EDITORIAL

Re-Thinking Re-Synching in Left Ventricular Assist Device Recipients

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With more than 2500 left ventricular assist devices (LVADs) implanted annually in the United States, there is a large and growing population of supported patients requiring longitudinal care, delivered at more than 160 implanting centers across the country in conjunction with numerous nonimplanting centers participating in shared care.[1] Clinical management around the time of LVAD surgery is largely routinized, guided by institutional protocols derived in part from device trial protocols, including surgical technique, pump speed selection, blood pressure management, and anticoagulation management. Additionally, nonrandomized prospective data have enriched this practice.[2,3] However, when it comes to long-term LVAD care, many elements remain uncertain, guided by limited and retrospective data. This includes the continued use of standard guideline-directed pharmacotherapies for systolic heart failure and the management of electrophysiology devices.

As evidenced by the recently published MOMENTUM 3 (The Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3) trial, improvements in clinical outcomes for patients supported by LVAD are likely to be measured in survival free of complications as opposed to raw survival. While the MOMENTUM 3 trial 2-year data provide encouragement that pump thrombosis can be drastically reduced by newer pump designs, several key complications of LVAD support remain challenging. Future design changes are likely to improve driveline infection rates and adjustments in pump flow characteristics, and anticoagulation strategies may impact gastrointestinal hemorrhage. Ventricular arrhythmia (VA) and electrophysiology device management present a different challenge. VAs are a common complication affecting LVAD-supported patients. While LVADs reduce LV pressure volumes and wall stress, ventricular tachycardia and implantable cardioverter defibrillator (ICD) shocks still occur in up to 45% of patients with LVAD with prior history of VAs.[4] While theoretically important, objective evidence suggests that physical interaction of the LVAD apical cannula and the LV myocardium is an uncommon stimulus for ventricular tachycardia in LVAD-supported patients. Presumably, even with excellent LVAD function, the pathologic substrate for ventricular tachycardia (focal scar) will remain a contributor to VAs in the setting of LVAD support. It is our reaction to these VAs that have changed because of the alteration in hemodynamic consequences of ventricular tachycardia/ventricular fibrillation in the patient with LVAD.

Cardiac resynchronization therapy (CRT) plays an important role in the treatment of heart failure with moderately to severely depressed LV ejection fraction in the setting of electrical dyssynchrony, particularly in the presence of left bundle branch block and a QRS duration of >150 ms.[5] However, even in a well-vetted trial population, clinical response to CRT is not universal, with somewhere between half and two thirds of patients reporting an improvement in New York Heart Association Functional Class.[6] Among those who do not experience improved LV volumes after CRT, prognosis is dramatically worse.[7] Among these patients with worse outcomes are LVAD recipients, who have, by virtue of achieving New York Heart Association Class IIIB or worse heart failure, arrived at a point where they are not clinically responsive to CRT. So what then is to be gained or lost by continuing CRT after LVAD implantation?

Relevant considerations for continued CRT post-LVAD include the impact of CRT on bridge to recovery strategies, right ventricular function, and proarrhythmia. The prospect of LV recovery is 1 possible reason to continue CRT. LV recovery remains elusive in practice, with only ≈3% of patients explanted for recovery by 3 years post-LVAD.[8] While it would seem unlikely that long-term CRT nonresponders would begin to derive a remodeling benefit after LVAD, patients who had experienced no or minimal previous exposure to CRT might see benefit from continued CRT. Adequate right ventricular function is crucial to clinical success in LVAD support. Is there

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reason to think continued CRT support would avail the right ventricle? Meta-regression data suggest that while CRT is associated with improved echocardiographic measures of right ventricular function, these changes fall out on multivariable analysis and suggest no independent right ventricular functional improvement contingent on CRT.[9] Finally, small studies have suggested CRT may have a proarrhythmic effect.[10] This is thought to be related to alteration of activation timing and point of entry into the scar, thus inducing reentrant rhythms. Also, pacing from both the right ventricular and LV creates 2 activation wavefronts that may collide to create unidirectional block, initiating reentry. It is likely that these possible proarrhythmic effects of CRT were greatly outweighed by the benefits of resynchronization in non-LVAD patients. In the setting of LVAD support, with its powerful actions to unload the LV and reduce wall stress, would the proarrhythmic risk of CRT be more meaningful if the clinical benefit of resynchronization is muted?

In this issue of the *Journal of the American Heart Association (JAHA)*, Gopinathannair et al provide meaningful clinical data to inform conjecture surrounding CRT and LVAD.[11] This multicenter retrospective study is the largest published experience to date on the utility of CRT in patients with LVAD. A total of 488 continuous flow (CF)-LVAD patients were studied, 265 with CRT-D versus 223 with ICD alone. During a mean follow-up of 620±509 days, no difference in mortality was seen between the CRT-D group compared with the ICD-only group (29% versus 25%, logrank *P*=0.28). In multivariate Cox regression, there was no evidence that CRT influenced survival (hazard ratio for mortality in patients with an ICD as opposed to CRT-D 1.469 [95% confidence interval 0.859–2.514, *P*=0.16]). The only variable significantly associated with lower survival was amiodarone use (hazard ratio for mortality 1.77, *P*=0.01). In other unadjusted analyses, there were no significant differences between CRT-D and ICD groups in terms of VA rates (43% versus 39%, *P*=0.3) or ICD shocks (35% versus 29%, *P*=0.2). All-cause hospitalization rates were nonsignificantly lower in the CRT-D group as opposed to the ICD group (0.46 per 100 days versus 0.59 per 100 days, *P*=0.06), while censoring at 1 year of follow-up, there was a nonsignificant trend toward higher mortality in the CRT-D group versus the ICD group (23% versus 15%, *P*=0.054). In the absence of statistical adjustment for baseline differences in covariates, particularly considering the older age of CRT patients, the meaning of these data is uncertain. Perhaps less ambiguous, the rate of generator changes was significantly higher in the CRT group compared with the ICD-only group (26% versus 15.5%, *P*=0.003), though it was not reported whether this higher rate of generator changes contributed to more device infections, or anticoagulation-related issues such as pocket hematomas or pump thrombosis.

Retrospective, uncontrolled, observational data such as these have inherent limitations, but this article raises several important management questions. First, the authors found no evidence of a benefit for CRT-D patients post-LVAD as compared with ICD-only patients in terms of mortality, hospitalization, ventricular arrhythmia, or ICD shocks. CRT-D patients did have an increased rate of device generator changes. Confounding by indication and unbalanced baseline covariates may have influenced some of these findings. Though LV dimensions were similar between groups, the CRT-D group was older, had a higher use of antiarrhythmic drugs including amiodarone, lower LV ejection fraction, and wider native QRS: variables that may have predisposed to higher mortality. This may explain the trend towards higher raw mortality for CRT-D patients during the first year of follow-up. The failure of CRT-D to demonstrate a significant survival difference in multivariate Cox regression (hazard ratio 1.469, 95% confidence interval, 0.859–2.514, *P*=0.16) suggests that there is at least no strong signal for advantage for CRT-D patients over ICD-only patients.

The second key observation made by Gopinathannair et al is that amiodarone use was the only variable analyzed that significantly influenced mortality. While the authors note no significant difference in measured baseline characteristics between amiodarone-exposed and nonexposed patients, it remains possible that amiodarone was in fact used in patients at higher risk of mortality, patients with greater burden of arrhythmia, and/or greater renal dysfunction prohibitive of other antiarrhythmic drug choices. It is, however, data that certainly compel the question of when to consider mitigation of amiodarone use for the purpose of avoiding the known long-term toxicities of the drug. In a bridge to transplant population, amiodarone use may have disadvantages for posttransplant survival.[12,13] Amiodarone use is common pre-LVAD (54% use) and 3 months post-LVAD (43%) in an INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) analysis.[14] Perhaps the authors have buried the lede here and it is in fact the epidemic of amiodarone use upon which we should focus our attention.

Overall, the observations of Gopinathannair et al are reason to reflect on local practice and ultimately warrant further exploration through prospective study. Electrophysiology device therapy in LVAD recipients may be particularly amenable to study since devices are often programmed and then left alone, and end points such as ICD shocks and pacing therapy are accurately recorded and easily discoverable through device interrogation. Does decommissioning of LV leads in post-LVAD patients result in less need for generator change with no additional risk of death or hospitalization? Does a strategy to minimize amiodarone use post-LVAD result in fewer adverse events? Does turning off CRT help to reintroduce a level of ventricular dyssynchrony that augments

Table. Proposed Post-LVAD Electrophysiology Check-Sheet

Turn Left Ventricular Lead Off
Program ICD settings to minimize shocks—raise therapy zones, extend detection, increase ATP use
Return device to pre-LVAD pacing rate or lower
Develop antiarrhythmic drug plan—maximize β-blockers and minimize amiodarone
Expedite transplant listing for patients with VA history
Assess ICD battery life and determine appropriateness of future generator changes
Consider elective, external cardioversion for slower monomorphic VT in clinically stable patients

ATP indicates anti-tachycardia pacing; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; VA, ventricular arrhythmia; VT, ventricular tachycardia.

LVAD filling? Other strategies to minimize ICD shocks should be considered. At Washington University in St. Louis, we reviewed patients with LVAD between 2009 and 2013 to determine whether ICD therapy rates zones were associated with poorer outcomes. A series of 222 consecutive patients with ICDs were stratified according the "permissive" MADIT-RIT (Multicentre automatic defibrillator implantation trial-reduce inappropriate therapy) high rate-zone programming criteria (ventricular fibrillation zone >200 beats per minute). Permissive programming compared with traditional programming was associated with similar rates of mortality and rehospitalization with a trend toward fewer ICD shocks (18% versus 33%, P=0.08). Does a systemic "permissive" strategy of ICD programming for VA reduce defibrillator shocks without resulting in other adverse events? One could envision comparing a combined strategy to minimize shocks, subsequent procedures, and drug-related adverse events to more traditional approaches to CRT, defibrillator programming, and antiarrhythmic drug use (Table).

As post-LVAD care matures, patients and providers look for more than mere survival. A focus on preventing post-LVAD complications weighed against the uncertain expectation of benefit for traditional heart failure therapies post-LVAD is needed. Multicenter retrospective studies such as these are a welcome step forward from single-center observations. Prospective study would be next.

Disclosures

Cooper is a consultant for Abbott and consultant/on the Advisory Board for Medtronic. Rao is a consultant for Abbott. Vader has no disclosures to report.

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