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EDITORIAL COMMENT

Time for MADIT-VAD?

ICDs Among LVAD Patients*

Robb D. Kociol, MD

Randomized controlled trials have shown implantable cardioverter-defibrillators (ICDs) to be lifesaving among patients with heart failure and a reduced ejection fraction (HFrEF) (1–5). Guidelines recommend ICDs as primary prevention of sudden cardiac death for patients with symptomatic HFrEF and those with asymptomatic systolic dysfunction with an EF <30% as a result of prior myocardial infarction (6). Among patients with stage D heart failure who are supported with left ventricular assist devices (LVADs), the utilization or implantation of ICDs is likewise recommended. However, the evidence supporting these recommendations is limited to extrapolation from the cohort of patients with heart failure not supported by an LVAD, expert consensus, or results of a few underpowered, retrospective observational studies (7). Patients with LVADs are at risk for ventricular arrhythmias (VAs), especially among patients with a pre-implant history of VA and those who are early post-LVAD implantation (8). These may be associated with increased mortality. Conversely, the unique physiology of LVAD support may allow for better hemodynamic tolerance of VAs when they occur (9). Several reports describe patients with an LVAD in situ tolerating rapid VT and even ventricular fibrillation without any hemodynamic compromise (10,11). Although it is likely that some proportion of those patients would develop circulatory collapse during VA, there is often time to receive medical attention and treatment.

In this issue of *JACC: Heart Failure*, Vakil et al. (12) performed a systematic review and meta-analysis of studies pertaining to the very important question of whether ICDs prolong survival in patients with LVADs. No randomized controlled trials exist to answer these questions, and they found 6 retrospective observational studies suitable for inclusion in their analysis. Included studies were from different LVAD eras, and thus included both pulsatile pumps and the continuous-flow pumps that are used in contemporary practice. Most patients had the LVAD implanted as a bridge to transplant (BTT) indication, and a minority of patients (39%) had

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continuous flow (CF)-LVADs. An ICD was present in 38% of patients. The indication for ICD (primary prevention vs. secondary prevention of sudden cardiac death) was not indicated. Mean follow-up time was 7 months. Among the 937 total patients in this analysis, 16% of patients with ICDs died in the follow up period versus 26% in the cohort without ICDs, resulting in a statistically significant 39% relative risk reduction in all-cause mortality among those with ICDs. When the analysis was restricted to patients with contemporary CF-LVADs, those with ICDs had a nonsignificant trend toward reduced mortality. The authors conclude that implantation of ICDs among patients with LVADs is associated with decreased mortality, and these data strengthen current guidelines recommending ICD implantation in this population. They also acknowledge that the association is no longer significant when analysis is restricted to CF-LVADs.

Although the study was well done given the paucity of existing data on this subject, the conclusion that these data strengthen current guidelines recommendations must be viewed with caution. The majority of patients included had less-durable

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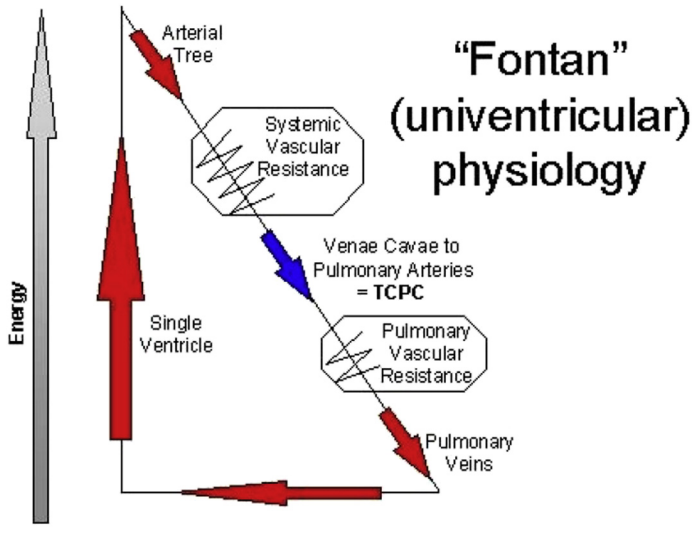
From the Division of Cardiology, Department of Medicine, Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. Dr. Kociol has received research funding from Biocontrol Medical. The research was funded by Medtronic.

pulsatile LVAD devices that are no longer used (12). Patients with CF-LVADs in the contemporary era were much more likely to have ICDs, and it has been shown in a randomized, controlled trial that CF-LVADs are associated with increased survival versus pulsatile pumps (13). Additionally, studies looking at temporal trends in LVAD survival have demonstrated improved 1-year survival among LVAD patients as one progresses through time to the current era. Hence, the presence of an ICD may serve as a marker for a population with CF-LVADs that were implanted more recently, whereas those without ICDs were more likely to have pulsatile pumps that were studied at an earlier time point (14). Indeed, among patients with CF-LVADs in this study, there was no significant difference in survival between groups.

Next, we do not know the indication for ICD implantation—was it for primary or secondary prevention? The utility of the ICD as a life-saving device is likely to be different among those with prior SCD versus those who received a device for primary prevention. Patients who are sicker (or less sick) may be more likely to receive ICDs once on VAD support; thus, there is the potential for confounding by severity. Finally, the lack of actual cause of death and the relatively short follow-up time call in to question the validity of these results when compared with randomized, controlled trials of ICDs for primary prevention. A 39% reduction in all-cause mortality is a very large effect size, especially over a period of 7 months. In the landmark trials of primary prevention devices, among those without LVADs, significant benefit did not accrue until a year after the device was implanted (1,2). If we knew the cause of death, for example, patients without ICDs tended to succumb to fatal arrhythmias or progressive right ventricular failure, the association would have additional biological plausibility; however, in the absence of these data and with the presence of significant confounding, the association remains tenuous.

As more data emerges to guide decision-making regarding ICD implantation among LVAD patients, one will need to take into account the individual patient's LVAD indication (destination therapy [DT] vs. BTT), personal physiology (such as the presence of pulmonary hypertension), prior history of VT on and off LVAD support, and if a patient with DT, specific wishes around end-of-life care. Although a randomized trial may not give us that level of personalized detail, it will be a step forward in evaluating ICDs in this population. A further understanding of each patient's physiology will help the provider further stratify risk to provide patients with the most complete risk/benefit analysis.

FIGURE 1 Fontan Physiology



A schematic illustration of the circulatory system relying on Fontan physiology Reprinted with permission from Degiovanni and Grech (16). TCPC = total cavopulmonary connection.

Patients supported with LVADs have unique physiology in that their LV is fully supported by a device capable of generating up to 10 l/min of flow. Yet, as in the native heart, the LV remains dependent on a functional right heart for delivery of adequate preload. In the extreme case of VA, ventricular fibrillation, the right ventricle has no intrinsic organized contractions. Hence, one might expect, in the absence of a functional right ventricle, underfilling of the LV would result in rapid circulatory collapse (7). At times, in the case of patients with LVADs, this does not occur, and the patient remains remarkably hemodynamically stable at least for a period of time. Here we must consider the concept of Fontan physiology. The Fontan procedure, first described by Fontan and Baudet (15) in 1971 for the correction of tricuspid atresia, was premised upon the contribution of potential energy in the central venous circulation to drive blood through the right heart, with minimal contribution from a hypertrophied right atrium, into the pulmonary circulation and left atrium (**Figure 1**) (16). Fontan and Baudet (15) noted that among patients who underwent successful procedures, they had normal pulmonary arteries, had normal pulmonary artery pressures, and were post-operatively quite pre-load dependent. Similarly, among patients with LVADs and VA, the right heart may be able to operate as a passive conduit, allowing blood flow from right to left; yet, the driving pressure must be sufficient to overcome the pulmonary vascular resistance (PVR).

Patients with elevated pulmonary pressures and PVR or those with low central venous pressures are unlikely to remain hemodynamically stable in case of VA, especially rapid VT or ventricular fibrillation.

Prior case reports support the notion of the potential for Fontan physiology among LVAD patients and describe such patients with complete hemodynamic stability despite potentially destabilizing VA (10). Knowing a patient's individual hemodynamic profile, specifically right heart function, pulmonary pressures, and PVR, will help clinicians better risk-stratify LVAD patients and determine if an ICD is more or less likely to rescue a patient from a destabilizing VA. Although implanting versus not implanting an ICD may be the first level of decision making, the ICD programming is the next consideration. Should there be a longer time period between detection of VA and delivery of shocks among patients with ICDs supported by a LVAD? Should there be more attempts at ATP prior to shock delivery? With the growing population of LVAD patients worldwide, prospective study is needed to answer these questions.

DT LVADs are essentially a palliative therapy for those with end-stage heart failure who are not transplant candidates. The goal of this therapy is to prolong life and improve quality of life. Prolonging life and improving quality of life are not always aligned directly—especially in the case of someone getting painful shocks for life-threatening or non-life-threatening VA. Although among BTT patients, it makes sense to err on the side of caution despite the potential for painful inappropriate shocks (assuming ICD effectiveness is proven in this population), among those with DT devices, careful discussion with the patient is needed to determine his or her wishes and goals regarding longevity versus quality prior to device implantation. These discussions should also be revisited after instances of ICD therapy or when the patient approaches end-of-life.

Although Vakil et al. (12) do an excellent job summarizing the present data regarding the utility of ICDs among LVAD patients and performing a meta-analysis, the evidence is not yet strong enough to recommend or not recommend ICD implantation among patients with LVADs. Evidence generated from prospective trials, consideration of the individual patient's unique physiology, LVAD indication, and patient goals should all ultimately inform the decision to place or activate ICDs in this group of patients, allowing for shared decision making with their providers.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Robb D. Kociol, Division of Cardiology, Department of Medicine, Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School 185 Pilgrim Road, Boston, Massachusetts 02115. E-mail: rkociol@bidmc.harvard.edu.

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