

Implantation of ventricular assist devices in hypertrophic cardiomyopathy with left ventricular systolic dysfunction

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Abstract

Aims The outcomes of patients with hypertrophic cardiomyopathy with left ventricular systolic dysfunction (HCM-LVSD) undergoing left ventricular assist device (LVAD) implantation remain unclear. We retrospectively evaluated the clinical impact of LVAD implantation on clinical outcomes, including haemodynamics and brain natriuretic peptide (BNP) levels, in patients with HCM-LVSD, in comparison with those with dilated cardiomyopathy (DCM).

Methods and results In this retrospective, single-centre, observational study conducted in Japan, the medical records of patients who underwent LVAD implantation in the National Cerebral and Cardiovascular Center between 2011 and 2020 were reviewed. We enrolled 96 patients with DCM (average age: 43.5 years; 73 men) and 24 patients with HCM-LVSD (average age: 48.3 years; 16 men). The HCM-LVSD group had smaller left ventricles with thicker ventricular walls than the DCM group, which became more prominent after LVAD implantation. Preoperatively, BNP values were comparable between both groups; however, 3 months post-implantation, they were significantly higher in the HCM-LVSD group. Pulmonary artery pulsatility index, right ventricular stroke work index, and cardiac index were lower, and right atrial pressure was higher, in the HCM-LVSD group, suggesting subclinical impairment of right ventricular function. The HCM-LVSD group demonstrated equivalent outcomes, including overall survival, cerebrovascular accidents, right ventricular failure, LVAD-related infections, arrhythmia, and aortic insufficiency, post-implantation.

Conclusions Despite a decreased right ventricular function with higher BNP values, patients with HCM-LVSD and DCM showed comparable outcomes post-LVAD implantation.

Keywords Left ventricular assist device; HCM-LVSD; Dilated cardiomyopathy; Advanced heart failure

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Introduction

Hypertrophic cardiomyopathy (HCM) is a common disease of the heart muscle that is characterized by hypertrophy of the myocardium with preserved left ventricular (LV) systolic function. Several genetic mutations, mainly in sarcomeric proteins, have been reported as inherited causes of HCM; however, sporadic HCM has also been identified in certain

populations. Considering the heterogeneous background of this disease, various patterns of disease progression and clinical presentation have been reported.^{1–4}

Hypertrophic cardiomyopathy with LV systolic dysfunction (HCM-LVSD) is an uncommon pattern of disease progression that is characterized by reduced LV systolic function [left ventricular ejection fraction (LVEF) < 50%] with or without LV wall thinning and LV cavity enlargement; therefore, some

cases morphologically resemble idiopathic dilated cardiomyopathy (DCM).^{5,6} This pattern of disease progression has been called the ‘dilated’ or ‘burned-out’ phase of HCM and is known for its poor clinical outcome, with a mortality rate as high as 11% each year.^{7–9} Therefore, patients with HCM-LVSD may often require advanced heart failure therapies, such as left ventricular assist device (LVAD) and heart transplantation.¹⁰ However, the impact of LVAD therapies on clinical outcomes, including haemodynamic and neurohormonal parameters, in patients with HCM-LVSD, has not been fully elucidated.

This study aimed to retrospectively evaluate the clinical impact of LVAD implantation in the context of clinical outcomes, including haemodynamics and brain natriuretic peptide (BNP) levels, among patients with HCM-LVSD in comparison with those of patients with DCM.

Methods

Study design

In this retrospective, single-centre, observational study, the primary endpoint was overall survival after LVAD implantation. The secondary endpoints included freedom from cerebrovascular accident, LVAD-related infection, right heart failure, arrhythmia, and aortic insufficiency. Serial BNP values, echocardiographic markers, and haemodynamic markers before and after LVAD implantation were also assessed. The definition of adverse events was based on the definition of adverse events listed in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). The guidelines are as follows: cerebrovascular accident including ischaemic stroke, transient ischaemic attack, and intracranial haemorrhage. LVAD-related infection was defined as a percutaneous driveline exit site or pump infection conformed by positive culture and clinical findings, requiring antimicrobial therapy, or surgical treatments including debridement or pump replacement. Right ventricular failure was defined as symptoms or findings of persistent right ventricular failure characterized by documented elevated central venous pressure by right heart catheterization or echocardiography, peripheral oedema, or laboratory evidence of worsening renal or liver functions. Arrhythmia was classified as sustained ventricular arrhythmia or sustained supraventricular arrhythmia requiring hospitalization or drug treatment, cardioversion, intracardiac defibrillator therapy, or ablation procedure. Aortic insufficiency was defined as the need for aortic valvuloplasty and new-onset moderate or severe aortic valve regurgitation after LVAD implantation.

This study was approved by the National Cerebral and Cardiovascular Center Institutional Review Board (IRB number, M30-026-5) and was designed to be carried out without

obtaining individual informed consent according to the ‘opt-out’ principle. This study conforms with the principles outlined in the ‘Declaration of Helsinki’.

Study subjects and variables assessed

Consecutive patients who underwent LVAD implantation for both bridge-to-transplant therapy (BTT) and destination therapy (DT) between 2011 and 2020 were enrolled in this study.

Patients’ medical records were retrospectively reviewed for baseline preoperative and post-operative clinical parameters, including demographics (age, sex, and body surface area), medical history [duration of heart failure, INTERMACS profile at the time of LVAD implant, pre-LVAD mechanical circulatory support, pre-implant history of hypertension, diabetes, dyslipidaemia, and smoking, and also pre-implant treatment with angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), β -blocker, and mineralocorticoid antagonist (MRA)], blood analyses (aspartate transaminase, alanine aminotransferase, serum creatinine, blood urea nitrogen, serum sodium, C-reactive protein, total protein, total bilirubin, white blood cells, platelets, haemoglobin, and BNP), echocardiographic parameters [interventricular septum thickness (IVST), posterior wall thickness (PWT), LV end-diastolic dimension (LVDd), LV end-systolic dimension (LVDs), and LVEF], and haemodynamic parameters [mean blood pressure, heart rate, pulmonary capillary wedge pressure (PCWP), pulmonary arterial pressure (PAP), right atrial pressure (RAP), cardiac output (CO), and cardiac index (CI)]. Changes in BNP values before and after LVAD implantation were also assessed as Δ BNP (preoperative BNP value – 3 months post-operative BNP value). Moreover, changes in echocardiographic parameters before and after LVAD implantation were assessed as Δ IVST, Δ PWT, Δ LVDd, Δ LVDs, and Δ LVEF (preoperative echocardiographic parameters – post-operative echocardiographic parameters). The pulmonary artery pulsatility index (PAPi), right ventricular stroke work index (RVSWI), and ratio of PCWP and RAP were calculated using the following formulae: $\text{PAPi} = (\text{systolic PAP} - \text{diastolic PAP}) / \text{mean RAP}$; $\text{RVSWI} = (\text{mean PAP} - \text{mean RAP}) \times \text{stroke volume index}$; and $\text{ratio of PCWP and RAP} = \text{RAP} / \text{PCWP}$. The type of LVAD implanted and the duration of LVAD support were also reviewed. Perioperative information including operation time, cardiopulmonary bypass time, and other concomitant cardiac surgery were also considered.

Diagnostic criteria

Hypertrophic cardiomyopathy was diagnosed through documentation of a hypertrophied left ventricle (wall

thickness ≥ 15 or ≥ 13 mm with a family history in one or more LV myocardial segments), in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy by echocardiography, at some point during the patient's clinical course. HCM-LVSD was defined as an LVEF $\leq 50\%$, with or without LV dilatation, as measured by echocardiography, during the follow-up period.

Left ventricular assist device implantation

All surgical procedures were performed through a median sternotomy under cardiopulmonary bypass. The outflow cannula was anastomosed to the ascending aorta, and the inflow cannula to the LV apex, without arresting the heart. The LVAD pump was then placed in the pericardial space or in the preperitoneal pump pocket. The driveline was externalized at the right or left upper quadrant using the double-tunnel technique.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or as the median (interquartile range), as appropriate. The two groups were compared using unpaired *t*-test for data with a normal distribution pattern or Mann–Whitney *U* test for data with an abnormal distribution pattern. Categorical variables were expressed as numbers and frequencies. The

χ^2 test was used for analysing categorical variables. Kaplan–Meier analysis and log-rank test were used to evaluate event-free survival. All *P*-values were two-sided, and values of *P* < 0.05 were considered statistically significant. Statistical analysis was performed using STATA® software Version 15 (Stata Corporation, College Station, TX, USA).

Results

Baseline demographics and clinical parameters

A total of 120 consecutive patients were enrolled in this study; of these, 96 patients with DCM and 24 patients with HCM-LVSD underwent LVAD implantation (DCM group, 25 centrifugal-flow and 71 axial-flow LVADs; HCM-LVSD group, 11 centrifugal-flow and 13 axial-flow LVADs) during the study period. Only three patients received LVAD therapy for DT; of these, two were all included in the DCM group, whereas one was included in the HCM-LVSD group. The patients' baseline preoperative demographics are presented in *Table 1*. There were no significant differences in the baseline demographics, including age range, sex, and pre-LVAD conditions, between the two groups.

Preoperative clinical parameters, including laboratory investigations and both echocardiographic and haemodynamic parameters, are listed in *Table 2*. There were no significant differences in the values of laboratory examinations, including BNP, between the two groups [DCM vs. HCM-LVSD:

Table 1 Baseline demographics

	All (n = 120)	DCM (n = 96)	HCM-LVSD (n = 24)	P-value
Age (years)	44.5 \pm 12.4	43.5 \pm 13.0	48.3 \pm 8.9	0.091
Male sex [n (%)]	89 (74.2)	73 (76.0)	16 (66.7)	0.348
Body surface area (m ²)	1.66 \pm 0.20	1.66 \pm 0.20	1.63 \pm 0.19	0.494
Duration of heart failure (days)	1700 (546–3401)	1608 (507–3556)	1712 (1343–3177)	0.461
Pre-LVAD MCS [n (%)]				
p-ECMO	0	0	0	
IABP	9 (7.5)	9 (9.4)	0	0.119
Pre-LVAD ventilation	2 (1.7)	2 (2.1)	0	0.476
INTERMACS profile [n (%)]				0.267
Bridge to bridge	24 (20.0)	19 (19.8)	5 (20.8)	
Profile 2	21 (17.5)	19 (19.8)	2 (8.3)	
Profile 3	63 (52.5)	51 (53.1)	12 (50)	
Profile 4	12 (10.0)	7 (7.3)	5 (20.8)	
Hypertension [n (%)]	7 (5.8)	6 (6.3)	1 (4.2)	0.697
Diabetes mellitus [n (%)]	19 (15.8)	14 (14.6)	5 (20.8)	0.64
Dyslipidaemia [n (%)]	50 (41.7)	38 (39.6)	12 (50.0)	0.355
Smoking [n (%)]	62 (51.7)	49 (51.0)	13 (54.2)	0.784
Preoperative ACEI or ARB use [n (%)]	93 (77.5)	76 (79.2)	17 (70.8)	0.382
Preoperative β -blocker use [n (%)]	106 (88.3)	87 (90.6)	19 (79.2)	0.118
Preoperative MRA use [n (%)]	107 (89.2)	87 (90.6)	20 (83.3)	0.341

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DCM, dilated cardiomyopathy; HCM-LVSD, hypertrophic cardiomyopathy with left ventricular systolic dysfunction; IABP, intra-aortic balloon pump; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; MCS, mechanical circulatory support; MRA, mineralocorticoid antagonist; p-ECMO, peripheral extracorporeal membrane oxygenation.

Table 2 The preoperative clinical characteristics

	All (n = 120)	DCM (n = 96)	HCM-LVSD (n = 24)	P-value
Laboratory examinations				
White blood cell count (/mL)	6040 (4800–7300)	6150 (4800–7400)	5850 (4870–6750)	0.684
Haemoglobin (mg/dL)	11.6 ± 2.0	11.6 ± 2.0	11.3 ± 1.8	0.541
Platelets (×10 000/mL)	18.2 (14.6–23.1)	18.5 (14.5–23.2)	17.8 (15.3–22.0)	0.755
Total protein (mg/dL)	6.5 ± 0.7	6.4 ± 0.7	6.6 ± 0.5	0.497
Total bilirubin (mg/dL)	0.9 (0.6–1.2)	0.9 (0.6–1.3)	0.9 (0.6–1.2)	0.802
Aspartate aminotransferase (IU/L)	24 (20–32)	24 (20–32)	26 (21–32)	0.427
Alanine aminotransferase (IU/L)	20 (13–30)	20 (13–30)	19 (14–29)	0.844
Serum creatine (mg/dL)	0.97 (0.79–1.25)	0.94 (0.76–1.24)	1.1 (0.84–1.30)	0.179
Blood urea nitrogen (mg/dL)	17 (12–24)	17 (12–23)	18 (16–25)	0.178
Serum sodium (mEq/L)	137 (135–140)	137 (136–140)	136 (135–139)	0.097
C-reactive protein (mg/dL)	0.35 (0.07–2.07)	0.35 (0.08–1.91)	0.34 (0.06–4.03)	0.703
Brain natriuretic peptide (pg/mL)	536 (270–891)	538 (235–905)	533 (315–887)	0.365
Echocardiographic parameters				
Left ventricular end-diastolic dimension (mm)	72.2 ± 11.8	74.6 ± 10.7	62.6 ± 11.2	<0.001
Left ventricular end-systolic dimension (mm)	66.0 ± 12.1	68.7 ± 10.9	55.7 ± 11.2	<0.001
Interventricular septum thickness (mm)	7 (6–8)	6 (5–8)	8 (6–9)	0.004
Posterior wall thickness (mm)	7 (6–8)	7 (6–8)	8 (7–9)	0.005
Left atrial diameter (mm)	47.9 ± 8.8	47.3 ± 9.0	50.5 ± 7.5	0.117
Left ventricular ejection fraction (%)	17 (13–21)	15 (13–20)	20 (17–26)	0.002
Preoperative haemodynamic parameters				
Heart rate (b.p.m.)	75 (70–90)	80 (70–93)	70 (64–78)	0.026
PCWP (mmHg)	21 (16–30)	23 (16–30)	19 (16–26)	0.107
Mean PAP (mmHg)	31 (23–39)	32 (23–42)	28 (21–35)	0.113
RAP (mmHg)	7 (4–11)	7 (4–12)	6 (3–11)	0.65
Cardiac index (L/min/m ²)	1.86 (1.52–2.2)	1.77 (1.53–2.14)	1.90 (1.45–2.30)	0.813
Pulmonary vascular resistance (units)	2.52 (1.76–4.00)	2.61 (1.82–4.00)	2.21 (1.62–4.05)	0.311
PAPi (n = 118)	2.71 (1.75–4.83)	2.67 (1.75–4.75)	3.2 (1.79–5.2)	0.447
RVSWI (n = 118)	472 (380–642)	464 (359–630)	495 (394–655)	0.63
RAP/PCWP (n = 119)	0.33 (0.21–0.5)	0.33 (0.21–0.5)	0.36 (.2–0.5)	0.728

DCM, dilated cardiomyopathy; HCM-LVSD, hypertrophic cardiomyopathy with left ventricular systolic dysfunction; PAP, pulmonary arterial pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVSWI, right ventricular stroke work index.

BNP, 538 (235–905) vs. 533 (315–887) pg/mL, $P = 0.365$]. Regarding echocardiographic parameters, the HCM-LVSD group had a significantly smaller LV cavity (LVDd, 62.6 ± 11.2 vs. 74.6 ± 10.7 mm, $P < 0.001$), thicker ventricular wall [PWT, 8 (7–9) vs. 7 (6–8) mm, $P = 0.005$], and higher LVEF [20 (17–26) vs. 15 (13–20) %, $P = 0.002$] than the DCM group. However, there were no significant differences in any haemodynamic parameters between the two groups apart from the heart rate [DCM vs. HCM-LVSD, 80 (70–90) vs. 70 (64–78) b.p.m., $P = 0.026$].

Perioperative outcome

Perioperatively, there were no significant differences in operative time or total cardiopulmonary bypass time between the two groups. Regarding concomitant cardiac surgery at LVAD implantation, 29 patients underwent tricuspid annuloplasty [DCM vs. HCM-LVSD, 26 (27.1%) vs. 3 (12.5%), $P = 0.136$], and 10 patients underwent aortic valvuloplasty [DCM vs. HCM-LVSD, 7 (7.3%) vs. 3 (12.5%), $P = 0.409$], showing no significant differences between the two groups.

Echocardiographic cut-off values for the differential diagnosis between dilated cardiomyopathy and hypertrophic cardiomyopathy with left ventricular systolic dysfunction

To further elucidate the clinical significance of echocardiographic parameters for the differential diagnosis between DCM and HCM-LVSD, receiver operating characteristic (ROC) curve analysis was conducted. ROC curves were generated to determine the optimal cut-off values of LVDd and PWT that can discriminate between HCM-LVSD and DCM. The cut-off value obtained for each parameter was 68 mm for LVDd [area under the curve (AUC), 0.79, $P = 0.062$] and 8 mm for PWT (AUC, 0.68, $P = 0.745$) (Figure 1).

Changes in clinical parameters before and after left ventricular assist device implantation

Post-operative results of BNP value, echocardiographic, and haemodynamic parameters are shown in Table 3. Although BNP remarkably decreased after LVAD implantation in both

Figure 1 ROC curve analysis to determine the optimal cut-off values of LVDd (left upper panel) and PWT (right upper panel) for differentiating patients with idiopathic dilated cardiomyopathy and those with HCM-LVSD. The cut-off values of LVDd and PWT for diagnosing HCM-LVSD were <68 and >8 mm, respectively. HCM-LVSD, hypertrophic cardiomyopathy with left ventricular systolic dysfunction; LVDd, left ventricular end-diastolic dimension; PWT, posterior wall thickness; ROC, receiver operating characteristic.

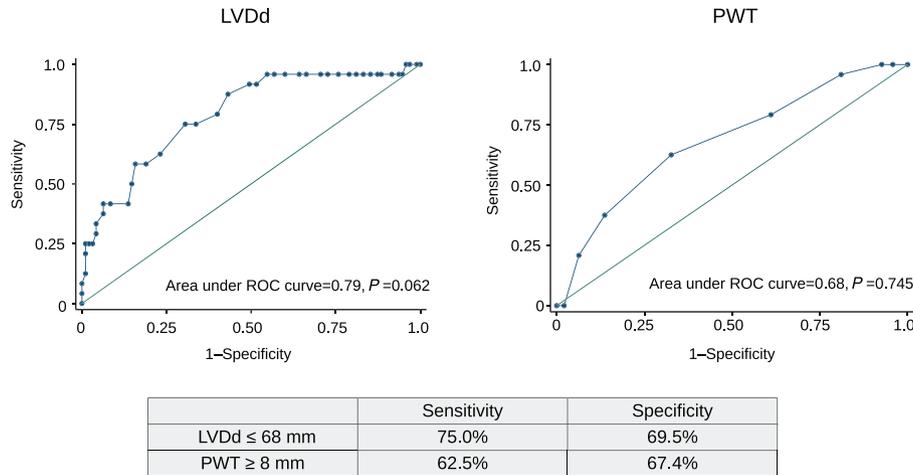


Table 3 The perioperative and post-operative clinical characteristics

	All (n = 120)	DCM (n = 96)	HCM-LVSD (n = 24)	P-value
Perioperative characteristics				
Operation time (min)	255 (203–304)	257 (214–297)	251 (182–315)	0.471
Cardiopulmonary bypass time (min)	80 (64–103)	82 (67–103)	73 (61–100)	0.22
Concomitant other cardiac surgery [n (%)]				
Tricuspid annuloplasty	29 (24.2)	26 (27.1)	3 (12.5)	0.136
Aortic valvuloplasty	10 (8.3)	7 (7.3)	3 (12.5)	0.409
Type of LVAD [n (%)]				0.058
Axial-flow LVAD	84 (70.0)	71 (74.0)	13 (54.2)	
Centrifugal-flow LVAD	36 (30.0)	25 (26.0)	11 (45.8)	
LVAD support period (days)	1051 ± 450	1081 ± 446	929 ± 455	0.139
Laboratory examinations (n = 118)				
BNP at 1 month post-LVAD implantation (pg/mL)	143 (84–308)	118 (73–195)	223 (166–386)	<0.001
BNP at 3 months post-LVAD implantation (pg/mL)	111 (59–194)	88 (48–142)	256 (155–466)	<0.001
Δ BNP from baseline to 3 months post-LVAD implantation (pg/mL)	399 (98–736)	432 (111–742)	273 (55–717)	0.245
Post-operative echocardiographic parameters (n = 118)				
Left ventricular end-diastolic dimension (mm)	54.3 ± 13.0	55.6 ± 13.0	49.3 ± 11.8	0.033
Left ventricular end-systolic dimension (mm)	48.1 ± 14.5	49.2 ± 14.9	43.8 ± 12.2	0.107
Interventricular septum thickness (mm)	7 (6–8)	7 (6–8)	9 (8–10)	<0.001
Posterior wall thickness (mm)	8 (6–9)	7 (6–8)	9 (8–11)	<0.001
Left ventricular ejection fraction (%)	18 (13–20)	14 (13–20)	18 (13–21)	0.203
Δ Interventricular septum thickness (mm)	–1 (–2 to 0)	–1 (–1 to 0)	1 (–3 to 0)	0.211
Δ Posterior wall thickness (mm)	–1 (–2 to 0)	–1 (–2 to 1)	–2 (–3 to –1)	0.017
Δ Left ventricular end-diastolic dimension (mm)	17.8 ± 10.6	19.0 ± 11.2	13.3 ± 6.3	0.018
Δ Left ventricular end-systolic dimension (mm)	18.0 ± 12.5	19.6 ± 13.3	11.9 ± 6.0	0.007
Δ Left ventricular ejection fraction (%)	–2 (–6 to 4)	–1 (–5 to 4)	5 (–3 to 9)	0.089
Post-operative catheterization (n = 116)				
Mean blood pressure (mmHg)	80 (70–89)	80 (70–87)	80 (69–90)	0.916
PCWP (mmHg)	5 (3–8)	5 (3–7)	6 (3–9)	0.48
Mean PAP (mmHg)	14 (11–17)	14 (11–18)	15 (13–17)	0.492
RAP (mmHg) (n = 114)	5 (3–7)	4 (3–6)	6 (4–10)	0.009
Cardiac index (L/min/m ²)	2.55 (2.27–3.00)	2.67 (2.31–3.14)	2.30 (2.08–2.49)	<0.001
PAPi (n = 114)	3.0 (3.0–4.7)	3.3 (2.3–4.7)	1.9 (1.5–3.1)	0.009
RVSWI	321 (224–439)	346 (238–463)	230 (194–321)	0.002
RAP/PCWP (n = 112)	1.0 (0.67–1.4)	1.0 (0.63–1.25)	1.1 (0.79–1.9)	0.03

BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; HCM-LVSD, hypertrophic cardiomyopathy with left ventricular systolic dysfunction; LVAD, left ventricular assist device; PAP, pulmonary arterial pressure; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; Δ, change values between pre-LVAD and post-LVAD implantation.

groups and there were no significant differences in Δ BNP values between the two groups [DCM vs. HCM-LVSD, 432 (111–742) vs. 273 (55–717) pg/mL, $P = 0.245$], the BNP values at 1 and 3 months after LVAD implantation were significantly higher in the HCM-LVSD group than in the DCM group [at 3 months post-LVAD implantation, 256 (155–466) vs. 88 (48–142) pg/mL, $P < 0.001$] (Figure 2). Morphological differences between the two groups were maintained after LVAD implantation, such that the HCM-LVSD group had a significantly smaller LV cavity and thicker ventricular wall than the DCM group [LVDD = 49.3 ± 11.8 vs. 55.6 ± 13.0 mm, $P = 0.033$; PWT = 9 (8–11) vs. 7 (6–8) mm, $P < 0.001$]. Concerning the morphological changes, there were significant differences in Δ LVDD and Δ LVDs between the two groups (Δ LVDD = 19.0 ± 11.2 vs. 13.3 ± 6.3 mm, $P = 0.018$; Δ LVDs = 19.6 ± 13.3 vs. 11.9 ± 6.0 mm, $P = 0.007$). Regarding post-operative haemodynamics, although the haemodynamic parameters were all compensated and reached normal values in both groups after LVAD implantation, there were significant differences in the surrogate indices of right ventricular function, including RAP, PAPI, RVSWI, PCWP/RAP, and CI

between the two groups [DCM vs. HCM-LVSD: RAP, 4 (3–6) vs. 6 (4–10) mmHg, $P = 0.009$; PAPI = 3.3 (2.3–4.7) vs. 1.9 (1.5–3.1), $P = 0.009$; RVSWI, 346 (238–463) vs. 230 (194–321), $P = 0.002$; RAP/PCWP, 1.0 (0.63–1.25) vs. 1.1 (0.79–1.9), $P = 0.03$; CI = 2.67 (2.31–3.14) vs. 2.30 (2.08–2.49) L/min/m², $P < 0.001$].

Clinical outcomes

All enrolled patients were followed up for a median of 3.9 (interquartile range, 2.2, 6.1) years. During the follow-up period, 7 (7%) patients died, 38 (40%) had successful heart transplantation, and 49 (51%) were still on LVAD support, in the DCM group. In the HCM-LVSD group, 4 (17%) died, 7 (29%) had successful heart transplantation, and 13 (54%) were still on LVAD support. Further, two patients with DCM (2%) were weaned from LVAD, whereas no patients were weaned from LVAD in the HCM-LVSD group.

Kaplan–Meier curves were generated for overall survival and various event-free survival rates in both groups and are

Figure 2 Serial changes in BNP (left upper panel), LVDD (right upper panel), and PWT (left lower panel) before (Pre) and after LVAD implantation (Post). Despite a remarkable decrease in BNP after LVAD implantation in both groups, BNP values at 3 months after LVAD implantation are significantly higher in the HCM-LVSD group than in the DCM group. LVDD significantly decreased after LVAD implantation in both groups, whereas PWT significantly increased after LVAD implantation. *, Wilcoxon signed rank, $P < 0.05$; **, Wilcoxon signed rank, $P < 0.001$; †, Mann–Whitney U test, $P < 0.001$; ††, Mann–Whitney U test, $P < 0.05$. BNP, brain natriuretic peptide; DCM, dilated cardiomyopathy; HCM-LVSD, hypertrophic cardiomyopathy with left ventricular systolic dysfunction; LVAD, left ventricular assist device; LVDD, left ventricular end-diastolic dimension; PWT, posterior wall thickness.

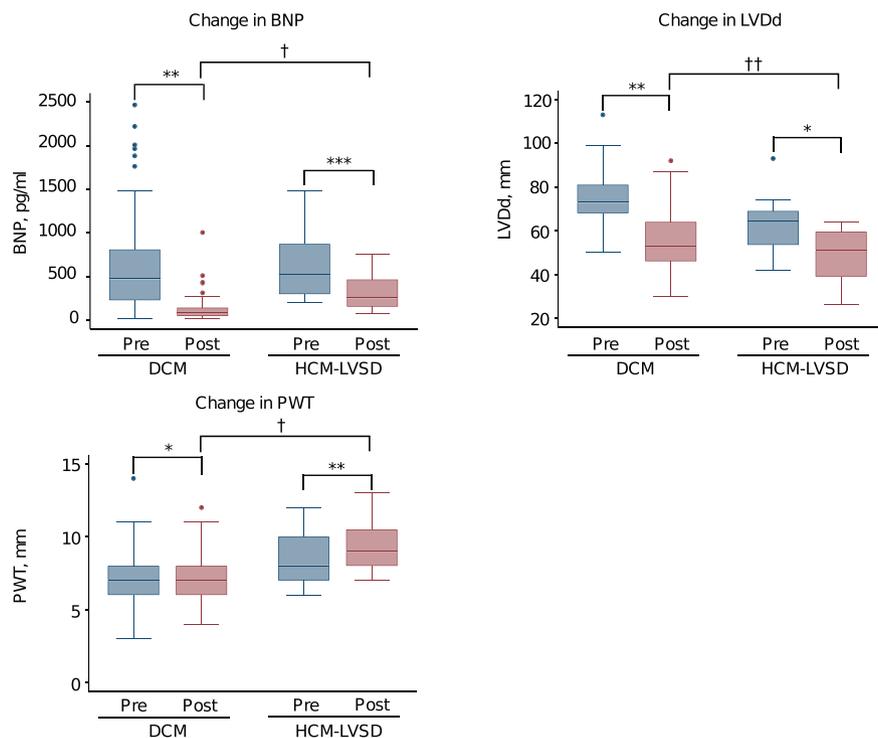
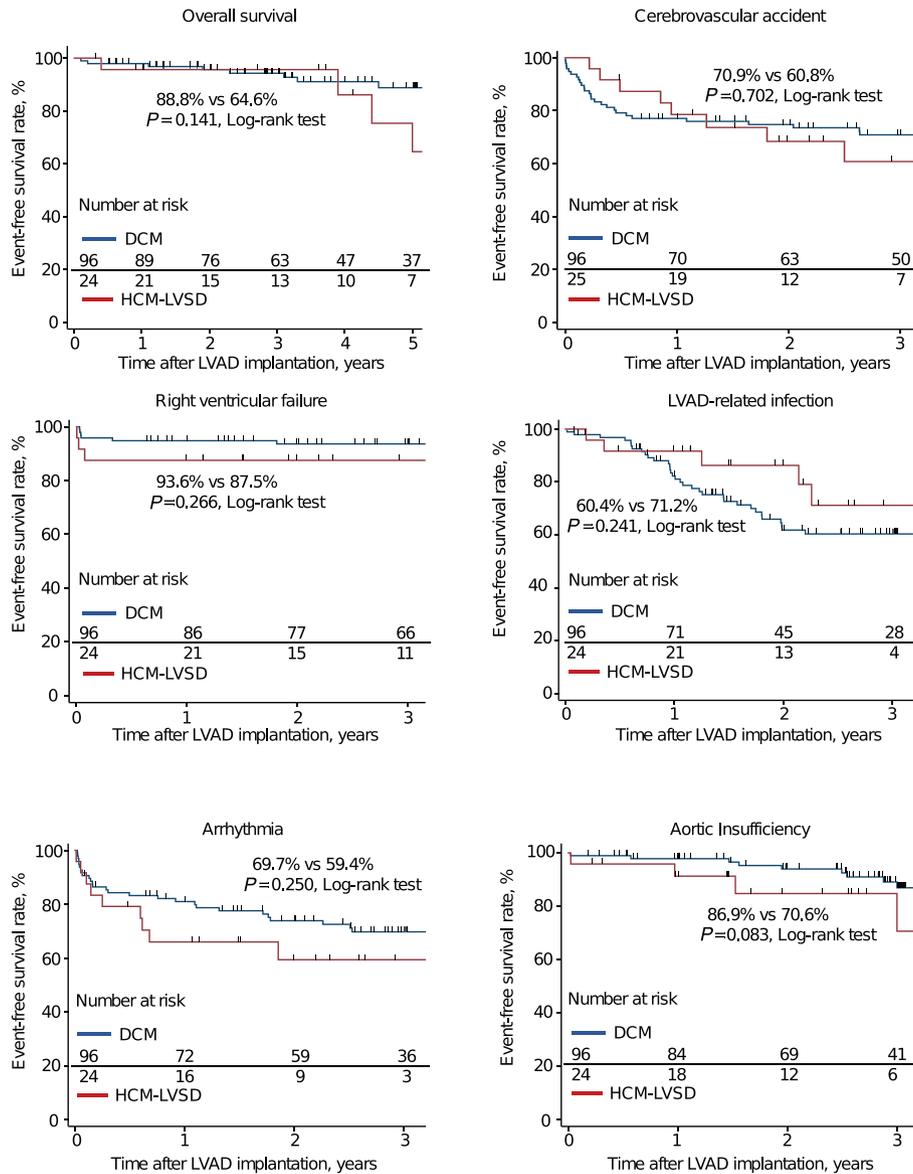


Figure 3 Kaplan–Meier curves for overall survival and freedom from the secondary endpoints stratified by patient group. Five-year overall survival was comparable in both groups (80.8% vs. 64.6%, $P = 0.141$; log-rank test) (left upper panel). There were no significant differences in the occurrence of cerebrovascular accident (3 year freedom from cerebrovascular accident rate = 70.9% vs. 60.8%, $P = 0.702$; log-rank test) (right upper panel), right ventricular failure (3 year freedom from right ventricular failure rate = 93.6% vs. 87.5%, $P = 0.266$; log-rank test) (left middle panel), LVAD-related infection (3 year freedom from LVAD-related infection rate = 60.4% vs. 71.2%, $P = 0.240$, log-rank test) (right middle panel), arrhythmia (3 year freedom from arrhythmia = 69.7% vs. 59.4%, $P = 0.250$; log-rank test) (left lower panel), and aortic insufficiency (3 year freedom from aortic insufficiency = 86.9% vs. 70.6%, $P = 0.133$; log-rank test) (right lower panel). DCM, dilated cardiomyopathy; HCM-LVSD, hypertrophic cardiomyopathy with left ventricular systolic dysfunction; LVAD, left ventricular assist device.



shown in Figure 3. There were no significant differences in the 3 year overall survival after LVAD implantation between the groups (DCM vs. HCM-LVSD, 94.3% vs. 95.7% at 1 year, and 88.8% vs. 64.6% at 5 years, respectively). Further, there were no significant differences in the incidence of cerebrovascular accidents, LVAD-related infection, aortic insufficiency, arrhythmia, or right ventricular failure between the two groups.

Discussion

This study compared the clinical characteristics and outcomes between HCM-LVSD and DCM patients after LVAD implantation. The prognosis of patients with HCM has been almost comparable with normal life expectancy, and most patients with HCM have been assumed to live equivalent lives to the

general healthy population, with or without mild symptoms.¹¹ Only a certain subset of patients with HCM experience adverse cardiac events, including sudden cardiac death and heart failure, and recent advances in prophylactic and therapeutic management for these adverse events (using implantable cardiac defibrillator, mechanical circulatory support, and heart transplantation) have further improved the prognosis of patients with HCM.^{12–14} However, continuing efforts are required to further elucidate the risk stratification and therapeutic strategies for patients with HCM. Among numerous heterogeneous HCM cohorts, HCM-LVSD is one of the recently recognized patterns of disease progression called ‘burned-out’, ‘end-stage’, or ‘dilated-phase’ HCM, which is characterized by reduced LV systolic function with frequent adverse cardiac events.^{15,16} A recent report regarding the clinical outcomes of HCM-LVSD revealed that, among 118 patients with HCM-LVSD, 61 patients (52%) developed refractory heart failure in under New York Heart Association (NYHA) functional class III/IV, 21 patients had appropriate implantable cardioverter defibrillator (ICD) shocks, 5 patients survived from resuscitated cardiac arrest, and 31 patients underwent heart transplantation.¹⁷ Another study that evaluated 553 patients with HCM-LVSD demonstrated that among 165 patients with NYHA functional class III/IV heart failure, 55 patients received heart transplantation, whereas 9 patients underwent LVAD implantation.⁶ These studies clearly demonstrated that patients with HCM-LVSD have a substantial risk of developing advanced heart failure; therefore, advanced therapies, including LVAD implantation and heart transplantation, are promising alternatives when HCM-LVSD is complicated by advanced heart failure that is refractory to conventional medical therapies.¹⁸

In the present study, we made three major observations with important clinical implications for the management of patients with HCM-LVSD who underwent LVAD implantation. First, compared with DCM patients, patients with HCM-LVSD still had smaller left ventricles with thicker ventricular walls, even in the advanced heart failure phase, such that they required LVAD implantation. Second, patients with HCM-LVSD had higher BNP values, thus compromising vulnerable haemodynamics and complicating the subclinical impairment of right ventricular function, compared with those with DCM, even after successful LVAD implantation. Third, despite higher BNP values with vulnerable haemodynamics, the clinical outcomes of patients with HCM-LVSD were comparable with those of patients with DCM after LVAD implantation.

Pathologically, HCM-LVSD has been reported to be characterized by diffuse, often transmural, fibrous replacement in the ventricular wall, and extracellular matrix metabolism has been associated with adverse ventricular remodelling.^{19,20} In the long run, these harmful patterns of ventricular remodelling gradually result in a decrease in LVEF, combined with dilation of the left ventricle and ventricular wall thinning. These features morphologically resemble DCM.^{5,21,22}

Therefore, if the transition of conventional HCM to HCM-LVSD has not been historically documented in a patient, it is often difficult to distinguish between HCM-LVSD and DCM. However, from our study results, we can infer that patients with HCM-LVSD had smaller left ventricles with thicker LV walls on echocardiography, and both echocardiographic findings of $PWT \geq 8$ mm and $LVDd \leq 68$ mm are strongly suggestive of HCM-LVSD especially in a specific patient population of end-stage heart failure requiring LVAD therapy. Although various modalities, such as pathological analysis and magnetic resonance imaging, have been recognized as useful for the correct diagnosis of HCM-LVSD in patients with DCM-like cardiomyopathy, our study results offer a novel and easier method of initial screening for the differential diagnosis between DCM and HCM-LVSD in advanced heart failure patients requiring LVAD therapy.^{21,23,24}

Although both groups in our study had almost comparable baseline characteristics (except for echocardiographic parameters), the post-operative BNP values and haemodynamic parameters highlight the potential pathophysiologic features of HCM-LVSD compared with those of DCM. Despite successful LVAD implantation with compensated post-operative haemodynamics in both groups, post-operative haemodynamic parameters clearly revealed impaired right ventricular function in patients with HCM-LVSD. Higher post-operative BNP values in HCM-LVSD may partially represent subclinical impairment of right ventricular function in HCM-LVSD, compared with DCM.

Despite impaired right ventricular function with higher BNP values in patients with HCM-LVSD compared with patients with DCM, there were no statistically significant differences between the two groups in the occurrence of adverse events (including overall survival, freedom from cerebrovascular accidents, LVAD-related infection, right ventricular failure, and aortic insufficiency) after LVAD implantation. These results were consistent with those of a previous study reporting LVAD implantation in patients with restrictive cardiomyopathy and HCM.²⁵ Previous studies regarding the clinical implication of post-operative BNP values in patients with LVAD reported that higher post-operative BNP values are predictors of adverse events, such as mortality, arrhythmia, and right ventricular failure.^{26–29} Hellman *et al.* reported that higher post-operative BNP values were associated with arrhythmic events in the early phase, specifically within 15 days after LVAD implantation. Furthermore, Yost *et al.* assessed the change in preoperative and 14 day post-operative BNP values, and patients with no improvement or with an increase in BNP levels after LVAD implantation were found to have higher mortality and more frequent occurrence of right ventricular failure. In fact, when we carefully reviewed our results, the Kaplan–Meier curve demonstrated that arrhythmic events tended to occur more frequently in the HCM-LVSD group (3 year freedom from arrhythmia, 69.7% vs. 59.4%, $P = 0.250$) (Figure 3). Furthermore, aortic

insufficiency also tended to occur more frequently in the HCM-LVSD group (3 year freedom from aortic insufficiency, 86.9% vs. 70.6%, $P = 0.133$) (Figure 3). Considering these non-statistically significant differences and the fact that, compared with the DCM group, the HCM-LVSD group had impairment in right ventricular function based on the results of the haemodynamic analysis, subclinical pathophysiological differences may exist in both groups after LVAD implantation, and these differences may potentially affect the ultimate patient prognosis. This speculation should be followed up by further assessment using a larger cohort with longer post-operative evaluation period.

Limitations

This study has several limitations. First, it is a retrospective observational study that was conducted at a single centre, using a relatively small patient cohort. Second, 117 patients (97.5%) underwent LVAD implantation for BTT; therefore, successful BTT during the study period may have biased the outcomes. Study subjects who had undergone LVAD implantation for DT may provide better information for purely assessing the clinical impact of LVAD therapy in this study setting. Third, patients with INTERMACS profile 1 are not indicated for implantable LVAD therapy in Japan; therefore, all enrolled patients with INTERMACS profile 2 or higher underwent LVAD implantation, a less sick profile even if they received LVAD through a bridge-to-bridge strategy. This may be another reason for the biased clinical outcomes.

Nevertheless, our findings are important because there is a paucity of data on the clinical outcomes of patients with HCM-LVSD after LVAD implantation in comparison with patients with DCM, and our study will offer novel insights into LVAD therapy in patients with HCM-LVSD.

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Conclusions

In conclusion, the current study demonstrated that patients with HCM-LVSD who underwent LVAD implantation had post-operative outcomes similar to those of patients with DCM, despite demonstrating higher BNP values and subclinical impairment of right ventricular function after LVAD implantation. Because of the smaller LV cavity with a thicker LV wall, LVAD implantation in patients with HCM-LVSD is often challenging. However, the results of current study serve as a favourable model and will facilitate the use of LVAD implantation in patients with HCM-LVSD.

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Conflict of interest

None declared.

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