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Appropriate and inappropriate electrical therapies delivered by an implantable cardioverter-defibrillator: Effect on intracardiac electrogram

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Abstract

Introduction—Local injury current (LIC) seen after induced ventricular fibrillation rescue ICD shock predicts heart failure progression. We sought to determine the frequency of LIC after spontaneous events in patients receiving ICD therapies.

Methods and Results—Near-field (NF) right ventricular (RV) EGM during 10 sec after delivered ICD therapy was compared with baseline EGM in 420 events that occurred in 134 patients (mean age 60.8±14.8, 106 [79%] male). The magnitude of elevated or depressed potential immediately after the major fast EGM deflection was defined as LIC, and its ratio to the peak-to-peak EGM amplitude was defined as relative LIC. LIC of at least 1 mV or relative LIC of at least 15% was considered significant. LIC was observed in 121 events (28.8%) and was detected more frequently after appropriate (43 [60.6%] events) and inappropriate (56 [64.4%] events) ICD shocks, as compared with appropriate (8 [9.2%] events) and inappropriate (3 [4.7%] events) antitachycardia pacing (ATP) or nonsustained ventricular tachycardia (11 [9.9%] events) [ANOVA $p<0.0001$]. Type of ICD therapy (ICD shock vs. ATP) was the most significant predictor of LIC (ATP β coefficient -0.81 ; 95%CI -1.19 – -0.44); $P<0.0001$), along with cycle length of tachycardia (β coefficient -0.0117 ; 95%CI -0.0167 – -0.0068 , $P<0.00001$) and shock energy (β coefficient 0.024 ; 95%CI 0.003 – 0.045 , $P=0.025$).

Conclusion—Appropriate and inappropriate ICD shocks are frequently characterized by the development of LIC in patients with structural heart disease. Type of electrical ICD therapy, shock energy and cycle length of ventricular arrhythmia are important determinants of LIC.

Keywords

defibrillation; ventricular arrhythmia; antitachycardia pacing

Introduction

Congestive heart failure afflicts over 5 million Americans¹ and is often associated with an increased risk for sudden cardiac death (SCD). It is estimated that approximately 250,000–400,000 deaths each year in the United States are due to SCD² and often are the result of

life-threatening ventricular arrhythmias.^{2, 3} Implantable cardioverter-defibrillators (ICDs) have been shown to reduce all-cause mortality in patients at risk for SCD.⁴⁻⁷

Although ICD shocks are life-saving, long-term follow-up has demonstrated that patients who experience ICD shocks are at increased risk of subsequent heart failure events^{8, 9} and nonsudden cardiac death.^{10, 11} An increased risk of sudden arrhythmic death in ICD recipients¹² with history of sustained VA and appropriate ICD therapies was shown. Moreover, inappropriate ICD shocks were also shown to be associated with increased all-cause mortality,^{11, 13} predominantly due to progressive heart failure. However, subsequent analysis¹⁴ showed that only appropriate ICD shocks were associated with increased mortality, whereas neither appropriate antitachycardia pacing (ATP)-treated VA events nor inappropriate ICD shocks showed the same association.

We previously demonstrated that local injury current (LIC), observed on the near-field (NF) right ventricular (RV) electrograms (EGM), can occur following an ICD shock during defibrillation threshold testing¹⁵. LIC, but not ICD shock, predicted subsequent pump failure death or hospitalization due to heart failure exacerbation, but it did not correlate with subsequent sustained VA events and appropriate ICD therapies. Acute LIC is a transient phenomenon, and whether LIC appears after appropriate and inappropriate ICD therapies is unknown. Furthermore, it is unclear if LIC is the result of ICD therapy or the underlying ventricular arrhythmia being treated. In this work, we systematically describe NF RV EGM morphology observed after appropriate and inappropriate ICD therapies, delivered due to spontaneous events, occurring at least 1 month after ICD implantation.

Methods

The study protocol was approved by the Johns Hopkins University and the Washington University Human Studies Committees, and all patients gave written informed consent before entering the study.

Study Population

We analyzed the data of patients with structural heart disease and systolic dysfunction who were enrolled in two prospective observational cohort studies. The ICD-EGMs study (NCT00916435) enrolled adult patients with a transvenous ICD device implanted for primary or secondary prevention of SCD,¹⁵ excluding patients with inherited channelopathies, pregnant patients, and patients with life expectancy less than 1 year because of concomitant noncardiac diseases. PROSE-ICD study (NCT00733590) enrolled patients with standard indications for primary prevention ICD, with exclusion of patients younger than 18 years of age, pregnant patients, patients with indications for secondary prevention ICD, or patients with Class I indications for pacing. Only patients with transvenous Medtronic devices and dedicated bipolar ICD leads were included in this study.

Data Acquisition

Baseline NF RV EGM was recorded during 5 minutes of sinus rhythm at rest simultaneously with one-lead (lead II) surface ECG via Medtronic programmer 2090 using the NI USB-9215A portable data acquisition system (National Instruments, Austin, TX) with 1000 Hz sampling frequency and 0.3mV/bit amplitude resolution during a routine office visit 1 week after the ICD implantation procedure and at every subsequent follow-up office visit in participants of the ICD-EGMs study. In PROSE-ICD participants NF RV EGM stored in the memory of the ICD device immediately before the onset of a spontaneous event served as a baseline. Patients visited the office at least once a year for follow-up. The ICD device was interrogated and all stored memory events were extracted. The stored EGMs were converted

into digital format using proprietary Medtronic software and further analyzed using a customized MATLAB (MathWorks, Inc., Natick, MA) software application.

Categories of spontaneous events stored in ICD memory

Programming of the ICD device was based on the discretion of the attending electrophysiologist. All ICD interrogation data were adjudicated by an independent endpoints adjudication committee. ICD therapies for monomorphic ventricular tachycardia (MMVT), polymorphic ventricular tachycardia (PVT), or ventricular fibrillation (VF) were classified, as appropriate. MMVT was defined as a sustained VT with stable cycle length and EGM morphology. PVT was defined as a sustained VT with unstable cycle length and EGM morphology and average cycle length ≥ 200 ms. VF was defined as sustained ventricular tachyarrhythmia with unstable cycle length and EGM morphology and average cycle length <200 ms. An appropriate event was considered as a single rhythm event, regardless of the total number of ATP sequences and shocks that were required to terminate the tachycardia.

The ICD therapies were categorized as appropriate ICD shock, appropriate ATP, inappropriate ICD shock, and inappropriate ATP. ICD therapies triggered by anything other than VA rhythm were considered to be inappropriate. Nonsustained ventricular tachycardia (NSVT), defined as three or more consecutive ventricular in origin beats, either MMVT or PVT, self-terminated without applied ICD therapy was considered to be an NSVT event category. Stored EGM recorded immediately before the onset of event (in PROSE-ICD study participants), or baseline EGM recorded during prior office visit at rest (in ICD-EGMs study participants), served as control EGM.

Assessment of intracardiac near-field EGM and measurement of local injury current

NF RV EGM was quantified as the difference of potentials between the tip and the ring of the dedicated bipolar ICD lead implanted in the RV apex. Only ventricular-sensed (VS), presumably sinus, beats were analyzed. The first 2 seconds after ICD therapy were excluded from analysis, and approximately 8 seconds of stored data were analyzed. Ventricular-paced (VP) beats, distorted beats of undetermined origin, and ectopic beats were excluded from the analysis as well. Custom-made MATLAB programs were created to automate measurements. The software automatically identified the baseline (the isoelectric portion before the major fast EGM deflection), the onset, the offset, and the peak-to-peak amplitude of the major fast deflection of filtered (3-100 Hz) bipolar NF RV EGM.

The magnitude of elevated or depressed potential immediately after the major fast EGM deflection (Figure 1), measured from the baseline to its highest J point in mV, was defined as LIC. J point was determined automatically by the change in the slope, i.e., change in the sign of second derivative. Relative LIC was calculated as the ratio of LIC to the peak-to-peak amplitude (p-p R) in each beat. All values were averaged across all analyzed beats. LIC of at least 1 mV or relative LIC of at least 15% was considered significant, as in our prior work.¹⁵

Length of arrhythmia, average cycle length of arrhythmia, and average heart rate before and after therapy were automatically measured as well. In addition, the difference between baseline and after-event values of p-p R, LIC, and relative LIC was calculated.

Statistical Analysis

Results are presented as mean $\pm$ standard deviation (SD) for normally distributed variables, and as median and interquartile range for skewed distributions. Continuous variables were compared using the independent samples *t* test if normally distributed and the Wilcoxon

rank sum test if skewed. Paired t test was used to compare control EGMs with EGMs after ICD therapies or after NSVT. The Pearson chi-square test was used to compare categorical variables. One-way ANOVA with Bonferroni correction for multiple comparisons was employed to compare characteristics of NF RV EGM after different types of ICD therapies, after NSVT, and in control. Linear random effects mixed model was used to determine factors associated with LIC. Mixed model was selected to account for associations among multiple events in the same patient (clusters) to make valid inferences. Coefficient β in our model describes the change in the average LIC for a unit change in explored factors (CL and duration of arrhythmia, and type of ICD therapy and shock energy) for a particular subject. A P -value of <0.05 was considered significant. STATA 10 (StataCorp LP, College Station, Texas) software package with gllamm function was used for calculations.

Results

Data from 672 patients (mean age 60.8 ± 14.8 , 484 [73%] male) who underwent ICD implantation for primary (477 patients, 71%) or secondary (195 patients, 29%) prevention of SCD were analyzed. Ischemic cardiomyopathy with MI history was diagnosed in 417 (62%) patients and nonischemic cardiomyopathy in 255 (38%). Active fixation leads (Sprint Fidelis™ model 6949 and Sprint Quattro Secure™ model 6947) were used in 120 (90%) patients, and passive fixation leads (Sprint Quattro™ model 6944) were used in 14 (10%) patients. All used leads system were true bipolar with standard electrode space 8 mm from tip to ring. Lead impedance as measured at the visit before spontaneous event ranged from 242 to 1500 ohms, mean 675 ± 242 ohms. During 30 ± 12 months of follow-up, 420 events with stored digital EGMs were extracted and analyzed from the ICD memory of 134 patients. Distribution of analyzed events is presented in Figure 2. Slightly more than one-third of patients with recorded events (50 patients, 37%) experienced at least two different types of events during the study period.

Significant LIC was observed in 121 events (28.8%). Appearance of LIC was a changeable phenomenon, i.e., LIC was frequently observed after one, but not another, appropriate ICD shock in the same patient. Significant LIC was detected more frequently after appropriate ICD shocks (43 [60.6%] events) and inappropriate ICD shocks (56 [64.4%] events), as compared with appropriate ATP (8 [9.2%] events), inappropriate ATP (3 [4.7%] events), and NSVT (11 [9.9%] events) [ANOVA $p < 0.0001$ and Pearson χ^2 test $p < 0.0001$], Figure 3. Examples of EGM changes before (in control) and after ICD therapies and NSVT are shown in Figure 4.

Clinical characteristics of patients with and without LIC

LIC after any ICD therapy or after NSVT was observed at least once in 55 patients (41%). There were no differences between clinical characteristics of patients who at least once exhibited LIC and those who never did, with few exceptions (Table 1). LIC was more frequently observed in patients with an ICD implanted for secondary prevention of SCD and when VF redetect number of intervals to detect (NID) was set to shorter values. No difference in the rate of LIC was observed in patients with active or passive lead fixation.

Comparison of different types of ICD therapies and NSVT

Sustained VA events treated with ICD shock were of a longer duration than VA treated with ATP (due to several failed ATP sequences before shock) [37.8 ± 23.4 vs. 19.4 ± 15.8 sec, t test $p = 0.0001$] and had shorter cycle length (CL) [303 ± 79 vs. 345 ± 52 ms, t test $p = 0.0003$]. There were no large variations in baseline NF RV EGM morphology between groups (Table 2). However, dramatic differences in EGM morphology after VA termination between two different types of electrical therapies were observed. P-p R amplitude significantly increased

after ATP-terminated sustained VA (on 4 mV average), but not after shock-terminated VA. Significant LIC resembling prominent ST depression was observed after appropriate ICD shock, whereas no changes were noted after appropriate ATP (Figure 4D-F). ATP during charging was performed in 37 (9%) of events and did not influence appearance of LIC.

Large significant LIC resembling significant ST depression was observed after both appropriate and inappropriate ICD shocks (Table 2). No differences in the amount of LIC or any other EGM characteristics between two types of ICD shocks were found. Delivered shock energy was also similar between groups. Multiple shocks were delivered during 12 events (8% of all shocks). Significant LIC was observed after 61% of events with single ICD shock, 83% of events with two shocks, 50% of events with three shocks, and 100% of events with four or more shocks (ANOVA $P=0.658$). There was no significant LIC observed in the groups of events after appropriate or inappropriate ATP. Interestingly, p-p R amplitude significantly increased after appropriate ATP events, but did not change after inappropriate ATP (difference in p-p R amplitude 4.64 ± 8.54 vs. -0.45 ± 4.72 mV, $p<0.0001$).

No significant absolute or relative LIC and no variations between LIC quantitative characteristics were found in the groups of events after sustained VT treated with ATP or after NSVT (Table 2). Notably, CL of VT and duration of VT event were similar between these groups.

Determinants of local injury current

We performed linear random effects mixed model regression analysis to determine what VA characteristics and ICD therapy parameters correlate with LIC. As absolute LIC values were not normally distributed, we log-transformed the absolute LIC variable before entering it into the model. Type of ICD therapy (ICD shock vs. ATP) was the most significant predictor of LIC (Table 3). CL of VA and ICD shock energy were significant predictors of LIC after treated sustained VA, but duration of VA was not.

Discussion

In this work we showed that significant LIC occurred more frequently after ICD shocks, both appropriate and inappropriate, than with ATP-treated VA and NSVT. The predominant waveform of NF RV EGM that was observed after spontaneous ICD therapies and NSVT resembled ST depression. We showed that type of electrical ICD therapy (ICD shock or ATP), CL of VA and delivered shock energy are important determinants of LIC.

In a previous publication, we described LIC on bipolar NF RV EGM after induced VF rescue ICD shocks¹⁵ and showed that the patients who exhibited significant LIC after induced VF rescue ICD shocks have a higher risk of HF progression and higher rates of hospitalization due to HF exacerbation and heart pump failure death. In our previous observation LIC was presented as ST segment elevation, likely due to a “triple-hit” event, associated with (1) an underlying condition that leads to progressive HF, (2) mechanical injury due to new lead placement,¹⁶ and (3) a rescue ICD shock. However, at least 1 month after ICD lead implantation, LIC was presented predominantly as ST segment depression, as we show in the current analysis. Further studies are needed to determine whether LIC after spontaneous appropriate and inappropriate ICD therapies is associated with worsening of heart failure and increased mortality.

ICD shock is associated with local injury current

In our study LIC was exhibited after more than 60% of appropriate and inappropriate ICD shocks. Previous works showed substantially higher mortality rate in appropriately shocked patients, as compared with ATP-only treated patients,¹⁴ and we speculate that significant

LIC after ICD shock might be a marker of transient myocyte damage and electroporation.¹⁷ At the same time, it is important to note that the mechanism of the LIC remains speculative and its prognostic significance after spontaneous events is unknown.

Conflicting evidence has been reported regarding the possible effect of inappropriate ICD shocks. An association between inappropriate shocks and increased mortality was demonstrated in MADIT II¹³ and SCD-HeFT¹¹ but not in PainFREE Rx, PainFREE RxII, EMPIRIC, and PREPARE.¹⁴ We observed comparably large significant LIC after both appropriate and inappropriate ICD shocks. It is possible that local injury produced by an ICD shock, perhaps similar in cases of appropriate and inappropriate ICD shocks, does not translate into worse outcomes unless other factors, introduced by VA or an underlying arrhythmogenic substrate, are present. However, additional studies are necessary to prove this hypothesis.

Interestingly, we observed variable LIC in the same patient. Several factors could be responsible for such variability. First, different VA CL results in different LIC. Second, an underlying heart condition, or “first hit” could be dynamic over time. Although LIC correlated with single shock energy, it was poorly correlated with numbers of shocks and was in fact lower after 3 shocks compared to those with 1 shock. We speculate that preconditioning phenomenon might be responsible for this observation. Previous experimental works¹⁷ showed that high-energy shocks (1-3 times above DFT) result in preconditioning phenomenon and, in particular, transiently reduce myocardial vulnerability to arrhythmias. Further investigation of preconditioning phenomenon and its mechanisms could improve ICD therapies and outcomes.

In our study, LIC was observed more frequently in patients with an ICD implanted for secondary prevention of SCD and if the ICD was programmed with short redetection NID values, i.e., in patients who get more ICD therapies. The question remains whether contemporary ICD programming strategy that (1) minimizes the chance of delivering an ICD shock to treat a ventricular tachycardia that would otherwise be self-terminated or successfully aborted by ATP and (2) shortens the shock episode duration by delivering ATP during charging¹⁸⁻²⁰ might result in decreased frequency of significant LIC.

Ventricular tachyarrhythmia is associated with local injury current

In addition to showing the negative effect of appropriate ICD shock, Sweeney et al.¹⁴ showed that shocked patients had a significantly higher VA burden. Similarly, we have found that VA events treated with ICD shock had a faster rate. Although uncoupling the effect of ICD therapy from the effect of VA is an especially difficult task in an observational study, we were able to show that LIC was present after NSVT with the same frequency as after ATP-terminated VA.

Ventricular arrhythmia might initiate several pathophysiological cascades that potentially explain the association of VA with LIC. Global ischemia-reperfusion and adrenergic stimulation increase production of reactive oxygen species (ROS) and NO, change the activity and/or expression of numerous signaling and effector molecules, and create a scenario for the opening of the mitochondrial permeability transition pore,²¹ which is a voltage-dependent, high-conductance channel located in the inner mitochondrial membrane, contributing to the loss of viability associated with post-ischemic reperfusion.^{22, 23} We speculate that under certain conditions transient electroporation induced by an ICD shock might facilitate the opening of the mitochondrial permeability transition pore and deepen myocardial injury. Understanding the mechanisms of LIC after VA with and without various ICD therapies might result in the development of novel protective therapeutic interventions.

Study Limitations

Our observations were limited to the 10-second post-therapy EGM recording storage of the ICD, and the duration of LIC after spontaneous events treated with ICD therapies remains unknown. Future investigations are needed to answer this question. Differences in detection and therapy programming could have influenced the results. The predictive value of observed LIC was not studied in this project but will be addressed in future reports.

Conclusions

More than 60% of appropriate and inappropriate ICD shocks are characterized by the development of significant LIC in patients with implanted ICD and systolic dysfunction. Significant LIC rarely occurs after appropriate ATP, inappropriate ATP, and NSVT. Type of electrical ICD therapy, shock energy and cycle length of ventricular arrhythmia are important determinants of LIC.

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Figure 1. Measurement of local injury current (LIC) and peak-to-peak amplitude (p-p R) of major fast deflection of bipolar near-field (NF) right ventricular (RV) electrogram (EGM).

Figure 2.
Distribution of analyzed events, stored in the ICD memory.

Figure 3.

Prevalence of significant LIC, significantly higher after appropriate and inappropriate ICD shocks, as compared with appropriate and inappropriate antitachycardia pacing (ATP) and nonsustained ventricular tachycardia (NSVT) events.

Figure 4.

Representative example of RV NF EGM recordings in 2 patients: upper panel at baseline (A), after inappropriate ICD shock (B), and after nonsustained ventricular tachycardia (NSVT) [C] in one patient, and lower panel at baseline (D), after appropriate antitachycardia pacing (ATT) [E], and after appropriate ICD shock (F) in another patient.

Table 1

Clinical characteristics of patients with and without significant LIC

Characteristic	LIC (+) [n = 55]	LIC (-) [n = 79]	P
Mean age $\pm$ SD, y	57.2 $\pm$ 14.3	59.5 $\pm$ 13.0	0.327
Male, n(%)	41(74.6)	65(82.3)	0.279
African Americans, n (%)	18(32.7)	18(22.8)	0.202
Ischemic CM with MI history, n (%)	34(61.8)	49(62.0)	0.981
Primary prevention of SCD, n(%)	33(60.0)	62(78.5)	0.021
Single-chamber ICD, n(%)	33(60.0)	49(62.0)	0.262
Active fixation ICD lead, n(%)	47(85.5)	73(92.4)	0.196
LVEF at ICD implantation $\pm$ SD, %	32.4 $\pm$ 13.5	30.8 $\pm$ 12.2	0.449
NYHA class I, n (%)	13(23.6)	16(20.3)	0.577
NYHA class III, n (%)	11(20.0)	17(21.5)	0.577
Diabetes mellitus, n (%)	21(38.2)	26(32.9)	0.529
CABG, n (%)	22(40.0)	24(30.4)	0.249
PTCA, n (%)	18(32.7)	24(30.4)	0.773
Class III antiarrhythmics, n(%)	18(32.7)	24(30.4)	0.773
History of atrial fibrillation, n(%)	17(30.9)	18(22.8)	0.573
VF NID initial 18/24	47(85.5)	73(92.4)	0.189
VF NID redetection = 12/16	31(56.3)	57(72.2)	0.052

NID – number of intervals detected

Table 2
 Characteristics of NF RV EGM after appropriate and inappropriate ICD therapies and NSVT

Characteristic	Appropriate ICD shock [n=71]	Appropriate ATP [n=87]	Inappropriate ICD shock [n=87]	NSVT [n=111]	ANOVA P1	ANOVA P2	ANOVA P3
Delivered shock energy, J	30.95±6.58	N/A	29.49±8.06	N/A	N/A	0.221	N/A
Cycle length of VA, ms	303.4±79.0	344.6±52.2	N/A	377.1±174.4	0.764	N/A	1.00
Duration of VA event, sec	16.1±13.3	6.9±1.8	N/A	8.1±9.98	0.113	N/A	1.00
Baseline p-p R amplitude, mV	10.6±4.2	8.0±5.5	9.22±4.21	11.6±5.84	0.019	0.927	<0.0001
Baseline EGM LJC, mV	-0.29±0.76	-0.37±0.60	-0.10±0.55	-0.46±0.90	1.00	1.00	1.00
Baseline relative LJC, %	-3.3±6.7	-4.0±7.3	-0.25±6.9	-3.4±6.5	1.00	0.067	1.00
P-p R amplitude after event, mV	10.2±5.0	12.7±8.7	8.94±4.31	12.9±6.3	0.112	1.00	1.00
LJC after event, mV	-1.37±1.9	-0.08±0.71	-1.69±1.73	-0.16±0.58	<0.0001	0.942	1.00
Absolute LJC after event, mV	1.7±1.6	0.35±0.63	1.84±1.56	0.44±0.41	<0.0001	1.00	1.00
Relative LJC after event, %	18.0±13.5	2.9±4.8	20.5±15.6	4.1±4.8	<0.0001	1.00	1.00
Difference in p-p R amplitude, mV	-0.44±5.21	4.64±8.54	-0.18±6.23	1.31±5.73	<0.0001	1.00	0.003
Difference in LJC, mV	-1.08±2.08	0.29±1.04	-1.59±1.70	0.30±1.07	<0.0001	0.228	1.00
Absolute LJC difference, mV	1.62±1.69	0.58±0.91	1.70±1.59	0.69±0.87	<0.0001	1.00	1.00
Relative LJC difference, %	12.4±13.4	-2.7±6.5	15.3±15.3	-1.4±5.7	<0.0001	0.731	1.00

NF RV EGM – near field right ventricular electrogram; NSVT – non-sustained ventricular tachycardia; ATP – antitachycardia pacing. One way ANOVA P values of groups comparison with Bonferroni correction: P1 – between appropriate ICD shock and appropriate ATP; P2 – appropriate ICD shock to inappropriate ICD shock; P3 – appropriate ATP to NSVT.

Table 3

Linear random effects mixed models predicting LIC value

Predictor	β coefficient (95% CI), and P value
Appropriate ATP therapy vs. ICD shock	-0.81(-1.19 — -0.44); P<0.0001
Cycle length of VA, ms	-0.0117(-0.0167 — -0.0068), P<0.00001
Energy of shock, J	0.024(0.003 — 0.045), P=0.025