American Heart Journal Plus: Cardiology Research and Practice 22 (2022) 100211

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research Paper

Baseline QRS duration associates with cardiac recovery in patients with continuous-flow left ventricular assist device implantation

Muhammad S. Khan [a,1], Christos P. Kyriakopoulos [a,b,1], Iosif Taleb [a,b], Elizabeth Dranow [b], Monte Scott [b], Ravi Ranjan [a,b,c], Michael Yin [b], Eleni Tseliou [b], Rami Alharethi [d], William Caine [d], Robin M. Shaw [a,b], Craig H. Selzman [a,e], Stavros G. Drakos [a,b,c,*], Derek J. Dosdall [a,b,c,e,**]

[a] Nora Eccles Harrison Cardiovascular Research and Training Institute, The University of Utah, Salt Lake City, UT, United States of America
[b] Division of Cardiovascular Medicine, Department of Internal Medicine, University of Utah Health & School of Medicine, Salt Lake City, UT, United States of America
[c] Department of Biomedical Engineering, The University of Utah, Salt Lake City, UT, United States of America
[d] Cardiovascular Department, Intermountain Medical Center, Salt Lake City, UT, United States of America
[e] Division of Cardiothoracic Surgery, Department of Surgery, University of Utah Health & School of Medicine, Salt Lake City, UT, United States of America

ARTICLE INFO

Keywords:
QRS duration
LVAD
Cardiac recovery
LVEF
LVEDD
Electrical remodeling

ABSTRACT

Objective: In chronic heart failure (HF) patients supported with continuous-flow left ventricular assist device (CF-LVAD), we aimed to assess the clinical association of pre-LVAD QRS duration (QRSd) with post-LVAD cardiac recovery, and its correlation with pre- to post-LVAD change in left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD).

Methods: Chronic HF patients ($n = 402$) undergoing CF-LVAD implantation were prospectively enrolled, at one of the centers comprising the U.T.A.H. (Utah Transplant Affiliated Hospitals) consortium. After excluding patients with acute HF etiologies, hypertrophic or infiltrative cardiomyopathy, and/or inadequate post-LVAD follow up (<3 months), 315 patients were included in the study. Cardiac recovery was defined as LVEF $\geq$ 40 % and LVEDD $<$ 6 cm within 12 months post-LVAD implantation. Patients fulfilling this condition were termed as responders (R) and results were compared with non-responders (NR).

Results: Thirty-five patients (11 %) achieved 'R' criteria, and exhibited a 15 % shorter QRSd compared to 'NR' (123 $\pm$ 37 ms vs 145 $\pm$ 36 ms; $p < 0.001$). A univariate analysis identified association of baseline QRSd with post-LVAD cardiac recovery (OR: 0.986, 95 % CI: 0.976–0.996, p < 0.001). In a multivariate logistic regression model, after adjusting for duration of HF (OR: 0.990, 95 % CI: 0.983–0.997, $p = 0.006$) and gender (OR: 0.388, 95 % CI: 0.160–0.943, $p = 0.037$), pre-LVAD QRSd exhibited a significant association with post-LVAD cardiac structural and functional improvement (OR: 0.987, 95 % CI: 0.977–0.998, $p = 0.027$) and the predictive model showed a c-statistic of 0.73 with $p < 0.001$. The correlations for baseline QRSd with pre- to post-LVAD change in LVEF and LVEDD were also investigated in 'R' and 'NR' groups.

Conclusion: Chronic advanced HF patients with a shorter baseline QRSd exhibit an increased potential for cardiac recovery after LVAD support.

1. Introduction

In patients with advanced heart failure (HF) refractory to medical therapy, continuous-flow (CF) left ventricular (LV) assist devices (LVADs) have been used as a bridge to transplantation [1,2], as destination therapy [3], as a bridge to transplant candidacy, and/or as a bridge to recovery [4,5]. The number of LVAD implantations has continued to grow in the US in comparison with the number of heart transplantations [6,7]. While left ventricular ejection fraction (LVEF) during mechanical unloading is used to identify patients achieving

* Correspondence to: S.G. Drakos, Division of Cardiovascular Medicine, Nora Eccles Harrison Cardiovascular Research and Training Institute, The University of Utah – Health, 30 North Medical Drive, Salt Lake City, UT 84132, United States of America.
** Correspondence to: D. J. Dosdall, Division of Cardiothoracic Surgery, Nora Eccles Harrison Cardiovascular Research and Training Institute, The University of Utah – Health, 95 South 2000 East, Salt Lake City, UT 84112, United States of America.
E-mail addresses: stavros.drakos@hsc.utah.edu (S.G. Drakos), derek.dosdall@utah.edu (D.J. Dosdall).
[1] Authors contributed equally.

https://doi.org/10.1016/j.ahjo.2022.100211
Received 5 July 2022; Received in revised form 14 September 2022; Accepted 16 September 2022
Available online 17 September 2022

cardiac recovery, it has showed no predictive value prior to LVAD implantation [8]. LV torsion has been found to play a pivotal role in facilitating the homogenous distribution of myocardial forces during systole [9]. Clinical studies in chronic HF patients have associated LV rotational dynamics with the degree of remodeling and the extension of myocardial fibrosis [10,11]. In addition, LV global longitudinal strain has been previously studied and correlated with the extent of myocardial fibrosis in patients with advanced HF [12,13]. Previous studies have focused on a prolonged QRS duration (QRSd) that appears common in patients with reduced LVEF and were hospitalized for HF management [14–16]. Further, the impact of LVAD unloading on the electrical properties (QRS, QT and QTc duration) of the failing heart has also been reported [17].

In this study, we sought to examine whether baseline QRSd associates with post-LVAD cardiac recovery in chronic heart failure (CHF) patients undergoing LVAD implantation. We further demonstrate the correlations for baseline QRSd with pre- and post-LVAD LVEF and LVEDD in LVAD patients, and compared the data of those who showed a successful cardiac recovery with those who did not show recovery within 12 months of LVAD support. Finally, in addition to univariate and bivariate analyses, a multivariate logistic regression model is reported including other clinical parameters to find whether the baseline QRSd is independently associated with post-LVAD cardiac recovery.

2. Materials and methods

2.1. Patient population

Advanced cardiomyopathy patients (n = 402) implanted with a continuous-flow LVAD from 2009 to 2017 are included and followed through 2018. Patients were prospectively consented and enrolled at the Utah Transplantation Affiliated Hospitals (U.T.A.H.) Cardiac Transplant Program (i.e. University of Utah Health, Intermountain Medical Center, and George E. Wahlen Veterans Affairs Medical Center). The study was approved by the Institute Review Board (IRB) - The University of Utah, Salt Lake City, UT 84112. Ethical approval was given, and the patients were consented under the IRB 30622 - "Effects of Mechanical Unloading on Myocardial Function and Structure in Humans study". Acute HF etiologies, hypertrophic or infiltrative cardiomyopathy, baseline LVEF $\geq$ 40 %, and inadequate post-LVAD follow up (<3 months) were the exclusion criteria. Our final study cohort included a total of 315 patients [56 $\pm$ 15 years old, 267 (85 %) male] as shown in Fig. 1. The patients' long-term medications regimen before LVAD implantation included β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), aldosterone antagonists, and diuretics. About 71 % patients were NYHA class IV. Implanted devices were HeartMate II™ (n = 121), HeartMate 3™ (n = 17), HeartWare™ (n = 156) and others (n = 21). After implantation, the LVAD speed was adjusted to achieve adequate flows and left ventricular decompression. The pump speed during the post-implantation hospitalization and at subsequent outpatient clinic visits was adjusted under echocardiographic guidance to achieve a midline position of the interventricular and interatrial septum, minimum mitral valve regurgitation, and intermittent aortic valve opening in order of decreasing priority. Patients were medically managed at the discretion of the treating physicians, with the goal to achieve maximum doses of guideline-directed HF medications as tolerated by the patient.

2.2. Responder and non-responder definitions

LVAD-induced cardiac recovery was defined as an LVEF $\geq$ 40 % and LVEDD < 6 cm within 12 months post-LVAD implantation, based on

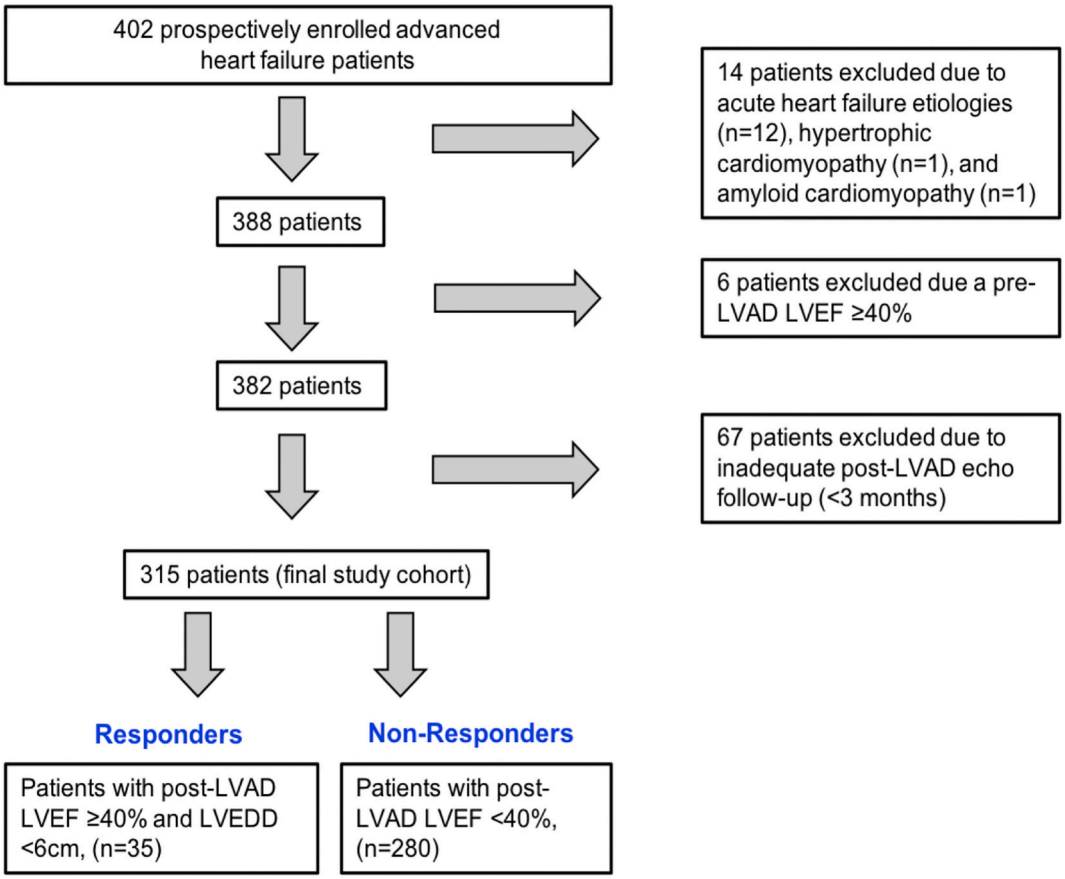

Fig. 1. Flowchart description of advanced HF patients undergoing LVAD implantation and included in the study.

prior publications [18,19]. Patients fulfilling the above criteria were termed responders (R) ($n = 35$) with their counterparts not achieving significant cardiac structural and functional improvement following LVAD implantation, constituting the non-responders (NR) group ($n = 280$). Of the 35 patients classified as Responders, 13 were explanted from their LVAD due to recovery after a median of 12 months (IQR 9,19) on LVAD support. Of the 13 explanted patients: 6 (46 %) are alive (May 2022) after a median of 75 months (IQR 64,84) post-LVAD explantation, 4 (31 %) died after a median of 9 months (IQR 5,22) post-LVAD explantation, 3 (23 %) received a heart transplantation after a median of 46 months (IQR 8,47) post-LVAD explantation. Of the 4 patients that died, 2 relapsed to illicit drug use and discontinued HF medications, 1 committed suicide 2 weeks after LVAD explantation (while his myocardial function was good), and 1 exhibited non-sustained recovery and died 9 months after LVAD explantation. Of the 3 patients that received a heart transplantation, 1 exhibited non-sustained recovery and was listed for transplantation, 1 relapsed to illicit drug use and discontinued HF medications, but subsequently abstained from drug use and was listed for transplantation, and 1 had a smoldering driveline infection that we could not eradicate due to surgical reasons, and this potentially contributed to the HF recurrence.

2.3. Echocardiograms and electrocardiograms

Transthoracic echocardiograms were performed within 1 week prior to LVAD implantation, 2 weeks preceding LVAD implantation, and then serially at months 1, 2, 3, 4, 6, 9, and 12 after implantation, using a protocol developed and tested at the Utah Cardiac Recovery Program [20]. Complete 2-dimensional, M-mode, and Doppler images were recorded from standard views in accordance with current American Society of Echocardiography guidelines and the European Association of Cardiovascular Imaging [19,21]. Last available reported LVEF and LVEDD values within 1-year post-LVAD implant were used to assess cardiac recovery.

The QRS interval was measured via the electrocardiogram performed prior to and closest to the LVAD implantation using lead II. In our prospective database, the QRS interval was captured using the automated electrocardiograph measurement, however for the purpose of this study it was manually measured via review of digitally stored electrocardiograms by two independent reviewers (C.P.K. and I.T.) using lead II.

2.4. Statistical analysis

Continuous variables are expressed as mean ± standard deviation and were compared using unpaired *t*-tests. Categorical variables are expressed as counts and percentages and were compared using chi-square test. Pearson's r correlations were computed to evaluate the association of QRSd with structural and functional measures (LVEDD and LVEF) pre and post LVAD implant. All assumptions for statistical tests including normality, homogeneity of variance, and linear association were assessed graphically, using histograms, P-P plots and scatter plots, as appropriate.

Univariable logistic regression analyses were performed to determine the effect of pre-implant parameters that included demographics, comorbidities, clinical, echocardiographic, hemodynamic, laboratory variables on responder status by 12 months. Odds ratios (OR) and the associated 95 % confidence intervals (CI) were calculated. For the development of the logistic regression multivariable model, predictors significant at the $p < 0.20$ level in unadjusted analyses were considered for inclusion as were variables suggested to be significant based on previous studies. Missing data were imputed using the multivariate imputation by chained equations method of multiple multivariate imputation [22,23], a method shown to be effective in logistic regression model [24]. Variables with >50 % missing data were excluded from model consideration, and no relevant variables had >5 % missing data.

The presence of collinearity among candidate covariates was assessed with the variance inflation factor diagnostic [25]. A bootstrap inclusion fraction (BIF) was calculated for each potential predictor, defined as the percentage of time that each variable would be retained in the model as a significant predictor in 1000 bootstrap resamples, in which the backwards elimination variable selection is repeated [26]. Variables with BIFs <50 % were dropped from the model as unreliable, as these would not likely remain significant predictors in external data sets. A p-value < 0.10 was used to screen covariates for inclusion in the multivariable analysis. Receiver-operator-characteristics curve analysis was performed to determine the accuracy of pre-LVAD QRSd along with other potential variables to predict post-LVAD cardiac recovery.

Continuous variables are expressed as mean ± standard deviation and were compared using unpaired *t*-tests. Categorical variables are expressed as counts and percentages and were compared using chi-square test. Pearson's r correlations were computed to evaluate the association of QRSd with structural and functional measures (LVEDD and LVEF) pre and post LVAD implant. All assumptions for statistical tests including normality, homogeneity of variance, and linear association were assessed graphically, using histograms, P-P plots and scatter plots, as appropriate. All significance tests were 2-tailed, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata 16.0 [27].

2.5. Data sharing

The data, analytical methods, and study materials will be made available to other researchers for the purposes of reproducing results or replicating procedures. Please contact the corresponding author.

3. Results

Among 315 chronic HF patients included in the analysis, 35 patients achieved cardiac recovery while on LVAD support (R). We summarized the baseline clinical characteristics, medications, laboratory results, hemodynamic and echocardiography parameters of 'R' and 'NR' in Table 1. Following sections will elaborate on the differences between the two groups of LVAD patients.

Among many baseline and clinical parameters outlined in Table 1, age, body surface area (BSA), previous thoracotomy, ischemic HF etiology and pre-LVAD HF duration were significantly different in the 'R' and 'NR' groups. For example, the group of patients who did not respond to LVAD support were older than those who responded within 12 months of LVAD support (57 ± 14 vs. 49 ± 20 years, $p = 0.014$), and also pre-LVAD BSA of 'NR' group was higher (2.05 ± 0.25 vs. 1.96 ± 0.23 m^2, $p = 0.021$) in comparison to the 'R' group. Further, in comparison to the 'R' group, patients in the 'NR' group had a significantly longer HF duration (96 ± 87 vs. 44 ± 53 months, $p < 0.001$) with a history of previous thoracotomy ($p = 0.014$) and an ischemic HF etiology ($p = 0.019$) as detailed in Table 1.

Regarding laboratory results, baseline B-type natriuretic peptide (BNP) level in the 'R' group was significantly higher in comparison to the 'NR' group (1902 ± 1380 pg/mL vs. 1330 ± 1171, $p = 0.039$). Finally, pre-LVAD LVEDD and LVESD of 'R' group LVAD patients were significantly lower as compared to 'NR' group and reported as 6.4 ± 0.9 vs. 6.8 ± 1.0 cm ($p = 0.040$) and 6.0 ± 0.9 vs. 6.2 ± 1.1 cm ($p = 0.048$), respectively. Details of other significant/non-significant clinical, laboratory, hemodynamic and echocardiographic parameters are listed in Table 1.

The mean baseline QRSd of the total study population was 143 ± 37 ms. Pre-LVAD QRSd in the 'R' group was 14.5 % shorter than the duration reported in the 'NR' group (123 ± 37 ms vs. 145 ± 36 ms, respectively, $p < 0.001$), as shown in Fig. 2. Interestingly, LVEF did not differ significantly between the 'R' and 'NR' groups before LVAD implantation (17.8 ± 7.5 vs. 18.1 ± 6.6 %, $p = 0.776$). Based on univariate logistic regression (Table 2), pre-LVAD QRSd shows a significant association with post-LVAD cardiac recovery in LVAD patients (OR: 0.983,

Table 1
Demographics, baseline clinical characteristics, medications, labs, hemodynamic and echocardiography measures of responders and non-responders.

Variables	All patients (N = 315)	Non-responders (n = 280)	Responders (n = 35)	p value
Age (years), M ± SD	56 ± 15	57 ± 14	49 ± 20	0.014
Race (Caucasian), n (%)	262 (83)	234 (84)	11 (78)	0.335
Ethnicity (Hispanic), n (%)	22 (7)	20 (7)	2 (5)	0.721
Male, n (%)	267 (85)	241 (86)	26 (74)	0.068
Clinical risk factors				
BSA (m^2), M ± SD	2.04 ± 0.25	2.05 ± 0.25	1.96 ± 0.23	0.021
BMI (kg/m^2), M ± SD	28 ± 6	28 ± 6	27 ± 6	0.118
Diabetes, n (%)	115 (37)	104 (37)	11 (31)	0.422
Smoking, n (%)	155 (49)	138 (50)	17 (47)	0.785
Alcohol, n (%)	132 (42)	117 (42)	15 (42)	0.948
Hypertension, n (%)	147 (47)	134 (48)	13 (36)	0.177
NYHA class IV, n (%)	223 (71)	200 (72)	23 (64)	0.333
MCS, n (%)	16 (5)	13 (5)	3 (8)	0.351
IABP, n (%)	22 (7)	19 (7)	3 (8)	0.736
Inotropes, n (%)	212 (67)	187 (67)	25 (69)	0.771
AF history, n (%)	133 (42)	123 (44)	10 (29)	0.080
Previous thoracotomy, n (%)	77 (24)	74 (27)	3 (8)	0.014
Ischemic HF, n (%)	127 (40)	119 (43)	8 (22)	0.019
Duration of HF, (months)	90 ± 85	96 ± 87	44 ± 53	<0.001
QRSd, (ms)	143 ± 37	145 ± 36	123 ± 37	<0.001
VAD type				
HeartMate2, n (%)	121 (38)	102 (37)	19 (53)	0.135
HeartMate3, n (%)	17 (5)	14 (5)	3 (8)	
HeartWare, n (%)	156 (49)	144 (52)	12 (33)	
Others, n (%)	21 (7)	19 (7)	2 (6)	
Medications and labs				
β-Blockers, n (%)	207 (66)	180 (65)	27 (75)	0.222
ACEI, n (%)	136 (44)	117 (42)	19 (54)	0.176
ARB, n (%)	46 (15)	41 (15)	5 (14)	0.935
Aldosterone, n (%)	190 (61)	168 (61)	22 (61)	0.957
Diuretics, n (%)	300 (95)	268 (96)	32 (89)	0.057
Platelets ($\times 10^9$/L), M ± SD	215 ± 80	214 ± 82	223 ± 67	0.743
Albumin (g/dL), M ± SD	3.7 ± 0.5	3.7 ± 0.5	3.6 ± 0.5	0.051
Hb (g/dL), M ± SD	12.5 ± 2.3	12.5 ± 2.3	12.2 ± 2.3	0.286
Bilirubin (mg/dL), M ± SD	1.4 ± 1	1.4 ± 0.9	1.6 ± 1.5	0.766
ALT (U/L), M ± SD	57 ± 118	56 ± 118	70 ± 122	0.498
AST (U/L), M ± SD	43 ± 47	42 ± 46	44 ± 57	0.821
ALP (IU/L), M ± SD	104 ± 54	101 ± 52	119 ± 61	0.063
Cr (mg/dL), M ± SD	1.4 ± 0.6	1.4 ± 0.5	1.3 ± 0.7	0.179
BUN (mg/dL), M ± SD	30 ± 16	30 ± 16	27 ± 18	0.087
Na (mmol/L), M ± SD	134 ± 5	134 ± 5	134 ± 5	0.686
K (mmol/L), M ± SD	4.1 ± 0.5	4.1 ± 0.6	3.9 ± 0.5	0.065
BNP (pg/mL), M ± SD	1404 ± 1258	1330 ± 1171	1902 ± 1380	0.039
Hemodynamic and echocardiography measures				
HR (bpm)	88 ± 20	87 ± 20	94 ± 25	0.069
RAP (mm Hg)	11.8 ± 6	11.9 ± 6.1	11.5 ± 5.7	0.687
PAP (mm Hg)	37 ± 10	37 ± 10	35 ± 10	0.164
PCWP (mm Hg)	25 ± 8	25 ± 8	24 ± 8	0.594
PVR (dynes - s/cm^{-5})	3.8 ± 2.5	3.8 ± 2.6	3.3 ± 2.2	0.304
RVSWI (g/m^2/beat)	7.4 ± 3.3	7.4 ± 3.4	7 ± 3.3	0.281
CI ($L/min/m^2$)	1.8 ± 0.6	1.8 ± 0.5	2 ± 0.7	0.120
SVR (dynes - s/cm^{-5})	1502 ± 566	1508 ± 575	1451 ± 508	0.721
LVEF (%)	18.1 ± 6.7	18.1 ± 6.6	17.8 ± 7.5	0.776
LVEDD (cm)	6.7 ± 1	6.8 ± 1	6.4 ± 0.9	0.040
LVESD (cm)	6.2 ± 1.1	6.2 ± 1.1	6.0 ± 0.9	0.048
IVSD (cm)	0.96 ± 0.24	0.97 ± 0.24	0.91 ± 0.26	0.104

Atrial fibrillation = AF, alanine aminotransferase = ALT, aspartate aminotransferase = AST, alkaline phosphatase = ALP, angiotensin-converting-enzyme inhibitor = ACEI, angiotensin receptor blockers = ARB, blood urea nitrogen = BUN, brain natriuretic peptide = BNP, body surface area = BSA, body mass index = BMI, cardiac index = CI, creatinine = Cr, heart rate = HR, hemoglobin = Hb, intra-aortic balloon pump = IABP, inter ventricular septal diameter = IVSD, left ventricular ejection fraction = LVEF, left ventricular end-diastolic diameter = LVEDD, left ventricular end-systolic diameter = LVESD, mechanical circulatory support = MCS, right atrial pressure = RAP, pulmonary atrial pressure = PAP, pulmonary capillary wedge pressure = PCWP, pulmonary vascular resistance = PVR, right ventricular stroke work index = RVSWI, systemic vascular resistance = SVR.

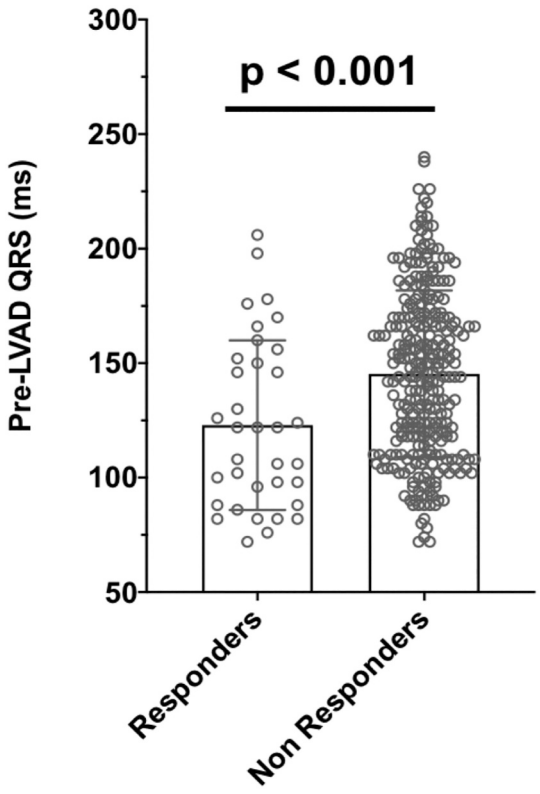

Fig. 2. Baseline QRS duration in responders (n = 35, 123 ± 37 ms) in comparison to non-responders (n = 280, 145 ± 36 ms).

95 % CI: 0.972–0.993, $p < 0.001$).

Before LVAD implant, as shown in Fig. 3a, there is a weak and non-significant correlation between QRSd and pre-LVAD LVEF in LVAD patients ($r = -0.04$, $p = 0.494$). Unlike LVEF, pre-LVAD LVEDD exhibits a significant correlation with baseline QRSd as shown in Fig. 3d ($r = 0.24$, $p < 0.01$). After CF-LVAD support, the baseline QRSd shows a significant correlation with post-LVAD LVEF ($r = -0.20$, p < 0.001) and similarly with pre- to post-LVAD LVEF change ($r = -0.19$, $p < 0.001$), as shown in Fig. 3b and Fig. 3c, respectively. Nevertheless, baseline QRSd correlates non-significantly with post-LVAD LVEDD ($r = 0.07$, $p = 0.208$) and pre- to post-LVAD LVEDD change ($r = -0.01$, $p = 0.966$) as shown in Fig. 3e and Fig. 3f, respectively.

The relationship of baseline QRSd with LVEF before and after LVAD support, and pre- to post-LVAD change in LVEF in the 'R' group was investigated (Top row) as shown in Fig. 4 and the results were compared with the 'NR' group (Bottom row). As shown in Fig. 4a, the 'R' group shows a significant improvement in LVEF (18 ± 8 vs. 46 ± 7 %, $p <$ 0.001) before and after LVAD implantation. However, the baseline QRSd is poorly and non-significantly correlated with pre-LVAD LVEF ($r =$ 0.15, $p = 0.386$), post-LVAD LVEF ($r = -0.15$, p = 0.386) and ΔLVEF ($r = -0.22$, $p = 0.205$) as shown in Fig. 4b, Fig. 4c, and Fig. 4d,

Table 2
Univariate logistic regression results of selected clinical parameters. Odds ratios (OR) < 1.0 indicate the odds of cardiac recovery.

Variables	OR	95 % CI	p value
Age	0.968	0.947–0.989	0.003
Male	0.487	0.213–1.114	0.074
BSA	0.226	0.053–0.935	0.043
BMI	0.962	0.902–1.021	0.237
Diabetes	0.736	0.348–1.558	0.423
Hypertension	0.612	0.298–1.256	0.180
NYHA class IV	0.699	0.337–1.448	0.335
MCS	1.846	0.499–6.818	0.358
AF history	0.507	0.225–1.067	0.084
Previous thoracotomy	0.252	0.075–0.846	0.026
Ischemic HF	0.384	0.169–0.873	0.022
Duration of HF	0.988	0.981–0.995	<0.001
β-Blockers	1.633	0.739–3.611	0.226
ACEI	1.624	0.801–3.291	0.179
Diuretics	0.328	0.098–1.092	0.069
Albumin	0.488	0.237–1.000	0.051
Bilirubin	1.173	0.874–1.573	0.287
ALP	1.004	0.999–1.012	0.071
Cr	0.708	0.341–1.469	0.354
BUN	0.982	0.957–1.008	0.176
K	0.601	0.312–1.159	0.129
BNP	1.000	1.000–1.000	0.014
HR	1.016	0.998–1.034	0.072
PAP	0.975	0.941–1.010	0.165
PVR	0.916	0.774–1.083	0.305
CI	1.502	0.889–2.538	0.128
LVEF	0.992	0.942–1.045	0.776
LVEDD	0.663	0.449–0.985	0.042
LVESD	0.719	0.502–1.031	0.073
IVSD	0.377	0.083–1.720	0.208
QRSd	0.986	0.976–0.992	<0.001

respectively. Though after CF-LVAD support, the change in LVEF in 'NR' group is significant as shown in Fig. 4e (18 ± 7 vs. 22 ± 6 %, $p < 0.001$), this group did not fulfill the criteria for post-LVAD cardiac recovery. Similarly, in the 'NR' group, the baseline QRSd is poorly and non-significantly related with pre-LVAD LVEF ($r = -0.07$, $p = 0.250$), post-LVAD LVEF (r = −0.07, $p = 0.257$) and ΔLVEF ($r = -0.10$, $p = 0.104$) as shown in Fig. 4f, Fig. 4g and Fig. 4h, respectively.

The impact of baseline QRSd on pre-LVAD LVEDD, post-LVAD LVEDD and ΔLVEDD (pre- to post-LVAD change in LVEDD) in the 'R' group (Top row) was studied as shown in Fig. 5, and compared with 'NR' group (Bottom row). As shown in Fig. 5a and e, both groups ('R' and 'NR') show a significant improvement in post-LVAD LVEDD in comparison to their pre-LVAD LVEDD measures, respectively. Specifically, the 'R' group exhibits a 28 % improvement in LVEDD following LVAD implant (6.4 ± 0.9 vs. 4.6 ± 0.6 cm, $p < 0.001$). However, there was no correlation of the baseline QRSd with the pre- and post-LVAD LVEDD, as shown in Fig. 5b ($r = 0.19$, $p = 0.268$) and Fig. 5c (r = 0.19, $p = 0.273$), respectively. Similarly, in the 'R' group, the pre- to post-LVAD change in LVEDD is not correlated with baseline QRSd as shown in Fig. 5d ($r = 0.06$, $p = 0.724$). On the other side, in the 'NR' group, a 12 % improvement in LVEDD is reported following LVAD implant (6.8 ± 1.0 vs. 6.0 ± 1.0 cm, p = p < 0.001) as shown in Fig. 5e, whereas their baseline QRSd is poorly and non-significantly correlated with pre- to post-LVAD LVEDD change, as shown in Fig. 5h ($r = -0.06$, $p = 0.315$).

In the bivariate models (Table 3), baseline QRSd is significantly associated with cardiac recovery after adjusting for age (OR: 0.983, 95 % CI: 0.972–0.993, $p = 0.001$), BSA (OR: 0.222, 95 % CI: 0.049–0.946, $p = 0.046$), previous thoracotomy (OR: 0.298, 95 % CI: 0.069–0.878, $p = 0.053$), ischemic HF etiology (OR: 0.430, 95 % CI: 0.175–0.949, $p = 0.047$), and BNP (OR: 1.000, 95 % CI: 1.000–1.001, $p = 0.005$). No other variables are associated with cardiac recovery in bivariate models when adjusted for baseline QRSd, though the baseline QRSd remained significant in those models (Table 3).

The multivariate model (Table 4) with three parameters including baseline QRSd (OR: 0.987, 95 % CI: 0.977–0.998, $p = 0.027$), duration of HF (OR: 0.990, 95 % CI: 0.983–0.997, $p = 0.006$) and gender: male (OR: 0.388, 95 % CI: 0.160–0.943, $p = 0.037$) shows association for predicting post-LVAD cardiac recovery in LVAD patients with an accuracy of 0.73 ($p < 0.0001$) as shown in Fig. 6.

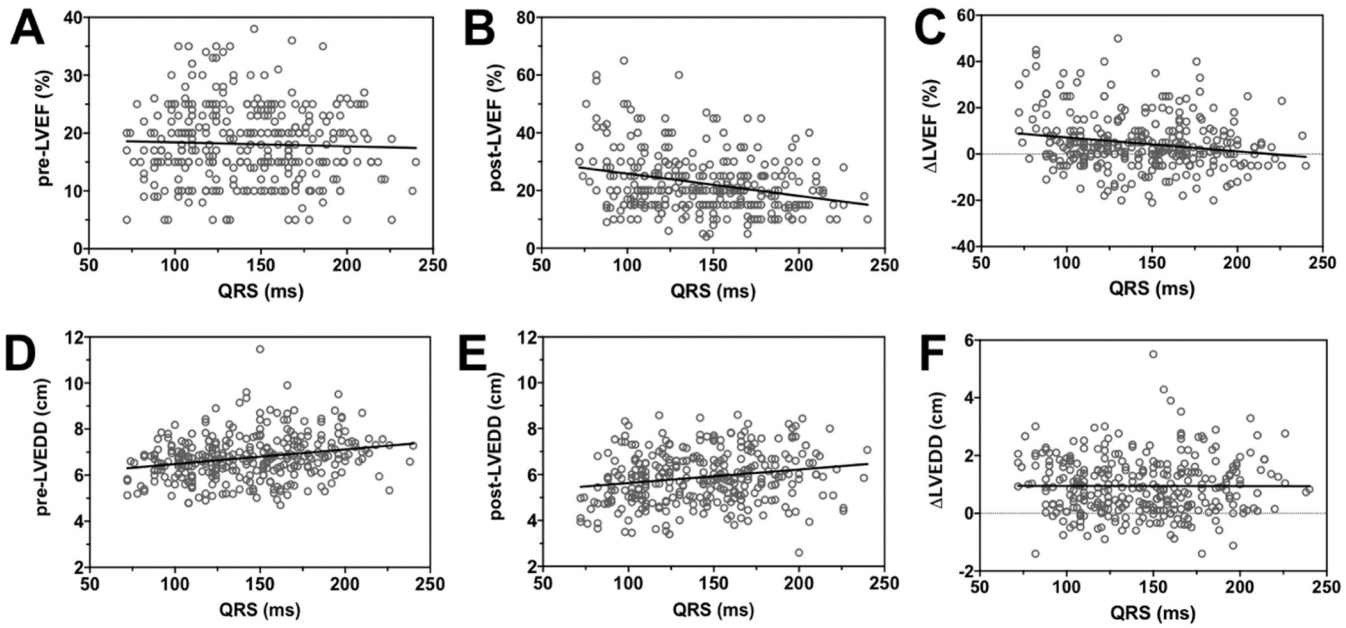

Fig. 3. Impact of baseline QRS duration on pre- and post-LVAD LVEF (top row) and LVEDD (bottom row) in LVAD patients, $n = 315$. (A) Correlation between QRS and pre-LVAD LVEF ($r = -0.04$, $p = 0.494$). (B) Correlation between QRS and post-LVAD LVEF ($r = -0.20$, $p < 0.001$). (C) Correlation between QRS and change (pre- to post-LVAD) in LVEF ($r = -0.19$, p < 0.001). Here the negative '−' in Pearson coefficient indicates the negative slope where EF reduces with increase in QRS duration. (D) Correlation between QRS and pre-LVAD LVEDD ($r = 0.24$, $p < 0.001$). (E) Correlation between QRS and post-LVAD LVEDD ($r = 0.07$, $p = 0.208$). (F) Correlation between QRS and change (pre- to post-LVAD) in LVEDD ($r = -0.01$, $p = 0.966$).

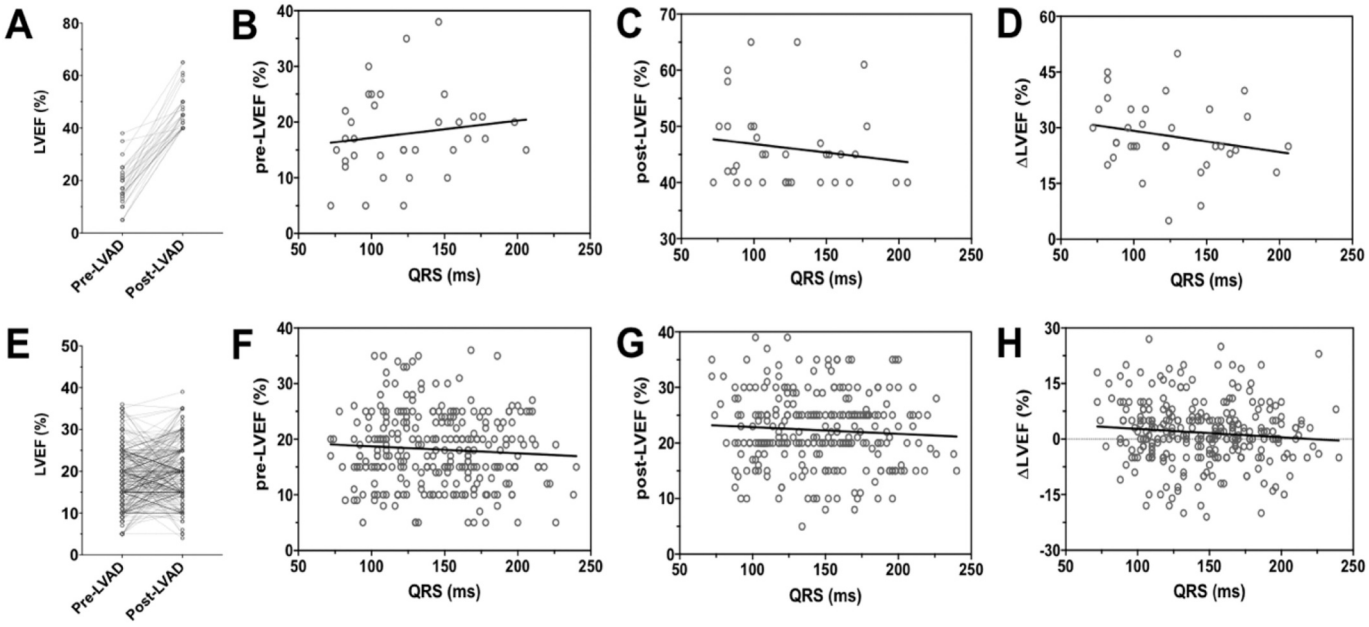

Fig. 4. Impact of baseline QRS duration on pre- to post-LVAD LVEF in responders ($n = 35$, top row) and non-responders ($n = 280$, bottom row). (A) Comparing pre- and post-LVAD LVEF in responders (18 ± 8 vs. 46 ± 7 %, $p < 0.001$). (B) Correlation between QRS and pre-LVAD LVEF ($r = 0.15$, $p = 0.386$). (C) Correlation between QRS and post-LVAD LVEF ($r = -0.15$, p = 0.386). (D) Correlation between QRS and change (pre- to post-LVAD) in LVEF ($r = -0.22$, $p = 0.205$). (E) Comparing pre- and post-LVAD LVEF in non-responders (18 ± 7 vs. 22 ± 6 %, p < 0.001). (F) Correlation between QRS and pre-LVAD LVEF ($r = -0.07$, $p = 0.250$). (G) Correlation between QRS and post-LVAD LVEF (r = −0.07, $p = 0.257$). (H) Correlation between QRS and change (pre- to post-LVAD) in LVEF ($r = -0.10$, $p = 0.104$). The negative sign '−' in Pearson coefficient indicates the negative slope where change in LVEF reduces with increase in QRS duration.

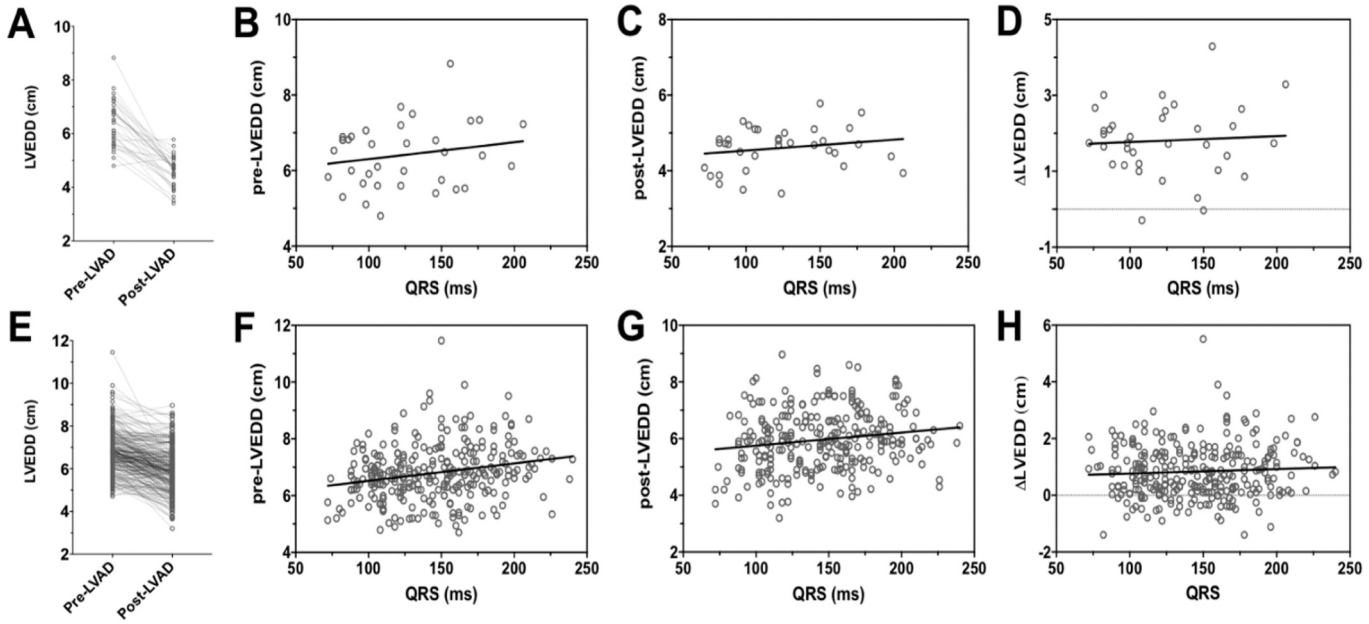

Fig. 5. Impact of baseline QRS duration on pre- to post-LVAD LVEDD in responders ($n = 35$, top row) and non-responders ($n = 280$, bottom row). (A) Comparing pre- and post-LVAD LVEDD in responders (6.4 ± 0.9 vs. 4.6 ± 0.6 cm, p < 0.001). (B) Correlation between QRS and pre-LVAD LVEDD ($r = 0.19$, $p = 0.268$). (C) Correlation between QRS and post-LVAD LVEDD (r = 0.19, $p = 0.273$). (D) Correlation between QRS duration and change (pre- to post-LVAD) in LVEDD ($r = 0.06$, $p = 0.724$). (E) Comparing pre- and post-LVAD LVEDD in non-responders (6.8 ± 1.0 vs. 6.0 ± 1.0 cm, p < 0.001). (F) Correlation between QRS and pre-LVAD LVEDD ($r = 0.23$, p < 0.001). (G) Correlation between QRS and post-LVAD LVEDD ($r = 0.16$, $p = 0.007$). (H) Correlation between QRS and change (pre- to post-LVAD) in LVEDD ($r = -0.06$, $p = 0.315$).

4. Discussion

In chronic HF patients undergoing LVAD implantation, baseline QRSd was found to be associated with post-LVAD cardiac recovery within 12 months post-LVAD implantation. The pre-LVAD QRSd in the 'R' group was significantly shorter (15 %) in comparison to the 'NR' group. It is noteworthy that patients who experienced cardiac recovery following LVAD implantation had a baseline LVEF similar to those who did not show post-LVAD cardiac recovery (Table 1). A comparable LVEF in the two groups is also consistent with previous studies [8,18,19].

Table 3
Bivariate logistic regression analysis to determine independent predictors of LVAD-induced cardiac recovery. OR < 1.0 indicate the odds of cardiac recovery.

Variables	OR	95 % CI	p value	AUC
Age	0.980	0.957–1.004	0.105	0.668
QRSd	0.987	0.975–0.998	0.022	
BSA	0.222	0.049–0.946	0.046	0.671
QRSd	0.983	0.972–0.993	0.002	
Prev. thoracotomy	0.298	0.069–0.878	0.053	0.695
QRSd	0.984	0.973–0.995	0.004	
Ischemic HF	0.430	0.175–0.949	0.047	0.684
QRSd	0.984	0.973–0.994	0.003	
Duration of HF	0.990	0.982–0.996	0.006	0.726
QRSd	0.989	0.977–0.999	0.042	
Albumin	0.498	0.236–1.032	0.063	0.681
QRS	0.983	0.972–0.993	0.002	
BNP	1.000	1.000–1.001	0.005	0.701
QRSd	0.982	0.971–0.992	0.001	
LVEDD	0.753	0.492–1.124	0.177	0.680
QRSd	0.985	0.973–0.995	0.005	

Table 4
Multivariate logistic regression model with AUC: 0.73 (p < 0.001).

Variables	OR	95 % CI	p value
QRSd	0.987	0.977–0.998	0.027
Duration of HF	0.990	0.983–0.997	0.006
Gender (male)	0.388	0.160–0.943	0.037

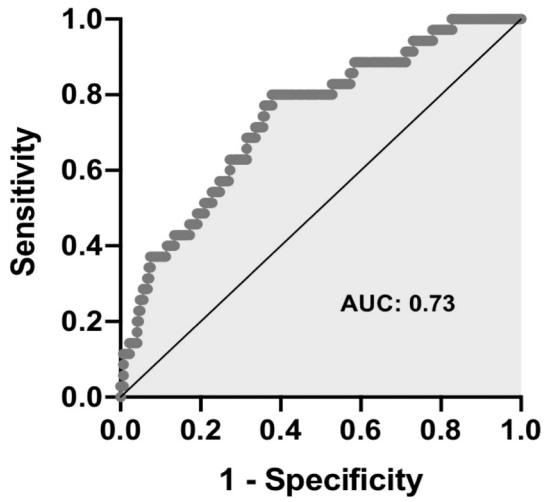

Fig. 6. Multivariate logistic regression model comprised of baseline QRSd, HF duration and gender (male) shows an accuracy of 0.73 with p < 0.001 predicting cardiac recovery within 12 months post-LVAD support.

Previous studies have identified younger age, non-ischemic HF etiology, shorter HF duration, and LV torsional mechanics as factors associated with a higher likelihood of cardiac recovery on LVAD support [9,20,28,29]. In concordance to these findings, our univariate data analysis showed that LVAD patients who achieved cardiac recovery within 12 months after LVAD implant were also more likely to be younger, with a history of non-ischemic cardiomyopathy, and a shorter HF duration. Additionally, in responders the time from the HF diagnosis to the implantation of the LVAD was significantly shorter, a previous thoracotomy was less common, and there was a trend toward significance for higher baseline BNP levels compared to non-responders.

Previous studies have focused on a prolonged QRSd that appears common in patients suffering from HF with reduced LVEF [14–16]. These studies emphasized that a baseline QRSd above ≥120 ms was associated with a significantly increased risk of death compared with a baseline QRSd < 120 ms. Two prospective studies with 36 and 12 LVAD-supported patients, respectively, have previously investigated the QRS complex shortening at different time points during mechanical unloading. However, these studies did not explore an investigation of the effect of pre-LVAD QRSd on LVAD-induced cardiac recovery. Similarly, another prospective study of 23 LVAD patients, investigated the trajectory of QRSd immediately prior to LVAD implantation, and subsequently early and late while on LVAD support [30]. Their findings did not focus on whether the pre-LVAD QRSd may predict the post-LVAD cardiac recovery in the same group of patients, instead they reported the comparison of baseline QRSd in LVAD patients ($n = 23$) with another 22 control patients undergoing coronary artery bypass grafting. None of these studies reported the relationship of pre-LVAD QRSd in LVAD patients to cardiac recovery. One of the potential reasons could be their small sample size.

Based on a meta-analysis, the effect of very low LVEF and prolonged QRSd on the mortality benefits of ICD therapy has been reported in the general HF population [31]. Further, pre- and post-LVAD fragmented QRS complex was studied in 98 LVAD patients to seek its association with survival following LVAD implantation over a 30-month follow-up period [32]. Their results were based on the prevalence of fragmented QRS quantified at anterior, inferior and lateral territories. They did not distinguish the role of fragmented QRS as a predictor of cardiac recovery following LVAD support. The impact of baseline QRSd on pre- to post-LVAD change in LVEF has not been previously studied in CHF patients undergoing LVAD implantation, although the relation between fragmented QRS and LVEF has been discussed in HF patients [33].

Similarly, the impact of baseline QRSd on LVEDD before and after LVAD support in chronic HF patients has not been reported yet. A positive association between QRSd and LV size in patients with bundle branch block was discussed previously [34,35], and it has been suggested that LV size does not modify the effect of baseline QRSd and its association with outcomes following cardiac resynchronization therapy [36]. In our study, we observed a significant correlation of baseline QRSd with pre-LVAD LVEDD and a non-significant correlation with post-LVAD LVEDD as shown in Figs. 3d and e, respectively. At a first glance, this suggests that QRSd could play a vital role with pre-LVAD LVEDD in LVAD patients, however, the proposed scientific evidence is not true neither for the individuals who improved their cardiac structure and function while on LVAD support, (Fig. 4b) nor for those who did not (Fig. 4f). Compared to the 'NR' group that exhibited a 12 % improvement in LVEDD, the 'R' group showed a 28 % improvement from pre- to post-LVAD change in LVEDD, and these data indicate that QRSd may reflect the dimension and muscle mass of the LV and may be a useful indicator of LVAD-induced cardiac recovery.

As shown in Table 5, the data on biventricular pacing percentage or right ventricular pacing percentage are not complete as there were missing data especially for patients implanted with an LVAD in earlier years. From the 180 patients on ventricular pacing pre-LVAD, 106 had available data on the percentage of pacing pre-LVAD and 90 post-LVAD. Additionally, LBBB assessment applies only to patients not on ventricular pacing prior to LVAD implantation. With regard to the differences in pre-LVAD ventricular pacing and resynchronization therapy in 'R' vs 'NR', we estimate this is a surrogate of disease chronicity as presumably patients with HF symptoms for a shorter time period, might not have undergone electrical therapies evaluation and implementation. With regard to post-LVAD HF medication therapy, since many patients did not reach the 1-year follow-up (heart transplantation, LVAD explantation for recovery, or death) we used the 3-month post-LVAD timepoint for the medication comparisons. As shown in Table 5:, although fewer 'NR' patients were on an ACEi/ARB/ARNI post-LVAD, the percentages of any GDMT implementation in 'R' vs 'NR' post-LVAD were comparable.

The number of patients that fulfilled the criteria for post-LVAD cardiac recovery was relatively small ($n = 35$). Future studies with a larger sample size are warranted to further explore the role of LV electrical remodeling in LVAD-induced cardiac recovery. LVAD patients with

Table 5
Percentage of HF patients received right ventricular, cardiac resynchronization therapy or biventricular pacing before and after LVAD implantation, and post-LVAD implant medication therapy at 3-month follow up comparing 'R' vs 'NR'.

Variables	All patients (N = 315)	Non-responders (n = 280)	Responders (n = 35)	p value
Pre-LVAD ventricular pacing, n (%)	180 (57)	166 (59)	14 (40)	0.03
Pre-LVAD cardiac resynchronization therapy, n (%)	154 (49)	144 (51)	10 (29)	0.01
Pre-LVAD LBBB, n (%)	23 (17)	22 (19)	1 (5)	0.13
Pre-LVAD biventricular pacing percentage, %	93 ± 11	93 ± 11	93 ± 8	0.98
Post-LVAD biventricular pacing percentage, %	96 ± 7	96 ± 7	100 ± 0	0.24
Pre-LVAD right ventricular pacing percentage, %	37 ± 40	34 ± 39	51 ± 60	0.62
Post-LVAD right ventricular pacing percentage, %	39 ± 36	42 ± 9	18 ± 23	0.29
Medication therapy at 3-month post-LVAD follow-up				
Post-LVAD use of any GDMT, n (%)	249 (82)	219 (82)	30 (86)	0.56
Post-LVAD ACEi/ARB/ARNI, n (%)	168 (55)	142 (53)	26 (74)	0.02
Post-LVAD B-blocker, n (%)	197 (65)	170 (63)	27 (77)	0.11
Post-LVAD MRA, n (%)	166 (56)	144 (54)	22 (65)	0.25

bundle branch block should ideally be studied separately regarding their baseline QRSd and the cardiac recovery potential. Integrating pre-LVAD QRSd to previously reported pre-LVAD clinical and translational cardiac recovery predictors may provide a highly sensitive and patient-specific electro-mechanistic method for predicting cardiac structural and functional improvement after LVAD unloading.

In conclusion, baseline QRSd effectively identified a subset of advanced cardiomyopathy patients prone to improve their cardiac structure and function following LVAD support. It could serve as a useful clinical indicator to guide the implementation of systematic monitoring and treatment strategies to promote cardiac recovery in selected LVAD candidates. Future research is warranted to further explore the association of baseline electrocardiographic indices with LV structural changes during mechanical support. Finally, strategies to facilitate cardiac recovery should be encouraged in such patients with the ultimate goal of LVAD weaning.

CRediT authorship contribution statement

Muhammad Khan: Writing - Original draft preparation, Revision, Methodology, Analysis, Validation. **Christos Kyriakopoulos**: Data curation, Validation, Methodology, Writing, Editing, Revision, Analysis. **Iosif Taleb**: Data curation, Validation, Methodology, Reviewing and Editing. **Elizabeth Dranow**: Data curation, Analysis, Software. **Monte Scott**: Validation. **Ravi Ranjan**: Investigation. **Michael Yin**: Investigation. **Eleni Tseliou**: Validation. **Rami Alharethi**: Investigation, Validation. **William Caine**: Investigation, Validation. **Robin Shaw**: Investigation. **Craig Selzman**: Investigation. **Stavros Drakos**: Supervision, Conceptualization, Methodology, Investigation, Reviewing and Editing. **Derek Dosdall**: Supervision, Conceptualization, Methodology, Investigation, Reviewing and Editing.

Conflict of interest

RR is a consultant for Abbott, Medtronic, and Biosense Webster. All other authors have no relevant financial or non-financial interests to disclose.

Acknowledgements

The research has been supported by NHLBI of NIH under award: 5R01HL128752 (DJD), 5R21HL156039 (DJD), R01HL135121-01 (SGD), R01HL132067-01A1 (SGD), AHA Heart Failure Strategically Focused Research Network 16SFRN29020000 (SGD), Merit Review Award I01 CX002291 U.S. Dept. of Veterans Affairs (SGD) and a research grant from the Nora Eccles Treadwell Foundation (DJD and SGD). 5T32HL007576-035 (MSK), 2T32HL007576-36 (CPK) and 5T32HL007576-33 (IT) are all supported through NHLBI training grants. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH, Dept. of Veterans Affairs and AHA.

References

[1] C.T. Holley, L. Harvey, R. John, Left ventricular assist devices as a bridge to cardiac transplantation, J.Thorac.Dis. 6 (2014) 1110–1119.
[2] D.G. Jakovljevic, M.H. Yacoub, S. Schueler, et al., Left ventricular assist device as a bridge to recovery for patients with advanced heart failure, J. Am. Coll. Cardiol. 69 (2017) 1924–1933.
[3] E.A. Rose, A.C. Gelijns, A.J. Moskowitz, et al., Long-term use of a left ventricular assist device for end-stage heart failure, N. Engl. J. Med. 345 (2001) 1435–1443.
[4] G.C. Stewart, M.M. Givertz, Mechanical circulatory support for advanced heart failure: patients and technology in evolution, Circulation 125 (2012) 1304–1315.
[5] C.B. Patel, K.M. Alexander, J.G. Rogers, Mechanical circulatory support for advanced heart failure, Curr.Treat.OptionsCardiovasc.Med. 12 (2010) 549–565.
[6] J.G. Copeland, R.G. Smith, F.A. Arabia, et al., Cardiac replacement with a total artificial heart as a bridge to transplantation, N. Engl. J. Med. 351 (2004) 859–867.
[7] J.K. Kirklin, D.C. Naftel, F.D. Pagani, et al., Seventh INTERMACS annual report: 15,000 patients and counting, J. Heart Lung Transplant. 34 (2015) 1495–1504.
[8] M. Dandel, Y. Weng, H. Siniawski, et al., Heart failure reversal by ventricular unloading in patients with chronic cardiomyopathy: criteria for weaning from ventricular assist devices, Eur. Heart J. 32 (2011) 1148–1160.
[9] M.J. Bonios, A. Koliopoulou, O. Wever-Pinzon, et al., Cardiac Rotational mechanics as a predictor of myocardial recovery in heart failure patients undergoing chronic mechanical circulatory support a pilot study, Circ. Cardiovasc. Imaging 11 (2018), e007117.
[10] B.A. Popescu, C.C. Beladan, A. Călin, et al., Left ventricular remodelling and torsional dynamics in dilated cardiomyopathy: reversed apical rotation as a marker of disease severity, Eur. J. Heart Fail. 11 (2009) 945–951.
[11] R.J. Taylor, F. Umar, E.L.S. Lin, et al., Mechanical effects of left ventricular midwall fibrosis in non-ischemic cardiomyopathy, J. Cardiovasc. Magn. Reson. 18 (2016) 1–8.
[12] M. Cameli, S. Mondillo, F.M. Righini, et al., Left ventricular deformation and myocardial fibrosis in patients with advanced heart failure requiring transplantation, J. Card. Fail. 22 (2016) 901–907.
[13] M. Bertini, A.C.T. Ng, M.L. Antoni, et al., Global longitudinal strain predicts long-term survival in patients with chronic ischemic cardiomyopathy, <sb:contribution><sb:title>Circ.</sb:title></sb:contribution><sb:host><sb:issue><sb:series><sb:title>Cardiovasc. Imaging</sb:title></sb:series></sb:issue></sb:host> 5 (2012) 383–391.
[14] A. Kashani, S.S. Barold, Significance of QRS complex duration in patients with heart failure, J. Am. Coll. Cardiol. 46 (2005) 2183–2192.
[15] A. Auricchio, C.M. Yu, Beyond the measurement of QRS complex toward mechanical dyssynchrony: cardiac resynchronisation therapy in heart failure patients with a normal QRS duration, Heart 90 (2004) 479–481.
[16] N.C. Wang, A.P. Maggioni, M.A. Konstam, et al., Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction, JAMA 299 (2008) 2656–2666.
[17] S.G. Drakos, J.V. Terrovitis, J.N. Nanas, et al., Reverse electrophysiologic remodeling after cardiac mechanical unloading for end-stage nonischemic cardiomyopathy, Ann. Thorac. Surg. 91 (2011) 764–769.
[18] O. Wever-Pinzon, S.G. Drakos, S.H. McKellar, J.C. Fang, J. Stehlik, C.H. Selzman, et al., Cardiac recovery during long-term left ventricular assist device support, J.Am. Coll.Cardiol. 68 (2016) 1540–1553.
[19] S.G. Drakos, O. Wever-Pinzon, C.H. Selzman, et al., Magnitude and time course of changes induced by continuous-flow left ventricular assist device unloading in chronic heart failure: insights into cardiac recovery, J. Am. Coll. Cardiol. 61 (2013) 1985–1994.
[20] P. Shah, M. Psotka, I. Taleb, et al., Framework to classify reverse cardiac remodeling with mechanical circulatory support: the Utah-Inova stages, Circ. Heart Fail. 14 (2021), E007991.
[21] R.M. Lang, L.P. Badano, V. Mor-Avi, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American society of echocardiography and the European association of cardiovascular imaging, Eur. Heart J. Cardiovasc. Imaging 28 (2015) 1–39.E14.
[22] P. Royston, Multiple imputation of missing values: update, Stata J. 5 (2005) 188–201.
[23] P. Royston, Multiple imputation of missing values: further update of ice, with an emphasis on categorical variables, Stata J. 9 (2009) 527–536.

[24] T.E. Raghunathan, What do we do with missing data? Some options for analysis of incomplete data, Annu. Rev. Public Health 25 (2004) 99–117.
[25] L.C. Hamilton, Statistics With Stata: Updated for Version 9, Brooks/Cole-Thomson, 2006.
[26] E. Vittinghoff, D.V. Glidden, S.C. Shiboski, C.E. McCulloch, Regression Methods in Biostatistics, Springer, US, Boston, MA, 2005.
[27] StataCorp, Stata Statistical Software: Release 16, StataCorp LLC., College Station, TX, 2019.
[28] D.J. Goldstein, S. Maybaum, T.E. MacGillivray, et al., Young patients with nonischemic cardiomyopathy have higher likelihood of left ventricular recovery during left ventricular assist device support, J. Card. Fail. 18 (2012) 392–395.
[29] M.A. Simon, R.L. Kormos, S. Murali, et al., Myocardial recovery using ventricular assist devices: prevalence, clinical characteristics, and outcomes, Circulation 112 (2005) 32–36.
[30] J.D. Harding, V. Piacentino, J.P. Gaughan, et al., Electrophysiological alterations after mechanical circulatory support in patients with advanced cardiac failure, Circulation 104 (2001) 1241–1247.
[31] D.G. Katritsis, K.C. Siontis, J.T. Bigger, et al., Effect of left ventricular ejection fraction and QRS duration on the survival benefit of implantable cardioverter-defibrillators: meta-analysis of primary prevention trials, Heart Rhythm 10 (2013) 200–206.
[32] I.C. Thomas, D.P. Cork, A.K. Bhatia, et al., QRS complex fragmentation and survival following left ventricular assist device implantation, IJC Heart Vasc. 7 (2015) 165–169.
[33] F. Alattar, N. Imran, F. Shamoon, Fragmented QRS and ejection fraction in heart failure patients admitted to the hospital, IJC Heart Vasc. 9 (2015) 11–14.
[34] D.D. Chan, K.C. Wu, Z. Loring, et al., Comparison of the relation between left ventricular anatomy and QRS duration in patients with cardiomyopathy with versus without left bundle branch block, Am. J. Cardiol. 113 (2014) 1717–1722.
[35] R. Dhingra, B. Ho Nam, E.J. Benjamin, et al., Cross-sectional relations of electrocardiographic QRS duration to left ventricular dimensions: the Framingham Heart Study, J. Am. Coll. Cardiol. 45 (2005) 685–689.
[36] J. Rickard, B. Baranowski, R.A. Grimm, et al., Left ventricular size does not modify the effect of QRS duration in predicting response to cardiac resynchronization therapy, Pacing Clin. Electrophysiol. 40 (2017) 482–487.