages of all patients unable to complete the 6MWT

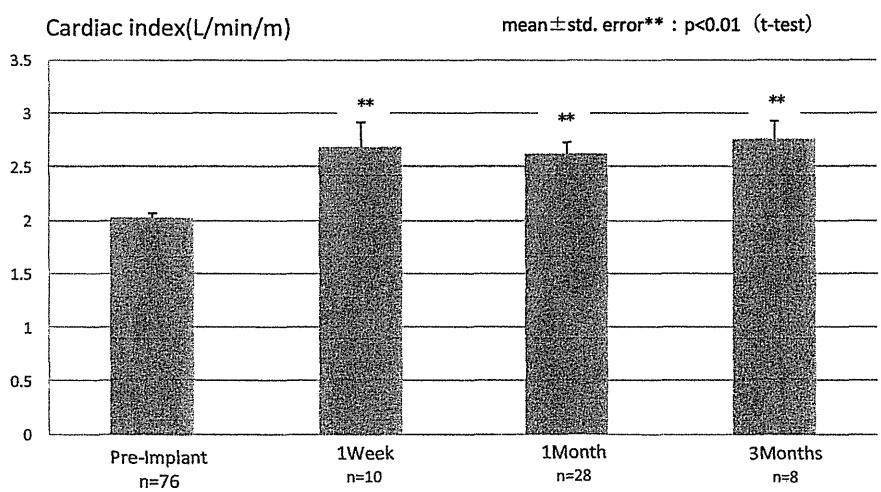

Figure 5 Cardiac indices. There was a significant improvement at every time-point up to 3 months post-operatively as compared with pre-implant status.

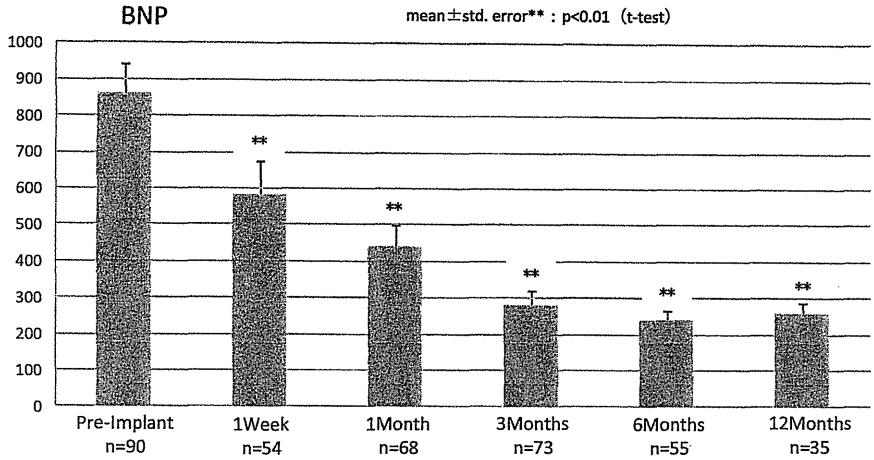

Figure 6 BNP values at pre-implant and 1 week and 1, 3, 6 and 12 months after EVAHEART LVAS implantation.

at these time-points were 76%, 7%, 5% and 2%, respectively, and thus a value of 0 was imputed for them. Overall, the 6MWT results improved significantly after implant from 21 meters pre-implant to 358 meters at 3 months, to 375 meters at 6 months and to 408 meters at 12 months (Figure 7).

Quality-of-life assessment (Euro-QOL)

Fifty percent of patients completed paired EQ-5D Visual Analog Scale (VAS) quality-of-life measurements. Paired data were obtained from 52 patients who were available for follow-up at 6 months (i.e., those who did not receive a transplant or device explant for recovery, were alive, or had attended the 6-month post-implant assessment). The score was significantly improved from 42.6 at pre-implant to 73.6 at 6 months (Figure 8).

Adverse events

Adverse event rates compared favorably with historic rates of LVADs for BTT (Table 2). Follow-up time ranged from 6 months to just over 26 months for patients alive on the original device. Drive-line exit-site infections occurred in 14 patients (14.6%), at an event rate of 0.28 event per patient-year (EPPY), and sepsis occurred in 1 patient (1.0%), at 0.01 EPPY.

Bleeding requiring reoperation occurred in 3 patients (3.1%) at a rate of 0.05 EPPY. Gastrointestinal bleeding did not occur. Cardiac arrhythmias were seen in 3 patients (3.1%). Ventricular tachycardia was more common in the peri-operative period (0 to 90 days).

Right heart failure occurred in 2 patients (2.1%), both treated with inotropic therapy. RVAD use was not required in any of the patients. Ischemic cerebrovascular accident (ICVA) events occurred in 17.7% of patients, a rate of 0.37 EPPY. Hemorrhagic CVA (HCVA) events occurred in 13.5% of patients for a rate of 0.21 EPPY, with 25% of these events being fatal. With respect to timing of events, after 90 days, ICVA and HCVA rates were reduced to 0.16 EPPY and 0.19 EPPY, respectively.

Three patients (3.1%) underwent aortic valve surgery for severe aortic insufficiency.

No device exchanges occurred during the entire support period. Both infectious device thrombosis and hemolysis occurred in 1 patient (0.01 EPPY), who died after a hemorrhagic stroke. The patient had not been on anti-coagulation therapy for more than 7 days.

Discussion

This study was the first clinical study with continuous-flow LVAD therapy in Japan, where the socio-medical situation is different from that in Western countries. This Japanese BTT trial was unlike other BTT studies in the USA in a number of ways, including patient background profiles, duration of support, number of transplants and availability of other implantable devices. Thus, a direct comparison of the results between this study and others is very difficult and may be inappropriate. Nevertheless, our findings support the findings from the EVAHEART BTT clinical trial regarding the safety and efficacy of the EVAHEART LVAS in patients with end-stage heart failure requiring an LVAD for BTT. Overall survival remains high, at 93.4% at 6 months, 87.4% at 1 year and 87.4% at 2 years, despite much lower transplant rates compared with other BTT trials.[8–10] The survival rates seem better than those for other commercially available VADs for BTT. The functional and quality-of-life improvements are similar to other reports of BTT trials.[11,12]

The EVAHEART LVAS improved patients' prognosis and quality of life, with excellent pump performance and reliability. As the waiting period for heart transplantation in Japan is usually longer than 2 years, the support duration of patients tended to be longer, almost comparable to that of destination therapy. In this study, the average support duration was 384.7 days, and cumulative support duration reached 101.2 patient-years. The average support duration of the 7 patients who reached heart transplant was 516 days. However, there were no critical mechanical problems requiring pump exchange. This is the longest support duration observed so far in a BTT study and equivalent to destination therapy trials. The results of this study suggest that the

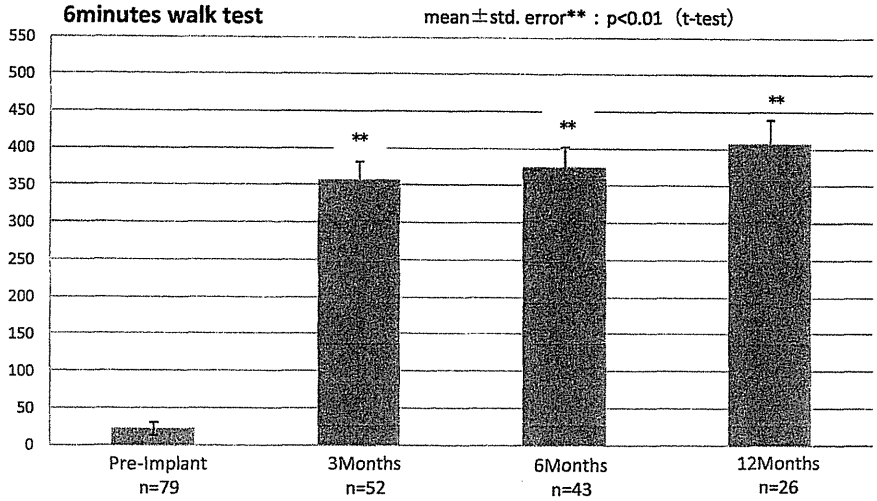

Figure 7 Results of the 6MWT at pre-implant and 3, 6 and 12 months after EVAHEART LVAS implantation. A value of 0 was given to patients unable to complete the assessment.

EVAHEART LVAS is a durable and reliable continuous-flow LVAD, suitable for long-term mechanical circulatory support.

The EVAHEART LVAS blood pump has a unique, hydrodynamically levitated bearing and mechanical seal design, which enables long-term support without mechanical wear of the pump. Moreover, its design is relatively simple and straightforward and can be maintained over long periods. The majority of patients with this device can be discharged to their homes.

Adverse event rates were low and were similar to those published with the currently approved device.[11,12] The baseline characteristics, especially younger average age, the high incidence of non-ischemic cardiomyopathy, and the small number of patients with previous cardiac surgery, of the patients in this Japanese study were different from those in other published studies.[11-13] However, bleeding and infection rates were lower compared with other BTT published data. Specifically, sepsis and pocket infection rates were very low, occurring at rates of 0.02 EPPY, respectively (Table 2). The incidence of cardiac arrhythmias was similar.

Bleeding requiring transfusion or reoperation was very infrequent compared with published rates, occurring at an overall rate of only 0.05 EPPY. None of the 14 centers at which this procedure is performed routinely leave the chest open after surgery. Patients' baseline characteristic differences may explain the lower rate of bleeding requiring reoperation.

Gastrointestinal bleeding was not observed. Hemolysis was noted in only 1 patient (0.01 EPPY) who had infectious device thrombosis and hemorrhagic stroke. This patient had not been on anti-coagulation therapy for more than 7 days.

The "pulsatility" characteristic of the EVAHEART may be a putative mechanism for reducing the incidence of gastrointestinal (GI) bleeding and preventing arterio-venous malformation in the GI tract. In this system, the flow rate change during the cardiac cycle (Figure 9) becomes more prominent, and the pulsatile pressure is amplified from the left ventricle to the aorta, unlike typical axial-flow pumps. Another explanation may be the lower share rate ($<1{,}500$ N/m^2) and wider clearance between the impeller and housing, which causes less "trauma" to blood components,

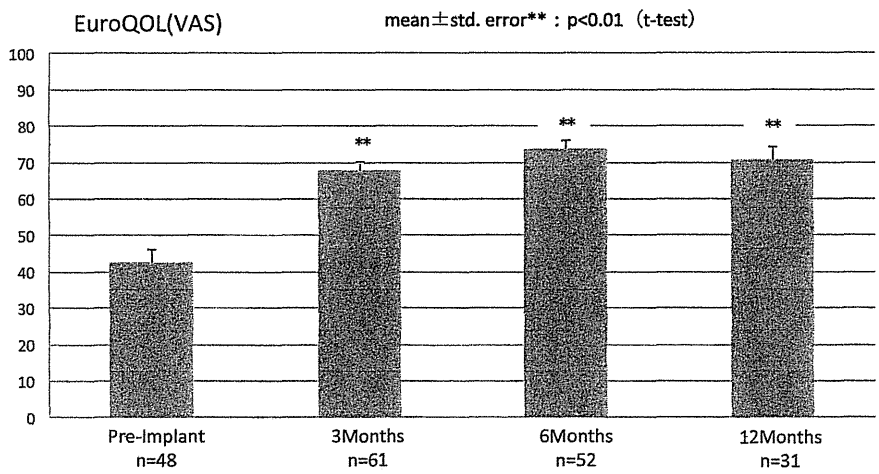

Figure 8 Quality of life with EQ-5D scores at pre-implant and 3, 6 and 12 months after EVAHEART LVAS implantation.

Table 2 Summary of Adverse Events

Events	Overall (PY = 84.7) (*N* = 96)			0–90 days (PY = 22.1)			>90 days (PY = 67.25)		
	Patients affected [% (*n*)]	Events (*n*)	Event rate (EPPY)	Patients affected [% (*n*)]	Events (*n*)	Event rate (EPPY)	Patients affected [% (*n*)]	Events (*n*)	Event rate (EPPY)
Bleeding									
Requiring reoperation	3.1 (3)	4	0.05	3.1 (3)	4	0.18	0.0 (0)	0	0.00
Gastrointestinal	0.0 (0)	0	0.00	0.0 (0)	0	0.00	0.0 (0)	0	0.00
Infection									
Drive-line exit site	14.6 (14)	24	0.28	4.2 (4)	4	0.18	13.5 (13)	20	0.32
Sepsis	1.0 (1)	1	0.01	1.0 (1)	1	0.05	0.0 (0)	0	0.00
Pump pocket	2.1 (2)	2	0.02	1.0 (1)	1	0.05	1.0 (1)	1	0.02
Neurologic events									
Ischemic stroke	17.7 (17)	31	0.37	12.5 (12)	21	0.95	9.4 (9)	10	0.16
Hemorrhage	13.5 (13)	18	0.21	4.2 (4)	6	0.27	11.5 (11)	12	0.19
Transient ischemic attack	3.1 (3)	3	0.04	1.0 (1)	1	0.05	2.1 (2)	4	0.06
Right heart failure									
RVAD	0.0 (0)	0	0.00	0.0 (0)	0	0.00	0.0 (0)	0	0.00
Inotrope therapy	2.1 (2)	2	0.02	2.1 (2)	2	0.09	0.0 (0)	0	0.00
Device exchange	0.0 (0)	0	0.00	0.0 (0)	0	0.00	0.0 (0)	0	0.00
Pump thrombus	1.0 (1)	1	0.01	0.0 (0)	0	0.00	1.0 (1)	1	0.02
Hemolysis	1.0 (1)	1	0.01	0.0 (0)	0	0.00	1.0 (1)	1	0.02
AI required for surgery	3.1 (3)	3	0.04	0.0 (0)	0	0.00	3.1 (3)	3	0.05
Arrhythmia									
Ventricular	3.1 (3)	6	0.07	3.1 (3)	3	0.14	1.0 (1)	3	0.05
Supraventricular	0.0 (0)	0	0.00	0.0 (0)	0	0.00	0.0 (0)	0	0.00
Renal dysfunction	1.0 (1)	1	0.01	1.0 (1)	1	0.05	0.0 (0)	0	0.00
Hepatic dysfunction	0.0 (0)	0	0.00	0.0 (0)	0	0.00	0.0 (0)	0	0.00
Respiratory dysfunction	2.1 (2)	2	0.02	2.1 (2)	2	0.09	0.0 (0)	0	0.00

AI, aortic insufficiency.

including von Willebrand factor. Our data suggest that the large molecule multimers of von Willebrand factor were well preserved in patients with the EVAHEART.[14] The increased physiologic pulsatile flow and reduced trauma to blood components produced by the EVAHEART device may reduce the number of GI bleeding events.

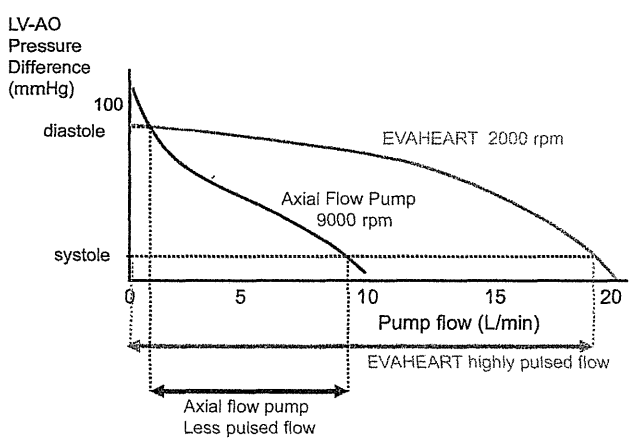

Figure 9 Comparison of pressure–flow curves between the EVAHEART device and a typical axial-flow pump. Pump flow pulsatility during the cardiac cycle is more significant in the EVAHEART than in the axial-flow pump. The high peak flow during systole maintains a higher mean pump flow rate.

RV failure requiring RVAD replacement was not observed in this study, despite the pre-operative cardiac function of these patients being similar to levels observed in previous series.[9–11] These lower incidences of RV failure, hemolysis and GI bleeding may be associated with the high-pulsed-flow and low-shear-rate design of the EVAHEART LVAS.

In this study, CVA was the major adverse event, and 25% of these cases resulted in death. Ischemic and hemorrhagic stroke was observed at rates of 0.37 and 0.21 EPPY, respectively, with incidence reduced to 0.16 and 0.19 EPPY, respectively, after 90 days. Pumps explanted at the time of autopsy or transplant were all free from thrombus, although some wedge thrombus formation around the inflow cannula was observed (Figure 10). Based on this finding, it is supposed that the strokes could be related to wedge thrombus formation.[15] Once a wedge thrombus is formed, portions of the thrombus can detach and cause strokes.[16,17]

Management practices and device design should be improved to reduce adverse events such as bleeding, stroke and infection.[17] Extensive medical treatment, including better

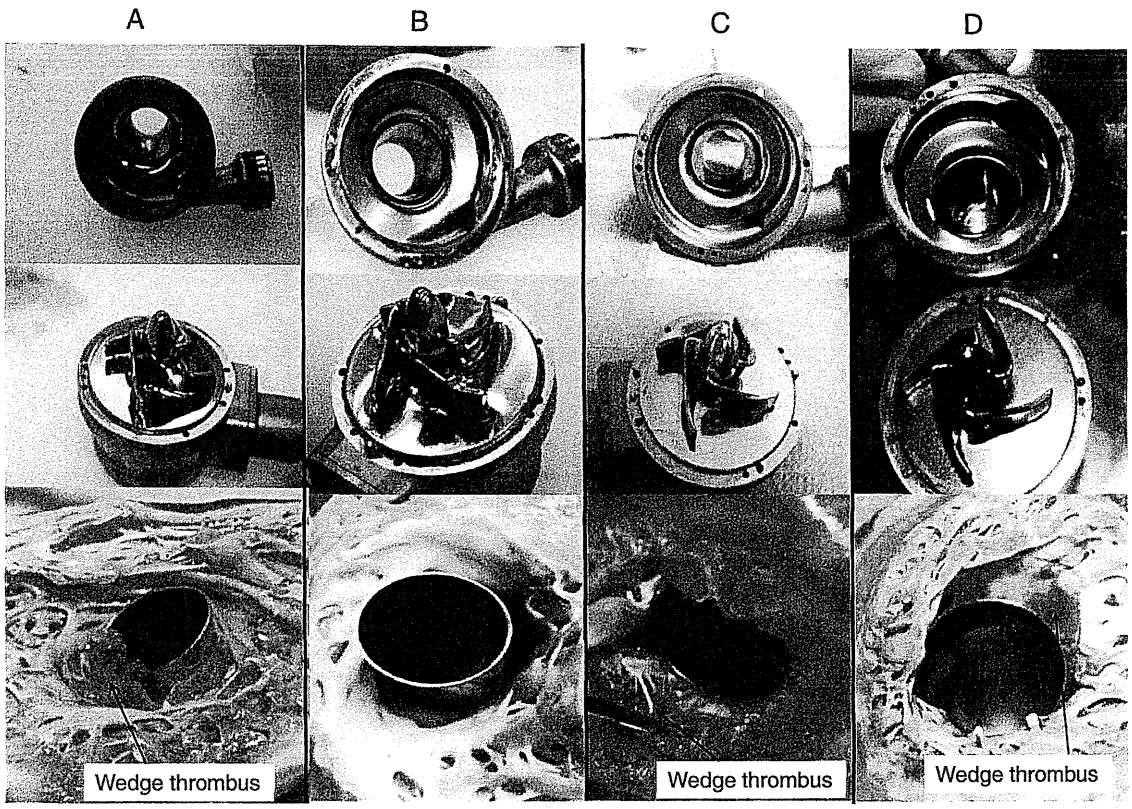

Figure 10 Detailed autopsy study of 4 patients (clinical trial) who died after cerebrovascular events. Although there was no thrombus in any part of the pumps, a wedge thrombus was observed around the inflow cannula in 3 patients.

INR control, various anti-platelet medications, and intensive volume management and echocardiographic monitoring of the distance between the ventricular septum and inflow cannula, had some effect on reducing neurologic events, especially those occurring more than 90 days after implantation. Nevertheless, we believe that a more fundamental solution may be the introduction of "a new textured surface inflow cannula." The textured surface modification to the inflow cannula can be expected to suppress such thromboembolic complications.[18] Clinical application of the new cannula design began in September 2013. One patient underwent EVAHEART implantation with the new textured cannula and had no neurologic event activity in the subsequent 3 months. Detailed information regarding the impact of the inflow cannula redesign will be reported as the number of cases accumulates.

Limitations

This study has several limitations. First, this was not a randomized trial, and therefore all patients had an EVAHEART LVAS. Another limitation is that the adverse event rates can only be compared with historic rates reported in the literature. The control data from the INTERMACS data set were limited by the availability of reported adverse event rates. However, the reference data sets from other controlled studies using different devices for BTT support the hypothesis that the EVAHEART LVAS is at least as safe as other commercially available LVADs.

In conclusion, the ongoing data from the J-MACS Registry of the EVAHEART LVAS BTT study continue to support overall improvements in survival, quality of life, safety and reliability of the EVAHEART LVAS in BTT patients with end-stage heart failure in Japan. Rates of bleeding, infection, device exchange and hemolysis were very low, and there was no RV failure requiring RVAD implantation. The survival rate was excellent among patients who eventually required cardiac transplantation. Ongoing patient management strategies and the introduction of textured surface inflow cannulas are expected to decrease the incidence of strokes and improve patient outcomes in this population. Importantly, this investigation represents the first use of the J-MACS Registry to conduct a post-market approval study with an LVAD, and an initial demonstration of prospective outcomes with standardized definitions.

Disclosure statement

K.Y. is a consultant for Sun Medical Technology Research Corp. The other authors have no conflicts of interest to disclose.

We thank all participants of the J-MACS Registry and all clinical institutions, surgeons and medical staff who contributed to this project.

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