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Does defibrillation threshold increase as left ventricular ejection fraction decreases?

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Aims Advanced cardiac disease, entailing more hypertrophy, fibrosis, scarring, dilatation and conduction delays, poses the question of whether defibrillation thresholds (DFTs) increase as left ventricular ejection fraction (LVEF) decreases. This question has been approached indirectly or insufficiently in previous studies. In this study we add and expand on our previous work, stratifying DFT for various LVEF ranges.

Methods and results This retrospective analysis included DFT data from three acute, multicentre, randomized studies that included 230 ICD/CRT-D patients. All DFTs were obtained with the SVC coil turned ON and with pulse-width optimized waveforms based on a 3.5 ms membrane time constant. As the LVEF decreased, DFT estimates increased from 395.2 $\pm$ 115 V for LVEF $\geq$ 46% to 425.8 $\pm$ 117.6 V for LVEF $\leq$ 25%. However, these changes in DFT estimates were very minor and not statistically significant. Only 3% of the patients in this population had an elevated DFT of $>$20 J.

Conclusion This analysis shows that over a very broad range of LVEF, DFT changes minimally (approximately 1 J), if at all. Our results are consistent with previous studies that demonstrated no difference in the DFT estimates: (a) between patient groups receiving ICD (typically higher LVEF) vs. CRT-D (typically lower LVEF) and (b) between patient groups receiving a device for primary prevention indications (typically lower LVEF) vs. secondary prevention indications (typically higher LVEF).

Keywords Defibrillation threshold • Implantable cardioverter defibrillator • Ejection fraction

Introduction

Implantation of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy-defibrillators (CRT-Ds) has significantly increased after the positive results of some landmark primary prevention trials showing the efficacy of ICD therapy in reducing mortality.[1–3] Defibrillation threshold (DFT) testing at implant is routinely done to ensure that the ICDs/CRT-Ds deliver appropriate amounts of energy and are functioning appropriately. The left ventricular ejection fraction (LVEF) of ICD patients implanted for either primary or secondary prevention can range from normal or near-normal ($>$45%) to severely impaired ($<$25%). Typically, patients with a low LVEF also have underlying cardiac disease that has progressed to an advanced degree. Among various other clinical parameters, depressed LVEF has been shown to be a potential predictor of high DFTs in patients implanted with unipolar or bipolar defibrillation systems.[4–8]

While clinical predictors of high DFTs have been extensively studied in patients receiving ICDs/CRT-Ds, stratification of DFTs by LVEF, one of the most commonly used indices for cardiac impairment, has never been done before. Accordingly, this analysis was undertaken to assess the change in DFT estimates as the LVEF goes from being normal to impaired in patients who are implanted with left-sided, active pectoral defibrillation lead systems.

Methods

This retrospective analysis included data from three different multicentre, prospective, randomized studies that were reviewed and approved by the appropriate Human Research Ethical Committees of each of the

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Table 1 Study inclusion/exclusion criteria

	Study 1[9]	Study 2[10]	Study 3[11]
Objective	To compare the DFT efficacy between 50/50% tilt and tuned defibrillation waveforms	To compare DFT efficacy between SVC coil ON and OFF un-tuned defibrillation waveforms	To compare DFT efficacy between the 2.5, 3.5, and 4.5 ms membrane time constant-based defibrillation waveforms
Inclusion criteria	Patient is a candidate for ICD implantation Patient is able to tolerate DFT testing	Patient is a candidate for ICD implantation Patient has had an echocardiogram, multiple gated acquisition (MUGA), or cath procedure within 6 months of ICD implant Patient is able to tolerate DFT testing	Patient is a candidate for ICD/CRT-D implantation Patient has a compatible transvenous defibrillation lead system Patient has had an echocardiogram, MUGA, or cath procedure within 6 months of ICD implant Patient is able to tolerate upper limit of vulnerability-guided DFT testing
Exclusion criteria	Patient has a mechanical valve in the tricuspid position Patient is pregnant Patient is <18 years old	Patient has a mechanical valve in the tricuspid position Patient has a chronic defibrillation lead, which will not be removed Patient has a right-sided ICD implant Patient is pregnant Patient is <18 years old	Patient has a mechanical valve in the tricuspid position Patient has epicardial defibrillation electrodes Patient is pregnant Patient is <18 years old

participating medical centres.[9–11] Study-specific objectives, inclusion, and exclusion criteria for all the three studies are listed in *Table 1*. Patients were enrolled by the study site after appropriate informed consent was obtained. The patient population consisted of 230 patients who were implanted with any FDA-approved Atlas®, Epic®, Current®, and Promote® ICDs/CRT-Ds and a compatible dual-coil defibrillation lead system. All patients who met the inclusion criteria in these three studies and underwent DFT testing using SVC coil turned ON were included in this analysis.

Defibrillation threshold testing

Two of three studies required the use of a binary search protocol and 72% of the data contributing to this analysis came from those studies.[9,10] One of the three studies required the use of a binary search protocol guided by upper limit of vulnerability and 28% of the data contributing to this analysis came from that study.[11] The defibrillation waveform for all patients was programmed to the optimal pulse width settings based on a theoretical 3.5 ms membrane time constant using a commercially available chart of optimal defibrillation pulse width (Phase 1/Phase 2) durations.[12] The RV coil was programmed as the anode for the first phase and the SVC coil was always turned on. Ventricular fibrillation was induced by T-wave shock, burst-pacing, or 'DC (direct current) Fibber' through the ICDs. For all the methods, DFT estimate was established only after observation of a failed shock.

Analysis

DFT estimates were stratified into four different LVEF groups ($\leq$25%, 26–35%, 36–45%, and $\geq$46%). A linear model in which the LVEF group is treated as a factor was used to analyse the data. A *P*-value < 0.05 was considered statistically significant.

Results

There were 230 patients included in this analysis (*Table 2*). The average age, LVEF, NYHA class, and gender distribution grouped by LVEF range is shown in *Table 3*. The mean DFT voltage for LVEF $\leq$25% was 425.8 $\pm$ 117.6 V, 26–35% was 417.5 $\pm$ 121.1 V, 36–45% was 394.1 $\pm$ 133.3 V, and $\geq$46% was 395.2 $\pm$ 115 V

Table 2 Patient population (n = 230)

Age	66.6 $\pm$ 12.4 years
Gender	81% males
NYHA class	
I	12.6%
II	40%
III	25.2%
IV	1.3%
Unknown	20.9%
Ischaemia	74.3%
Implant indication	
Primary	63%
Secondary	33%
Unknown	4%
Hypertension	54%
Amiodarone usage	9.1%

Table 3 Patient population and DFT estimates grouped by LVEF

LVEF range	LVEF (%)	Gender	Age (years)	NYHA class	Impedance (Ω)	DFT voltage (V)	DFT energy (J)
≤25% ($n = 102$)	20.7 ± 4.0	85% male	65 ± 12.2	2.5 ± 0.6	40.9 ± 6.6	425.8 ± 117.6	8.6 ± 4.9
26–35% ($n = 90$)	32.7 ± 4.3	82% male	67 ± 12.2	2.0 ± 0.7	41.2 ± 6.3	417.5 ± 121.1	8.4 ± 5.1
36–45% ($n = 17$)	41.2 ± 3.4	71% male	67 ± 11.6	1.8 ± 0.7	40.1 ± 6.2	394.1 ± 133.3	7.6 ± 4.4
≥46% ($n = 21$)	54.9 ± 5.2	62% male	74 ± 12.4	1.3 ± 0.6	40.5 ± 5.2	395.2 ± 115.0	7.5 ± 4.2

P = not significant.

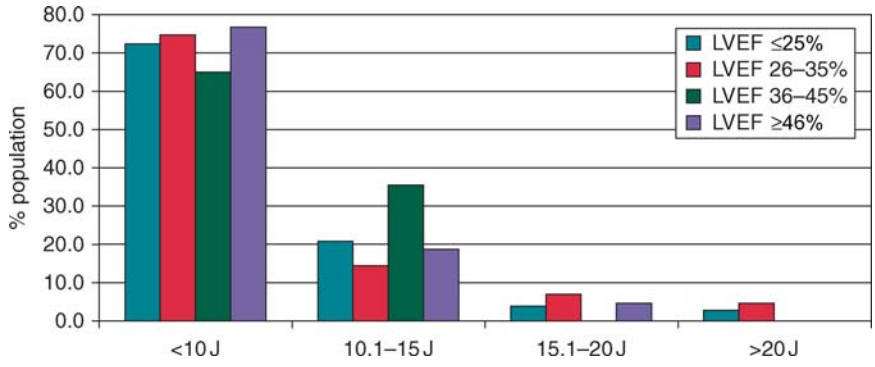

Figure 1 Distribution of DFT energies by different LVEF ranges.

(*Table 3*). Similarly, the mean DFT energies for LVEF ≤25% was 8.6 ± 4.9 J, 26–35% was 8.4 ± 5.1 J, 36–45% was 7.6 ± 4.4 J, and ≥46% was 7.5 ± 4.2 J (*Table 3*). DFTs (voltage and energy) trended higher for lower LVEF but this trend is not statistically significant ($P = 0.58$ for DFT voltage and $P = 0.69$ for DFT energy). Only 3% of the patients ($n = 7$) had a DFT of >20 J and all of these high-DFT patients had an LVEF <35% (*Figure 1*). Of these seven high-DFT patients, a >10 J safety margin could not be achieved in three patients.

All of the patients ($n = 7$) with DFT > 20 J were men with an LVEF ≤ 35%. In this group, five patients received an ICD/CRT-D for primary prevention, four had ischemic cardiomyopathy, four had hypertension, and four had undergone previous ablation for sustained ventricular tachycardia. Two of these patients were below the age of 50 years, three of them were between 50 and 65 years, and two were above 65 years of age. Similarly, each of the patients ($n = 4$) with DFT > 25 J had received an ICD/CRT-D for primary prevention; two had ischaemic cardiomyopathy and two had hypertension. One of the patients was younger than 50 years, two were between 50 and 65 years, and one was above 65 years.

A multiple variable regression estimation model constructed to estimate the effect of age, gender, NYHA class, LVEF, implant indication, type of study, and method of VF induction on DFTs revealed that gender was the only significant predictor of higher DFTs in this patient population, with men having higher DFTs than women ($P = 0.02$). The mean DFT in men was greater than that in women by 58.7 V (15.2%) and 2.3 J (31.3%).

Discussion

This is the first analysis that attempts to stratify the DFT estimates by LVEF in patients tested with biphasic, tuned waveforms that are optimized based on the high-voltage lead impedance. The primary results indicate that both DFT voltage and energy increase as LVEF decreases, but the difference in DFT energy between each adjacent LVEF group is very small and, even between the highest and the lowest LVEF groups is minimal (approximately 1 J).

In previous studies, the association of LVEF and DFT has been inconsistent.[4,7,8,13–18] Burke *et al.*[13] analysed DFTs in 50 ICD/CRT-D patients. Although the mean LVEF in CRT-D group was significantly lower than that of the ICD group (23 ± 5% for the CRT group vs. 31 ± 10% for the control group), the mean DFTs of the two groups were not significantly different (10.2 ± 6.1 J for the CRT group vs. 9.5 ± 5.0 J for the control group). Similarly, Cuoco Jr. *et al.*[14] found no significant difference in DFT between ICD and CRT-D groups ($n = 537$). In the ASSURE study,[15] Doshi *et al.* showed that patients receiving CRT-D devices do not have higher defibrillation energy requirements when compared with ICD patients. Val-Mejias *et al.*[16] found no difference in the DFT estimates between ICD/CRT-D patients implanted with primary and secondary prevention indications, in spite of significant differences in the LVEF between the two indication groups. In an analysis of 128 patients who received Ventak ICDs, Horton *et al.*[17] did not find LVEF to be a significant factor in predicting high DFT. However, several studies have shown that LVEF was one of the significant predictors of a high DFT. In their review of 1139 patient records with all manufacturer's devices, Russo *et al.*[18] found that 71 patients (6.2%)

had high DFTs (<10 J safety margin). Lower LVEF had a borderline predictive value for the need for system revision owing to lack of a 10 J safety margin ($P = 0.054$). Similarly, Shukla *et al.*[17] analysed 968 patients with Medtronic devices and found that patients with higher threshold (≥18 J) had lower LVEF, a worse functional class, less frequently done bypass surgery, amiodarone and history of more frequent VF. Both Lubinski *et al.*[7] ($n = 168$) and Pinski *et al.*[8] ($n = 125$) found that low LVEF was a significant predictor of high DFT. In an older study involving 128 patients who received epicardial defibrillators, high LVEF was found to be an important determinant of improved defibrillation efficacy.[4]

In this study, only 7 of the 230 patients had a DFT > 20 J which is slightly lower than the incidence reported in other studies that employed fixed tilt waveforms.[5–8,19,20] This could be because the DFT protocol in some of these studies was neither uniform nor was it followed consistently and the definition of high DFT was different from the current study. Interestingly, all the 'high DFT' patients in our study had an LVEF of <35% suggesting that the occurrence of high DFT is not a common problem in patients with normal to near-normal LVEF. It should be noted that the results from the current study were obtained with fixed pulse-width waveforms that are optimally tuned per impedance and assumed cardiac membrane time constant. Fixed pulse-width waveforms have been shown to provide lower voltage and energy DFTs than fixed-tilt waveforms, particularly when DFT is higher than 400 V. This might explain our lower DFT per LVEF range as well as our lower incidence of 'high DFT'.[21,22] It should be noted that concerns regarding DFTs between 20 and 26 J may not be as great when a device with maximum delivered energy capability of 36 J is used because a 10 J safety margin would be available.

This analysis should be interpreted under the light of certain limitations. First, this is a retrospective analysis, hence there is an unequal number of patients in the four stratified LVEF groups. Second, DFT estimates in all the patients were obtained with a left-sided, active pectoral pulse generator that utilized biphasic, tuned waveforms with SVC coil turned ON. We cannot assure that similar results would be observed if the different waveforms, generator pocket location, shocking vector, or lead configurations are used. In addition, the impact of infiltrative cardiomyopathy (i.e. sarcoidosis, amyloidosis, etc.) could not be assessed because there were no patients in the cohort with those diseases. The impact of kidney disorders could not be evaluated because data reflecting renal function was not collected in any of the three studies.

Conclusion

This analysis shows that across a very broad range of LVEF, changes in DFT are minimal. No patient with a near-normal to preserved LVEF had an occurrence of high DFT, and among the patients with severely impaired LVEF only a few (3%) had high DFTs. These results should reassure implanters that patients with severely impaired LVEF implanted with left-sided ICD/CRT-D devices employed with tuned defibrillation waveforms and dual-shocking leads will not necessarily have elevated DFTs.

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