Prospective Randomized Evaluation of Implantable Cardioverter-Defibrillator Programming in Patients With a Left Ventricular Assist Device

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Background—Ventricular arrhythmias are common in patients with left ventricular assist devices (LVADs) but are often hemodynamically tolerated. Optimal implantable cardioverter defibrillator (ICD) tachy-programming strategies in patients with LVAD have not been determined. We sought to determine if an ultra-conservative ICD programming strategy in patients with LVAD affects ICD shocks.

Methods and Results—Adult patients with an existing ICD undergoing continuous flow LVAD implantation were randomized to standard ICD programming by their treating physician or an ultra-conservative ICD programming strategy utilizing maximal allowable intervals to detection in the ventricular fibrillation and ventricular tachycardia zones with use of ATP. Patients with cardiac resynchronization therapy (CRT) devices were also randomized to CRT ON or OFF. Patients were followed a minimum of 6 months. The primary outcome was time to first ICD shock. Among the 83 patients studied, we found no statistically significant difference in time to first ICD shock or total ICD shocks between groups. In the ultra-conservative group 16% of patients experienced at least one shock compared with 21% in the control group (P=0.66). There was no difference in mortality, arrhythmic hospitalization, or hospitalization for heart failure. In the 41 patients with CRT ICDs fewer shocks were observed with CRT-ON but this was not statistically significant: 10% of patients with CRT-ON (n=21) versus 38% with CRT-OFF (n=20) received shocks (P=0.08).

Conclusions—An ultra-conservative programming strategy did not reduce ICD shocks. Programming restrictions on ventricular tachycardia and ventricular fibrillation zone therapy should be reconsidered for the LVAD population. The role of CRT in patients with LVAD warrants further investigation.

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Key Words: cardiac resynchronization therapy • implantable cardioverter defibrillator • left ventricular assist device

Pivotal randomized controlled trials have established the role of the implantable cardioverter-defibrillator (ICD) in the treatment of patients with systolic heart failure.1–5

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Clinical Perspective

What Is New?

- This study is the first to prospectively examine the effects of implantable cardioverter-defibrillator (ICD) programming on the timing and rate of ICD shocks in patients with implanted left ventricular assist devices in a randomized fashion.
- The study additionally demonstrates that ICD shocks are common in this group, though in no case did ventricular arrhythmia result in symptoms.
- Patients with cardiac resynchronization therapy (CRT) devices were also randomized to CRT ON or OFF, and we observed fewer ICD shocks in patients with CRT ON.

What Are the Clinical Implications?

- Currently available maximally conservative programming schema do not appear to be sufficient to meaningfully decrease ICD shocks in the left ventricular assist devices population.
- The effect of CRT on ventricular arrhythmias and ICD shocks requires further prospective evaluation.

Methods

Study Design

Patients with an existing ICD undergoing de novo continuous flow LVAD implantation at Vanderbilt University Medical Center were randomized to either a UC ICD programming strategy or programming at the discretion of their treating physician during their index hospitalization. In addition, those patients with a CRT capable ICD were randomized to either have CRT turned OFF or remain ON. Patients with complete atrioventricular block and no escape rhythm (pacemaker dependent) were excluded from CRT randomization. Enrollment and ICD programming occurred after the patient had left the cardiac intensive care unit following LVAD implant but before hospital discharge to minimize the impact of peri-procedural arrhythmias on outcomes. All patients were followed for a minimum of 6 months after enrollment. Patients were required to have an existing transvenous ICD and had to be a minimum of 18 years of age at the time of enrollment. The primary end point within each randomization was time to first ICD shock. Secondary end points included inappropriate shocks (defined as ICD shock for a rhythm other than ventricular tachycardia or ventricular fibrillation as determined by review of stored electrograms), hospitalization for arrhythmia, implantable cardioverter-defibrillator hospitalization for congestive heart failure, and death. All patients provided written informed consent. This study was approved by the institutional review board of Vanderbilt University. Participants received no compensation for participation in the study. The trial was designed as a single center pilot study, and as such a strict sample size calculation was not performed. We planned to enroll 80 patients over the course of 2 years based on the clinical volume at our center. Assuming a 25% incidence of ICD shocks, our trial would have 70% power to detect an absolute risk reduction of 15% in ICD shocks with UC programming. The power to detect an effect of CRT therapy was lower than this given the smaller sample size. The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure upon individual requests addressed to the corresponding author.

ICD Programming

Patients randomized to an UC programming strategy underwent changes to tachycardia therapies on their devices with the intention of allowing maximal time to detection of ventricular arrhythmia, as well as treating only rapid tachycardia. Programming parameters are shown in Table 1. No changes were made to tachycardia therapies in patients randomized to the control group. In patients with CRT capable ICDs randomized to CRT-OFF, CRT (left ventricular pacing) was inactivated provided a reliable baseline rhythm >35 beats per minute (bpm) was present. In the CRT OFF group devices were reprogrammed to DDI 40 or VVI 40 for dual and single chamber devices respectively, minimizing ventricular pacing.

Follow-Up

Follow-up data were obtained by in-office or remote monitoring ICD checks, review of the electronic medical record, phone calls with patients and/or their treating physicians, or direct in-office visits with the LVAD and advanced heart failure service. Initial follow-up occurred at 1-month and then at 6-month intervals thereafter. Follow-up continued for all
subjects until all patients had been followed for a minimum of 6 months. At each follow-up interval ICD shocks, hospitalizations for either heart failure or arrhythmia, and mortality were assessed. All ICD shocks were reviewed by the study investigators and adjudicated as either appropriate or inappropriate. Shocks for either sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), as determined by available clinical information, were deemed appropriate. All shock events were reviewed for tachycardia cycle length, zone of therapy, delivery of ATP, acceleration of tachycardia by ATP, and report of patient symptoms.

**Statistical Analysis**

Baseline characteristics are expressed as median (interquartile range) for continuous variables and frequency (percentage) for categorical variables, respectively. Univariate comparisons were performed using the Pearson chi-square test for categorical variables or the Wilcoxon Rank-sum test for continuous variables. Statistical significance was taken as a two-tailed \( P \leq 0.05 \). Outcomes were assessed using an intention to treat analysis. Time to first ICD shock as well as mortality was assessed using the Kaplan–Meier method for the UC versus control analysis. Statistical analysis was performed using R version 3.4.2 (September 28, 2017).

**Results**

Eighty-three patients, recruited from November 2013 to April 2016, were included in the final analysis (44 UC and 39 control). One patient withdrew consent on the day of enrollment and 5 patients were removed within a month of enrollment due to conflicts with other investigations (Figure 1). Median duration of follow-up was 11 months (4 to 18 interquartile range). The majority of patients were white males. A similar proportion of patients had ischemic and non-ischemic cardiomyopathy. Twenty of the 83 patients (24%) had an LVAD implanted as destination therapy. Baseline characteristics were similar

### Table 1. ICD Programming Schema

| Manufacturer         | VT Zone Detection | VT Zone Therapy | VF Zone Detection | VF Zone Therapy |
|----------------------|-------------------|-----------------|-------------------|-----------------|
| Medtronic Inc        | Rate: 180 bpm 100 intervals (33 s) to detection | ATP×5, 25 J×2 | Rate: 222 bpm 120/160 intervals to detection (32.4 s) | 25 J, 35 J×5 |
| Boston Scientific Inc| Rate: 180 bpm 30 s to detection | ATP×8, 21 J, 41 J×6 | Rate: 220 bpm 15 s to detection | 29 J, 41 J×7 |
| St. Jude Medical      | Rate: 180 bpm 100 intervals (33 s) to detection | ATP×3, 36 J, 40 J×2 | Rate: 240 bpm 100 intervals to detection (25 s) | 36 J, 40 J×5 |

ICD programming schema for the three device manufacturers involved in the trial. A number followed by “J” indicates a shock therapy with the number referring to the shock energy in joules (J). ATP indicates anti-tachycardia pacing; bpm, beats per minute; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Figure 1.** Randomization strategy and enrollment. CCU indicates cardiac critical care unit; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device.
between the 2 groups as presented in Table 2. Programming in the control group is summarized in Table 3. Of the patients in the control group (n = 39), all patients had a VF tachy-therapy zone active with a median detection rate of 214 bpm [200 to 228] and a median of 16 intervals to detection. Twenty-six patients (68%) had a VT therapy zone active with median rate of 176 bpm [167 to 181] and 19 intervals to detection. All VT programming zones had ATP therapy active before shocks. Nine patients (24%) had a second VT zone active with median rate of 187 bpm [182 to 188] and 24 intervals to detection. ATP therapy was active in all fast VT (FVT)/VT-2 zones.

UC Programming

No statistically significant difference was seen in the total number of ICD shocks between patients randomized to a UC programming strategy versus control, with 16% of patients in the UC group and 2% in the control group experiencing at least one shock (P = 0.66). Additionally, there was no difference in the time to first ICD shock in the Kaplan–Meier analysis (Table 4 and Figure 2). Inappropriate shocks remained common with 6% of patients receiving at least one inappropriate shock. Even in the UC group, subjects received inappropriate shocks for rapid atrial fibrillation despite maximally extended detection when ventricular rate was sustained above the FVT or VF detection limit. Details of shock events are presented in Table 5. The majority of shocks were delivered within the VF therapy zone in both the UC and control group. ATP was frequently delivered (10 of 23 shock events), acceleration was observed once. No differences were observed in the rates of mortality, arrhythmic hospitalization, or hospitalization for congestive heart failure between groups. Five patients (2 UC, 3 control) died within 30 days of LVAD implantation, all during their initial hospitalization. None of these deaths were due to arrhythmia.

Cardiac Resynchronization Therapy

No baseline differences were observed in patients with CRT-ON versus OFF. In patients with CRT-ON the median percent BiV pacing was 99% [94 to 99%]. We found a nonsignificant trend toward reduction in ICD shocks with CRT-ON compared with CRT-OFF, with 10% of patients with CRT-ON versus 38% with CRT-OFF receiving at least one shock (P = 0.08). No differences were observed in the time to first ICD shock, rates of inappropriate

### Table 2. Baseline Characteristics

|                        | Ultra-Conservative (N=44) | Control (N=39) | Combined (N=83) | P Value |
|------------------------|---------------------------|----------------|----------------|---------|
| Age, y                 | 55 (47 to 62)             | 57 (48 to 63)  | 56 (48 to 63)  | 0.51    |
| Male                   | 34 (77%)                  | 31 (82%)       | 65 (79%)       | 0.63    |
| Ethnicity              |                           |                |                | 0.68    |
| White                  | 33 (75%)                  | 30 (79%)       | 63 (77%)       |         |
| Black                  | 8 (18%)                   | 7 (18%)        | 15 (18%)       |         |
| Other                  | 3 (7%)                    | 1 (3%)         | 4 (5%)         |         |
| Heart failure etiology |                           |                |                | 0.35    |
| Ischemic               | 18 (41%)                  | 19 (51%)       | 37 (46%)       |         |
| Non-ischemic           | 26 (59%)                  | 18 (49%)       | 44 (54%)       |         |
| Diabetic               | 17 (39%)                  | 17 (41%)       | 34 (40%)       | 0.53    |
| CRT pacing             |                           |                |                | 0.84    |
| CRT-ON                 | 10 (23%)                  | 10 (27%)       | 20 (25%)       |         |
| CRT-OFF                | 11 (25%)                  | 10 (27%)       | 21 (26%)       |         |
| No CRT                 | 23 (52%)                  | 19 (46%)       | 40 (49%)       |         |
| Comorbidities          |                           |                |                | 0.52    |
| Prior VT/VF therapy    | 4 (9%)                    | 3 (8%)         | 7 (8%)         |         |
| Arrhythmic syncope     | 3 (7%)                    | 2 (5%)         | 5 (6%)         |         |
| RBBB, LBBB, or IVCD    | 11 (25%)                  | 13 (33%)       | 24 (29%)       |         |
| Atrial fibrillation, flutter, or SVT | 9 (20%) | 3 (8%) | 12 (14%) |         |
| Destination LVAD therapy | 11 (25%) | 9 (23%) | 20 (24%) | 0.67 |

All values presented as number of patients followed by percent of group, other than age, which is presented as the median and interquartile range. Wilcoxon rank test used for continuous variables and Pearson test used for ordinal variables. CRT indicates cardiac resynchronization therapy; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; LVAD, left ventricular assist device; RBBB, right bundle branch block; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
shocks, arrhythmic hospitalization, or hospitalization for congestive heart failure between groups. While inappropriate shocks were rare in the CRT cohort, we did observe an instance of inappropriate shocks for regular SVT in the CRT OFF group when inactivating CRT pacing altered intrinsic QRS morphology leading to a lack of waveform recognition.

Discussion

The role of ICD therapy in patients with LVAD is unclear. Further, optimal programming of these devices is entirely uninvestigated. This trial is the first to prospectively investigate any ICD programming strategy in the LVAD population. We assessed the effect of a UC ICD programming strategy in patients with an existing transvenous ICD undergoing de novo LVAD implantation. While we did not demonstrate a reduction in total ICD shocks delivered, no adverse outcome was seen such as an increase in arrhythmic or heart failure-related hospitalizations or mortality. Notably, no patient in our trial who received a shock experienced symptoms related to their arrhythmia. As such, more conservative approaches may be safe in the LVAD population and different programming restrictions should be considered for these patients. When designing the UC programming parameters, we were significantly limited by the Food and Drug Administration and manufacturer restrictions. For example, the maximal time to detection in the VT zone that we could program for any manufacturer was 33 s (or 100 intervals at 180 bpm). While this may be appropriate in a patient without LVAD support, in this population it would be preferable to extend this time frame much farther, potentially into the range of minutes to hours. The variation amongst manufacturers in programming limits at the extremes of VF and VT zone therapy largely stems from intellectual property restrictions and established Food and Drug Administration approval of the firmware in ICD generators, which cannot be altered. Opening ICD programming limits to practitioners managing patients with LVAD has the potential to improve quality of life and reduce healthcare utilization in this resource-intensive population by avoiding ICD shocks, limiting emergency room visits for stable VAs, and potentially extending device longevity.

In the LVAD population with ICDs in place there may be a role for a VA monitoring-only strategy using remote alerts. With this approach, care providers could be prompted to call patients in sustained VA and evaluate symptoms before determining treatment. Thus, a monitoring-only strategy

Table 3. Control Group Programming

| Zone                  | Control (n=38) | Ultra-Conservative (n=44) |
|-----------------------|---------------|--------------------------|
| VF zone active        | 38 patients (100%) | 38 patients (100%) |
| Detection rate        | 214 bpm (200 to 228) | 214 bpm (200 to 228) |
| Intervals to detection| 16 (12 to 24)  | 16 (12 to 24)  |
| Shocks active         | 38 (100%)     | 38 (100%)     |
| ATP active            | 31 (82%)      | 31 (82%)      |
| VT zone active        | 26 patients (68%) | 26 patients (68%) |
| Detection rate        | 176 (167 to 181) | 176 (167 to 181) |
| Intervals to detection| 19 (16 to 27)  | 19 (16 to 27)  |
| Shocks active         | 24 of 26 (92%) | 24 of 26 (92%) |
| ATP active            | 26 of 26 (100%) | 26 of 26 (100%) |
| FVT/VT-2 zone active  | 9 patients (24%) | 9 patients (24%) |
| Detection rate        | 187 (182 to 188) | 187 (182 to 188) |
| Intervals to detection| 24 (18 to 30)  | 24 (18 to 30)  |
| Shocks active         | 9 of 9 (100%)  | 9 of 9 (100%)  |
| ATP active            | 9 of 9 (100%)  | 9 of 9 (100%)  |

Values are presented as the number of patients with each zone active followed by the percentage of the control group (n=38 patients), or the median followed by the interquartile range. ATP indicates anti-tachycardia pacing; bpm, beats per minute; FVT, fast ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 4. Outcomes

|                          | Ultra-Conservative (N=44) | Control (N=39) | Combined (N=83) | P Value |
|--------------------------|---------------------------|---------------|----------------|---------|
| Patients experiencing ICD shock | 7 (16%)          | 8 (21%)       | 15 (18%)       | 0.66    |
| Patients experiencing inappropriate shocks | 4 (9%)           | 1 (3%)        | 5 (6%)         | 0.35    |
| Patients hospitalized for arrhythmia or CHF | 11 (26%)        | 8 (22%)       | 19 (24%)       | 0.16    |
| Mortality                | 8 (18%)            | 8 (21%)       | 16 (19%)       | 0.79    |
| CRT-ON (n=20)            | CRT-OFF (n=21)      | Combined (n=41) | P Value |
| Patients experiencing ICD shocks | 2 (10%)          | 8 (38%)       | 10 (24%)       | 0.08    |
| Patients experiencing inappropriate shocks | 0 (0%)           | 2 (10%)       | 2 (5%)         | 0.16    |
| Patients hospitalized for arrhythmia | 0 (0%)          | 2 (9.5%)      | 2 (4.8%)       | 0.16    |
| Patients hospitalized for CHF | 5 (25%)          | 6 (28%)       | 11 (27%)       | 0.71    |

All values presented as number of patients followed by percent of group, P-value calculated using Pearson test. CHF indicates congestive heart failure; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

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would allow VA to be treated similarly to atrial fibrillation, with cardioversions occurring electively in the outpatient setting or observation for spontaneous conversion, which is known to occur even 24 hours after the onset of sustained VT. While ICDs have not been proven to reduce mortality in the LVAD population, there remains a reluctance to turn off all ICD therapies, particularly in patients awaiting heart transplantation. If a robust monitoring-only strategy was available, this may be a more viable option. As has recently been proposed,\textsuperscript{19,20} randomized prospective evaluation of the role of ICD therapy in this population is desperately needed. While this trial does not directly address the question of whether ICD therapy is necessary in the LVAD population, we feel that this work, along with the clinical experience of ourselves and others, supports the safety of such a prospective evaluation.

The benefit of CRT once the left ventricle is hemodynamically supported is also uncertain. Based on our observations, active CRT pacing appears to be protective from VA and ICD shocks. Conversely, turning off the left ventricular lead or disabling CRT may significantly improve CRT-D longevity and spare the LVAD patient from additional unnecessary ICD generator changes, which themselves carry significant risk in this vulnerable population. As such, which of these strategies is the “right” approach is an important question. Data aimed at addressing this are extremely limited. A single retrospective study suggested that the presence of a CRT-D as compared with an ICD did not affect mortality, hospitalization rates, or ICD shocks.\textsuperscript{21} However, a single-center prospective evaluation of patients with CRT inactivated in a nonrandomized fashion following LVAD implantation did demonstrate decreased incidence of ICD shocks in patients with CRT active.\textsuperscript{22} An antiarrhythmic effect of CRT, at least in CRT responders, has been demonstrated in patients without LVAD.\textsuperscript{23} While our investigation did not demonstrate any difference in hospitalizations for congestive heart failure or arrhythmia, fewer ICD shocks were seen in patients with CRT-ON, possibly in part because of the antiarrhythmic effect of CRT. Notably, when we turned CRT-OFF the pacing mode was changed to minimize ventricular pacing, as such our study does not address the effect of RV only pacing in this population. Given the importance of RV function in the LVAD population, this is another area that requires further investigation.

**Study Limitations**

Despite the high volume of LVAD implants at our center, the main limitation of this pilot study is its small sample size,
Fewer patients in the CRT-ON arm had shocks compared with programming, would be necessary to reduce total shocks. programming limits of current ICDs, potentially monitor-only in both groups, it is likely that a strategy well beyond the patients with an LVAD. As the rate of ICD shocks remained high to ICD shock or reduced the number of total ICD shocks in demonstrate that a UC ICD programming strategy affected time Due to the small sample size in our trial we were not able to

Conclusions

which limits our statistical power to detect small, clinically meaningful differences in outcomes. A multicenter investigation will be necessary to overcome this limitation. Additionally, the majority of shocks in our control group were delivered in the VF zone, this suggests that patients in the control group were already programmed conservatively. This may have limited our ability to observe a clinical difference with the UC programming strategy.

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