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Incidence, predictors, and clinical impact of electrical storm in patients with left ventricular assist devices: New insights from the ASSIST-ICD study

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BACKGROUND Ventricular arrhythmias (VAs) can occur after continuous flow left ventricular assist device (LVAD) implantation as a single arrhythmic event or as electrical storm (ES) with multiple repetitive VA episodes.

OBJECTIVE We aimed at analyzing the incidence, predictors, and clinical impact of ES in LVAD recipients.

METHODS Patients analyzed were those included in the multicenter ASSIST-ICD observational study. ES was consensually defined as occurrence of ≥ 3 separate episodes of sustained VAs within a 24-hour interval.

RESULTS Of 652 patients with an LVAD, 61 (9%) presented ES during a median follow-up period of 9.1 (interquartile range [IQR] 2.5–22.1) months. The first ES occurred after 17 (IQR 4.0–56.2) days post LVAD implantation, most of them during the first month after the device implantation (63%). The incidence then tended to decrease during the initial years of follow-up and increased again after the third year post LVAD implantation. History of VAs before

LVAD implantation and heart failure duration > 84 months were independent predictors of ES. The occurrence of ES was associated with an increased early mortality since 20 patients (33%) died within the first 2 weeks of ES. Twenty-two patients (36.1%) presented at least 1 recurrence of ES, occurring 43.0 (IQR 8.0–69.0) days after the initial ES. Patients experiencing ES had a significantly lower 1-year survival rate than did those free from ES (log-rank, $P = .039$).

CONCLUSION There is a significant incidence of ES in patients with an LVAD. The short-term mortality after ES is high, and one-third of patients will die within 15 days. Whether radiofrequency ablation of arrhythmias improves outcomes would require further studies.

KEYWORDS Electrical storm; Mortality; Left ventricular assist device; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia

Introduction

Continuous flow left ventricular assist devices (LVADs) have emerged as an alternative therapy for patients with end-stage heart failure, and implantation rates are constantly increasing.¹ The long-term unloading of the left ventricle mediated by the LVAD decreases heart failure symptoms and improves quality of life.

However, many complications can occur during follow-up, such as stroke, bleeding, infections, or ventricular arrhythmias (VAs). Indeed, the rates of VAs occurring in the early postoperative period or during follow-up have been described to range between 22% and 24.8%^{2,3} and between 11.6% and 39.0%,^{3–9} respectively, after 8–15 months of follow-up. Antiarrhythmic drugs and/or ablation of the ventricular substrate could help to avoid recurrences and improve outcomes.

The presentation of VAs is highly variable and can occur as a single ventricular tachycardia (VT) or fibrillation (VF) event or as electrical storm (ES) with multiple repetitive VT/VF episodes. ES is a life-threatening event in patients without an LVAD, increasing mortality, and hospitalization rates, both in the acute phase and during long-term follow-up,¹⁰ but its impact in patients with an LVAD has been evaluated only in a small series of patients.¹¹ Thus, we aimed at analyzing the incidence, predictors, and clinical impact of ES in the large cohort of patients included in the ASSIST-ICD study.

Methods

Study design

ASSIST-ICD is a retrospective multicenter observational study (ClinicalTrials.gov identifier NCT02873169) of durable mechanical circulatory support devices implanted at 19 tertiary French centers. The methods of this study have been previously published.⁶

Briefly, patients 18 years and older implanted with axial HeartMate II (Abbott, Chicago, IL), Jarvik2000 (Jarvik

Heart, Inc., New York, NY), or centrifugal HeartWare pumps (Medtronic, Columbia Heights, MN) between February 2006 and December 2016 were included in the final analysis. The type of pump implanted depended on the local heart team's decision in each center. Exclusion criteria were as follows: patients who underwent total artificial heart placement or pulsatile flow LVAD implantation, those with a history of heart transplantation, and VentrAssist (Ventricor, Chatswood, New South Wales, Australia) recipients. Patients lost to follow-up or LVAD recipients with lacking data were excluded from the final analysis.

This study was approved by the regional ethics committees, the French Advisory Committee on the Treatment of Research Information in the Field of Health (CCTIRS), and the French National Commission of Informatics and Civil Liberties (CNIL). A nonopposition letter was sent to patients as requested by French authorities for retrospective studies.

Baseline assessment and follow-up

Baseline data, including demographic characteristics, cardiac disease and heart failure, history of VAs and supraventricular tachycardia before or after LVAD implantation, echocardiographic data, and blood chemistry values, were collected from hospital files for all enrolled patients. Regarding perioperative data, data on combined surgery with LVAD implantation and need of right extracorporeal life support were collected. Follow-up was performed according to each institution's protocols. The last day of follow-up was December 31, 2016, the date of heart transplantation, or death, whichever occurred first.

VAs

As previously described,⁶ VAs were defined as sustained (> 30 seconds) VT or VF without an acute reversible cause and treated medically, by external electrical shock, or by appropriate therapy from an implantable cardioverter-defibrillator (ICD; antitachycardia pacing or shock). The

type of arrhythmias was collected. *ES* was consensually defined as the occurrence of ≥ 3 separate episodes of sustained VAs within a 24-hour interval.

In the article,⁶ we included a subset of the entire ASSIST-ICD cohort and consequently, the number of LVAD recipients with *ES* is different compared to the number of patients with *ES* in the current paper. Indeed, in this work, we included the overall ASSIST-ICD population.

Study end points

The primary end points of the study were the rates of *ES*. Secondary end points included all-cause mortality during follow-up, depending on the occurrence of *ES* or not. Deaths were classified as cardiovascular death (cardiac or vascular cause) or noncardiac death.

Statistical analysis

Qualitative variables are expressed as number (percentage); continuous data as mean \pm SD or median (interquartile range [IQR]) depending on their distribution, which was assessed using the Kolmogorov-Smirnov test. Survival rates were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. Predictors of *ES* were analyzed using univariate and multivariate proportional hazards models (cumulative outcomes). The proportional hazards assumption was tested and verified for each covariate. All univariate analyses were performed on complete cases. For the purposes of multivariate analysis, assuming missing data were randomly missing, multiple imputation using Monte Carlo Markov chained equations was used to generate 10 data sets without missing values. Only 2 variables of interest had missing data: left ventricular end-diastolic diameter (12.0%) and total bilirubin level (13.7%). At this point, receiver operating characteristic curves were used on the original data to dichotomize continuous variables with a *P* value of $<.1$ in univariate analysis using the Youden's index to choose the optimal cutoff. Variables with a *P* value of $<.1$ in univariate analysis were included in the multivariate analysis to derive adjusted hazard ratios with their 95% confidence intervals, which were then combined using Rubin's rule. Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY).

Results

Study population

From 2006 to 2016, a total of 659 patients were implanted with a continuous flow LVAD and included in the study. Seven patients were excluded (3 patients received a VentrAssist device and 4 patients died during the LVAD surgery). Thus, a total of 652 patients were included in the final analysis. Of these patients, 61 (9%) presented *ES* during a median period of 9.1 (IQR 2.5–22.1) months of follow-up. Patients' characteristics are described in [Table 1](#). Briefly, patients presenting *ES* during follow-up had a significantly higher body mass index, a longer history of heart failure, and larger ventricles. A significantly higher proportion of patients with a

history of VAs was observed in patients with *ES* (64.0% vs 31.1%; $P < .001$), and consequently, these patients were more often implanted with an ICD. Of 39 patients having experienced VAs before LVAD implantation, 23 (59%), 5 (12.8%), and 11 (28.2%) had VT, VF, or both VT/VF episodes, respectively. Interestingly, both groups had a similar proportion of the underlying heart disease and LVAD indication. Lastly, the type of LVAD implanted was similar between groups. Of note, patients with *ES* had a significantly higher VT-LVAD score than did those without *ES* (6.0 [4.75–8.0] vs 4.0 [2.0–6.0]; $P < .001$).

In multivariate analysis, history of VAs before LVAD implantation (hazard ratio 2.620; 95% confidence interval 1.484–4.627; $P = .001$) and heart failure duration > 84 months (hazard ratio 1.966; 95% confidence interval 1.074–3.597; $P = .028$) were independent predictors of the occurrence of *ES* ([Table 2](#)).

Characteristics and temporal trend in ES occurrence after LVAD implantation

Of 61 patients, 37 (61%), 10 (16%), and 14 (23.0%) had VT, VF, and both VT/VF episodes during the initial *ES* event, respectively. The relationship between the type of VAs before LVAD implantation and the type of VAs during *ES* in 39 patients with a history of arrhythmias is shown in [Figure 1](#). As one can observe, patients having experienced VT episodes mainly had only VT recurrences during *ES*. [Figure 1](#) also illustrates that 22 patients without VA (36.1%) before LVAD implantation experienced at least 1 *ES* after LVAD implantation.

ES occurred after a median of 17 (IQR 4.0–56.2) days after LVAD implantation. As shown in [Figure 2](#), the temporal trend in *ES* occurrence in LVAD recipients tended to follow a U-shaped curve. Indeed, most of the *ES* events occurred during the first month (63%) after the implantation of the device. Twenty-two *ES* events occurred during the first week after LVAD implantation, including 6 within the first 24 hours of surgery. Thereafter, few *ES* events occurred during the first year after implantation and no event occurred during the following 2 years. After the third year, new *ES* episodes were observed (6 *ES* episodes in 89 patients alive after 1000 days of follow-up [7%]). Three groups of patients experiencing *ES* were compared depending on the time of occurrence: early *ES* (<30 days), late *ES* (>30 days), and very late *ES* (>1000 days). As shown in [Supplemental Table 1](#), LVAD recipients who experienced very late *ES* had significantly more idiopathic cardiomyopathy, with a trend in longer heart failure duration and more history of supraventricular tachycardia.

In addition to the usual medical management with antiarrhythmic drugs and/or cardioversion/defibrillation shocks or antitachycardia pacing, 6 patients (10%) had radiofrequency ablation of VAs. A total of 9 VTs were targeted: 1 was related to the LVAD cannula, 2 were bundle branch reentrant VTs, and the intrinsic myocardial scar was involved in 6 VTs (septal region [$n = 3$], anterior region [$n = 2$], and inferior

Table 1 Patients' characteristics

Variable	Patients with ES (n = 61)	Patients without ES (n = 591)	P
Age (y)	59.0 (54.0–65.0)	60.0 (51.0–66.0)	.86
Men	53 (87)	508 (86.0)	.99
BMI (kg/m ²)	26.0 (24.0–29.0)	25.0 (22.0–28.0)	.01
Heart failure etiology			
Ischemic	38 (62.0)	374 (63.0)	
Idiopathic	19 (31.0)	159 (27.0)	.61
Other	4 (7.0)	58 (10.0)	
Heart failure duration (mo)	133.0 (56.0–226.0)	55.0 (2.0–158.0)	<.001
Echocardiographic data			
LVEDD before LVAD implantation (mm)	73.0 (66.0–76.0)	69.0 (63.0–75.0)	.008
LVEF before LVAD implantation (%)	20.0 (15.0–23.0)	20.0 (15.0–25.0)	.176
History of arrhythmias			
History of VAs	39 (64.0)	184 (31.0)	<.001
VT ablation before LVAD implantation	4 (7.0)	32 (5.0)	.938
History of supraventricular tachycardia	36 (59.0)	266 (45.0)	.051
Devices before LVAD implantation			
ICD before LVAD implantation	50 (82.0)	353 (60.0)	.001
CRT before LVAD implantation	23 (38.0)	175 (30.0)	.245
Arrhythmic drugs before LVAD implantation			
β-Blockers	51 (84)	372 (63.0)	.002
Amiodarone	33 (54.0)	258 (44.0)	.154
Laboratory values			
Serum creatinine level (μmol/L) (n = 598)	123.0 (98.0–154.0)	113.0 (86.0–147)	.135
Serum sodium level (mmol/L) (n = 599)	136.0 (132.0–138.0)	136.0 (132.0–139.0)	.826
Total bilirubin level (μmol/L) (n = 563)	18.0 (11.0–31.0)	16.0 (10.0–26.0)	.102
Type of LVAD			
HeartMate II	44 (72.0)	431 (73.0)	
HeartWare	15 (25.0)	112 (19.0)	.273
Jarvik2000	2 (3.0)	48 (8.0)	
LVAD indication			
Bridge to transplantation	38 (60.0)	349 (59.0)	
Destination therapy	21 (34.0)	226 (38.0)	.829
Bridge to decision/recovery	2 (3.0)	16 (3.0)	
Combined surgery with LVAD	9 (15.0)	86 (15.0)	.882
Right ECLS during surgery	7 (11.0)	74 (12.0)	.975
VT-LVAD score	6.0 (5.0–8.0)	4.0 (2.0–6.0)	<.001

Values are presented as median (interquartile range) or as n (%).

BMI = body mass index; CRT = cardiac resynchronization therapy; ECLS = extracorporeal life support; ES = electrical storm; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; VA = ventricular arrhythmia; VT = ventricular tachycardia.

basal region [n = 1]). Of these 6 patients, 2 had ES recurrences during follow-up, 1 died 65 days after the occurrence of ES, 4 were heart transplanted, and 1 was alive at the end of follow-up. Of note, no LV- or LVAD-related thrombosis was reported after VT ablation.

Clinical outcomes after ES

The occurrence of ES was associated with a high early mortality. As shown in the Kaplan-Meier curve in [Figure 3A](#), 11 patients (18.0%) died within 24 hours of ES, 20 patients (33.0%) died within the first 2 weeks of ES, and 28 patients (41.0%) died during the first 2 months. Notably, as illustrated in [Figure 3B](#), patients experiencing ES had a significantly lower 1-year survival rate than did those free from ES ($P = .039$).

Of the 20 deaths during the first 2 weeks, 15 were due to ES (as a consequence of multiple organ failure and/or right ventricular dysfunction), 1 due to LVAD thrombosis, 2 due to sep-

tic shock, 1 due to hemorrhagic shock, and 1 due to a stroke. Twenty-two patients (36.0%) presented at least 1 recurrence of ES, occurring a median of 43.0 (IQR 8.0–69.0) days after the initial ES. Eight of these patients died, including 7 because of the second ES (death occurring 8 [0.75–22.0] days after ES recurrence), and 1 patient had a fatal stroke 1 year later. The remaining 14 patients were still alive after 225.0 (IQR 31.0–538.0) days of follow-up. The causes of deaths in the study population are presented in [Table 3](#). Of note, the rate of arrhythmic death did not differ between patients implanted and those not implanted with an ICD. Of 61 patients with ES, 16 (26.0%) were transplanted after a median of 188.5 (IQR 52.0–565.0) days of the occurrence of ES.

Discussion

Main results

The main results of this study are as follows: (1) Almost 10% of patients implanted with an LVAD will present

Table 2 Multivariate analysis for risk prediction of ES

Variable	β coefficient	Multivariate hazard ratio (95% confidence interval)	<i>P</i>
VAs before LVAD implantation	0.963	2.620 (1.484–4.627)	.001
Heart failure duration > 84 mo	0.676	1.966 (1.074–3.597)	.028
BMI > 24.5 kg/m ²	0.556	1.743 (0.981–3.097)	.058
Bilirubin level > 22 mmol/L	0.518	1.679 (0.993–2.839)	.053
LVEDD > 71 mm	0.276	1.318 (0.737–2.357)	.352
ICD before LVAD implantation	0.221	1.247 (0.595–2.614)	.559

Values are presented as median (interquartile range) or as n (%).

Receiver operating characteristic curves were used to dichotomize continuous variables with a *P* value of <.1 in univariate analysis using the Youden's index to choose the optimal cutoff, as described above.

BMI = body mass index; ES = electrical storm; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; LVEDD = left ventricular end-diastolic diameter; VA = ventricular arrhythmia.

ES after mid-term follow-up; (2) history of VAs before LVAD implantation and long heart failure duration are predictors of the occurrence of ES during follow-up; and (3) ES in patients with an LVAD is a severe event, and one-third of the patients presenting ES will die within 15 days of the arrhythmic event.

VAs in patients with an LVAD

VAs in patients with an LVAD can occur early during the postoperative period or later during long-term follow-up. Data on early VAs are scarce, but have been shown to occur in 1 in every 4 patients.^{2,3} Mechanisms such as suction, inotropic medication, ionic imbalance, or high catecholamine state can precipitate early VAs, although many early VAs occur despite any identifiable factor.² Early VAs significantly increase postoperative mortality,³ although no impact on long-term survival was observed. A history of VAs,^{2,3} age,² non-ischemic cardiomyopathy,² and a history of cardiac surgery before LVAD implantation³ were described as predictors of early VAs. Late VAs have been thoroughly studied and are

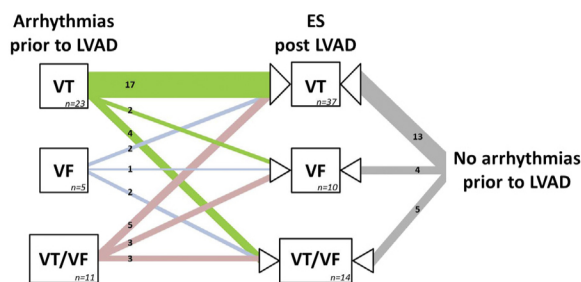


Figure 1 Relationship between the type of arrhythmias before LVAD implantation and the type of arrhythmias at the time of ES in 39 patients with a history of VAs and 22 patients with no history of VAs. ES = electrical storm; LVAD = left ventricular assist device; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

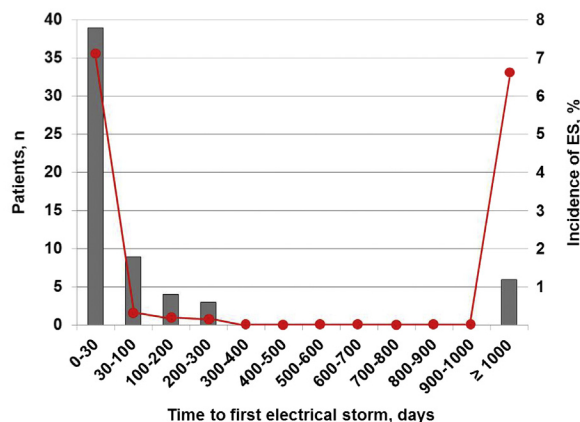


Figure 2 Temporal trend in the occurrence of ES. The absolute number of patients with a first episode of ES and the respective incidence are depicted as gray bars and red dots, respectively. ES = electrical storm.

often the consequence of the underlying cardiomyopathy. A wide range of incidence was described (from 11.6% to 39.0%),^{3–9} and the clinical impact of late VAs is still controversial since most of the patients are implanted with an ICD quickly detecting and terminating VT before an overt hemodynamic consequence may occur. Many predictors of late VAs were described in the literature,^{4–6,8,9} recently summarized in the larger series published so far as the VT-LVAD score⁶ (predictors: history of VAs, no angiotensin-converting enzyme inhibitors, heart failure duration > 12 months, early VAs after implantation, and history of atrial fibrillation and non-ischemic cardiomyopathy).

To our knowledge, only 1 study specifically evaluated the incidence and clinical consequences of ES in LVAD recipients.¹¹ Forty-three patients implanted with HeartMate II were included and followed for 18.5 ± 18.5 months. Of these patients, 12 (27.9%) experienced ES after an average of 9.1 ± 7.8 days and most of them during the initial 2 weeks after implantation. Early ES was associated with a significantly higher mortality rate at 1 month, although 1-year survival did not differ between patients having experienced and those not having experienced ES. In our larger population of 652 patients, a lower ES incidence of 9.4% was observed, a comparable rate as described in patients with an ICD implanted in primary (4% after 20.6 months)¹² or secondary (10%–20%) prevention.¹³

As shown in Figure 2, the large majority of episodes occurred during the first month after implantation. As stated above, the postoperative period is a critical time point for the occurrence of VAs. Inotropic drugs or electrolyte imbalance may predispose to VAs and specifically to ES.² A transient postoperative QT interval prolongation has also been described and may contribute to the occurrence of VAs and ES.¹⁴ Interestingly, the incidence of ES tended to decrease over the first year, suggesting an anti-arrhythmic-like mechanism of LVAD. Indeed, few studies showed that the rate of VAs was reduced in patients with an LVAD,¹⁵ probably explained by an initial reverse ventricular remodeling at the molecular level,¹⁶ maybe because of ventricular unloading. However, the arrhythmic substrate may progress later,

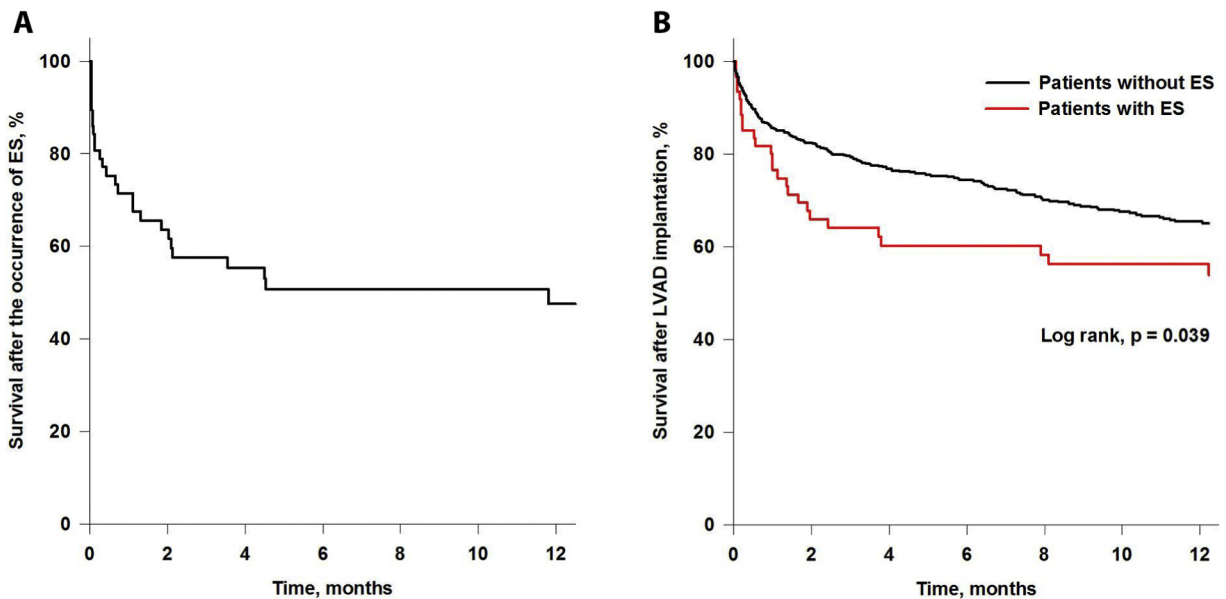


Figure 3 Kaplan-Meier survival curve. **A:** Survival probability after the occurrence of ES. **B:** Survival probability after LVAD implantation, depending on the occurrence of ES during follow-up. ES = electrical storm; LVAD = left ventricular assist device.

explaining the recrudescence of ES after few years of follow-up, as observed in our study. Lastly, as previously demonstrated in populations with an ICD,¹⁷ we show that a history of VAs increased the risk of ES in patients with an LVAD.

Impact of ES on clinical outcomes

The adverse prognosis of ES has been thoroughly studied. A meta-analysis comprising 857 patients with ES demonstrated a 3-fold increased risk of death.¹⁷ A negative impact on hospitalization rates and patients' quality of life was described.¹⁷ In our study, a similar negative impact of ES was observed. Indeed, a high mortality rate was observed on the following days and weeks after ES, with the vast majority of deaths being directly due to ES.

Table 3 Causes of deaths

Variable	Patients with ES (n = 61)	Patients without ES (n = 591)	P
Total death	33 (54.0)	258 (44.0)	.154
Cause of death			
Cardiovascular death	24 (73.0)	101 (39.0)	.001
Noncardiovascular death	9 (27.0)	153 (59.0)	
Unknown cause	0 (0)	4 (2.0)	
Cardiovascular death			
LVAD thrombosis	2 (8.0)	28 (28.0)	<.001
Right ventricular failure	4 (17.0)	50 (49.0)	
Electrical storm	17 (71.0)	0 (0.0)	
LVAD dysfunction	1 (4.0)	1 (1.0)	
Others	0 (0.0)	9 (9.0)	
No precision	0 (0.0)	13 (13.0)	

Values are presented as n (%).

ES = electrical storm; LVAD = left ventricular assist device.

As recently demonstrated by Vergara et al,¹⁸ patients with ES are the population with VT at the highest risk of recurrence and mortality. The mechanism leading to the higher mortality observed after ES is still a matter of debate, but may be the consequence of the arrhythmia itself; of the deleterious effect of the multiple cardioversion/defibrillation shocks delivered to restore sinus rhythm, inducing myocardial damage; or of the advanced cardiomyopathy presented by the patient.¹⁹ In our recent report on VA occurring lately after LVAD implantation, we showed that late VA did not increase mortality. Indeed, having just 1 isolated late VA or multiple ones separated by a certain period of time in a hemodynamically stable patient is probably less pejorative than having multiple repetitive episodes of arrhythmias within 24 hours, specifically during the postoperative period, where patients are more prone to hemodynamic instability and electrical disturbances, potentially explaining the adverse outcomes observed.

However, successful radiofrequency ablation of VAs has been shown to improve survival in patients with ES, specifically in those with no inducible VT at the end of the procedure.¹⁸ Data on VA ablation in patients with an LVAD are scarce, but recent data reported the safety and efficacy of the procedure, with good arrhythmia-free survival after mid-term follow-up.²⁰ To note, most of the VAs were related to the underlying substrate rather than the apical cannula. In our study, we found similar results with only 1 VT related to the LVAD cannula. Indeed, the underlying cardiomyopathy substrate was involved in the majority of targeted VTs.

Since VAs and specifically ES increase short-term mortality and since many electrophysiologists would be reluctant to perform ablation in a patient with an LVAD implanted, it would be interesting to analyze whether an invasive

management of VAs before LVAD implantation would reduce the rate of VAs and thus improve survival. Further studies are warranted to validate this assumption. This is indeed crucial since epicardial VT ablation may be needed in some patients with non-ischemic cardiomyopathies—ablation that cannot be performed after LVAD implantation. An intraoperative approach for VA ablation may also be discussed in such patients.

Limitations

This study has some limitations, including its retrospective design that may have affected the results. Specific antiarrhythmic drugs used during ES events were not available, and consequently, conclusions on outcomes depending on the treatment used cannot be drawn. Indeed, as stated above, successful radiofrequency ablation of VAs has been shown to improve outcomes and survival.¹⁸ However, in our study, only 6 of 61 patients were offered an ablation procedure and therefore similar conclusions on outcomes or survival in patients with an LVAD cannot be drawn.

Conclusion

In this large multicenter study, we demonstrate a relatively high incidence of ES in patients with an LVAD. Indeed, 1 in every 10 patients will experience ES during follow-up, specifically those with a history of VAs before LVAD implantation, and occurring in the first postoperative month for two-thirds of them. The short-term mortality after ES is elevated, and one-third of the patients will die within 15 days. Whether invasive radiofrequency ablation of arrhythmias, in association with antiarrhythmic therapy, improves outcomes would require further studies.

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