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Effect of cardiac resynchronization therapy on the incidence of electrical storm

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Abstract

Background: Hemodynamic improvement from biventricular pacing is well documented; however, its electrophysiologic effects have not been systematically studied. In this study, incidence and risk factors for electrical storm (ES) were investigated in 729 ICD and biventricular defibrillator (CRT-D) heart failure patients.
Methods: 168 consecutive CRT-D and 561 ICD patients were retrospectively analyzed for the occurrence of VT/VF and predisposing factors. Electrical storm was defined as ventricular tachycardia or fibrillation ≥3 times during 24 h. Mean follow-up was 41 months.
Results: In 168 CRT-D patients only one patient experienced electrical storm compared to 39 patients out of 561 ICD patients (0.6% vs. 7%, $p<0.01$). 33% of the patients with electrical storm died within one year. In the CRT-D group 81 patients (48%) developed VT or VF and received at least one appropriate therapy, compared to 281 patients (50%) in the ICD group. Mean ejection fraction was 21.7% in the CRT-D group and 34.7% ($p<0.01$) in the ICD group. Stratifying the patients according to primary or secondary prevention and ejection fraction demonstrated that VT/VF clusters were significantly associated with ICD indication for secondary prevention, previous myocardial infarction and LVEF <30%.
Conclusion: The development of electrical storm is accompanied with a highly increased mortality risk even if an ICD/CRT-D is implanted. In CRT-D patients electrical storm is much less common than in ICD patients. Secondary prevention and ejection fraction <30% are predictors of electrical storm. Beside hemodynamic improvements cardiac resynchronization therapy may reduce the arrhythmia burden in heart failure patients.

Keywords: CRT; Ventricular tachycardia; Electrical storm

1. Introduction

About 40% of ICD recipients experience recurrent arrhythmias and 7 to 20% of this patients experience electrical storm, defined as 3 or more episodes of VT/VF within 24 h [1,2]. In fact, the known precipitating factors for electrical instability can cause single episodes of ventricular tachycardia/ventricular fibrillation but the reason for some patients to develop electrical storm (ES) is not clear. Some studies suggest that electrical storm is more frequently exhibited as heart failure worsens [1,2], whereas others could not identify precipitating factors for the development of ES [3]. As recurrent episodes of VT/VF terminated by high-energy delivery are very traumatic to the patients [4], a better identification of the reasons is necessary.

Cardiac resynchronization therapy (CRT) devices stimulate the left ventricular (LV) epicardium through leads implanted via coronary veins, or direct surgical access. CRT improves symptoms, exercise capacity, functional class, ventricular function, and ventricular geometry in patients

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with moderate-to-severe congestive heart failure (CHF) and ventricular conduction system abnormalities [5–7]. Combining CRT with an implantable cardioverter–defibrillator (CRT-D) reduces all-cause mortality in a similar population [8].

However, electrophysiologic effects of CRT are poorly understood. Recent reports from CRT-D systems demonstrate no difference in total arrhythmia burden between active CRT-D and control ICD patients [4,9]. However, anecdotal reports of increased VT or the development of electrical storm after initiation of CRT have raised concerns that epicardial LV pacing might promote ventricular arrhythmia in some patients [10–13]. In contrast there are also case reports of successful treatment of recurrent VT after biventricular pacing [10,14].

Since there are a number of contradictory reports related to the proarrhythmic or antiarrhythmic potential of biventricular pacing it seems necessary to further investigate the proarrhythmic potential of biventricular pacing. Therefore, we conducted a retrospective study to assess the effect of CRT on the incidence of electrical storm in patients with CRT-D devices to determine whether the theoretical risk of proarrhythmia during active left ventricular pacing translates into clinical significance.

2. Methods

2.1. Patient population

We investigated all consecutive patients with standard indications for ICD-implantation [15–17] which received a transvenous or epicardial ICD system between 1997 and 2006 at our institution. Only CRT-D and ICD patients were included which were heart failure patients with reduced systolic function. We did not include patients with normal ejection fraction (Brugada syndrome, long QT syndrome, Primary VF…). Patients routinely underwent predischarge device testing.

Indication for CRT-D implantation was also according to current recommendations [18]. For the patients that received CRT-D's the success of resynchronization therapy was tested by measurement of arterial blood pressure and echocardiography during implantation, and by echocardiographic assessment of the ejection fraction (EF) and determination of QRS duration during follow-up examinations.

2.2. ICD systems

Patients underwent implantation of ICD systems from five different manufacturers, the majority being manufactured by current market leaders. All devices were implanted by means of standard surgical techniques and were activated on discharge from the operating suite or from the hospital. Each patient had appropriate sensing confirmed and each device was interrogated for recorded tachycardia events before hospital discharge and at each follow-up examination after implantation.

Patients were followed up according to a scheduled protocol, with regular follow-up visits after 1, 3, and 6 months, and every 6 months thereafter. Pharmacological treatments were based on clinical evaluation by the attending physician.

The ICD and CRT-D systems detected ventricular tachyarrhythmias according to two or three zones and were able to deliver up to six therapies, including antitachycardia pacing, and low- and high-energy shocks. VT detection cut-off was set to at least 350 ms to avoid under-reporting of VT episodes. VT/VF therapy was programmed according to the attending physician's discretion.

2.3. ICD intervention and events

ICD therapies were characterized retrospectively using stored electrogram data or R–R interval data. Electrical storm was defined as the occurrence of 3 or more separate episodes of VT/VF within 24 h. ICD therapy included antitachycardia pacing or delivery of shocks. Non-related episodes of VT/VF, i.e. less than three episodes of VT/VF within 24 h, were not classified as electrical storm.

2.4. Statistical analysis

Variables are expressed as mean ± SD and percentage. Differences in the frequency of characteristics were assessed by independent sample Student's *t*-test for unpaired values. Chi-square test was used for discrete variables. The time to first appropriate ICD therapy was plotted according to the Kaplan–Meier method. To evaluate predictors of electrical storm covariate values were used in a Cox proportional hazard model. Two-tailed $P<0.05$ was considered significant.

3. Results

3.1. Patient characteristics

We investigated a total of 729 patients which received either an ICD or CRT-D between 1997 and 2006 and met the inclusion criteria. The underlying heart diseases were coronary artery disease/ischemic cardiomyopathy, dilative cardiomyopathy, hypertensive heart disease, and/or valvular heart disease, and were identical for both groups.

168 consecutive patients received CRT-D devices. Averaged follow-up duration was 39 months (range 6–84 months). Mean age was 67 ± 12 years; mean ejection fraction was 21.7% ± 9. Six months after CRT implantation, EF showed an increase to 28% ± 7 ($p<0.05$). QRS duration decreased from 159 ± 21 ms to 117 ± 19 ms in paced QRS complexes ($p<0.01$). The programmed AV delay was short (typically 120 ms) to assure 100% biventricular pacing.

561 ICD patients received a single or dual chamber ICD in the same period of time. Average follow-up duration in this group was 47 months (range 6–84 months). Mean age of the ICD patients was 61 ± 14 years; mean ejection fraction was 34.7% ± 11.

An overview on the variables in both patient groups is given in Table 1.

Table 1
Patient characteristics.

	CRT-D	ICD	*p* value
Patients	168	561	n.a.
Age	67 ± 12	61 ± 14	n.s.
Gender			
Male	120 (71%)	363 (65%)	n.s.
Female	48 (29%)	198 (35%)	n.s.
Disease			
CAD	127 (76%)	451 (80%)	n.s.
NICM	41(24%)	110 (20%)	n.s.
LVEF	21.9 ± 9%	34.7 ± 11%	<0.05
Electrical storm	1	39	<0.001

Overview on the ICD and CRT-D patient characteristics. CAD = coronary artery disease, NICM = non-ischemic cardiomyopathy, and LVEF = left ventricular ejection fraction.

3.2. ICD therapies

Mean programmed VT detection cut-off was 350±24 ms; mean programmed VF detection cut-off was 310±16 ms. In terms of programming features, such as VF, VT and FVT detection cut-off, or number of intervals to detect (NID), there were no statistically significant differences between primary and secondary prevention ICD indication or between ischemic and non-ischemic HF etiology. In the following, significances are given between ICD and CRT-D patients.

In the CRT-D group 81 patients (48%) developed VT or VF and received at least one appropriate therapy over the time of the study. The time course to first VT/VF over the first 18 months after implantation is shown in Fig. 3. The first episode that required therapy was VT in 69 (41%) patients and VF in 12 patients (7%). Most CRT-D patients had VT/VF in the second year after implant (53%) with an average of 19±8 months after implantation. From IEGM data we found that the majority of initial episodes were ventricular tachycardia (87%). In the remaining 13% ventricular fibrillation was the initial arrhythmia of the episode (Fig. 1). Only 1 patient (0.6%) with CRT-D had electrical storm.

In the ICD group 281 patients (50%, n.s.) developed VT or VF and received at least one appropriate therapy over the time of the study. The first episode that required therapy was VT in 231 (41%, n.s.) of patients and VF in 50 (9%, n.s.) of patients. Similar to the CRT-D group, ICD patients had VT/VF in the second year after implant (49%) with an average of 21±6 months (n.s.) after implantation (Fig. 2A). From IEGM data we found that the majority of initial episodes were ventricular tachycardia (79%). In the remaining 21% ventricular fibrillation was the initial arrhythmia of the electrical storm episode.

Of note, ICD patients with an EF of less than 30% required therapy significantly earlier than ICD patients with better left ventricular function ($p<0.05$) (Fig. 2B).

Electrical storm occurred in 39 patients in the ICD group (7%) including one patient that had 6 episodes within 5 months. An average of 7 events of VT/VF was recorded in the IEGM store for patients presenting with electrical storm (range 3 to 27). In 27 patients episodes were accompanied by syncope. The majority of events were successfully treated by initial shock delivery (93%). First line treatment was antiarrhythmic drug therapy. In 7 patients drug therapy was not successfully terminating recurrent VT/VF in the long term. In these patients subsequent RF ablation therapy was performed which then terminated ventricular arrhythmias.

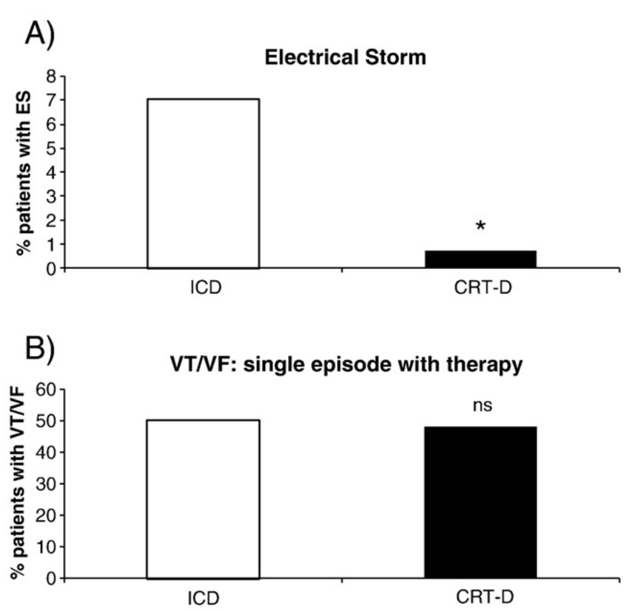

Fig. 1. Development of tachyarrhythmias in both patient groups. A) Percentage of patients which developed electrical storm. B) Percentage of patients with single VT/VF and ATP/shock delivery.

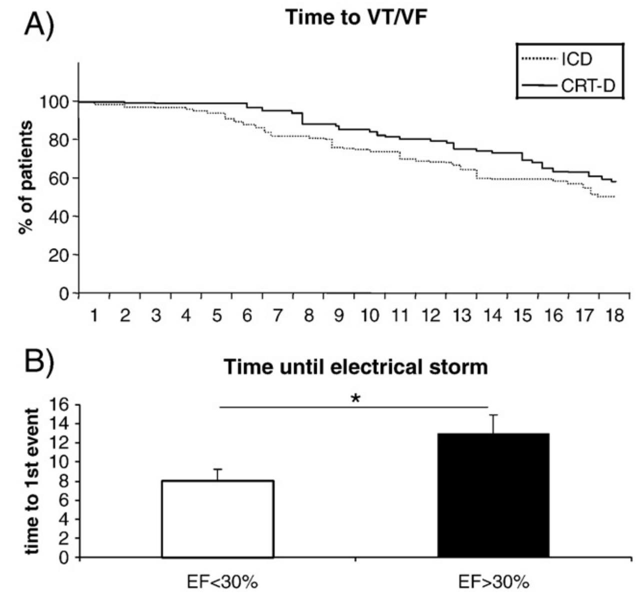

Fig. 2. A) Cumulative events of VT/VF within 18 months of implantation. There was no significant difference between CRT-D and ICD patients. B) Patients with reduced EF (<30%) experienced electrical storm significantly earlier than patients with EF>30%. Time in months.

3.3. Primary vs. secondary prevention

From the 561 ICD patients, 251 patients received an ICD for secondary prevention (survived sudden cardiac death or sustained ventricular tachycardia that required iv therapy or electrical cardioversion). The remaining 310 ICD's were implanted for primary prevention according to current criteria [15–17] or after personal consideration of the treating physician and the patient. Beside treatment of heart failure the 168 CRT-D devices were implanted in 47 patients for secondary prevention of SCD and in 121 patients for primary prophylaxis. Specifically, from the total of 298 patients that received devices for secondary prevention 202 patients experienced sudden cardiac death and 96 had sustained and documented VT. In the patients with primary prevention non sustained VT was documented in 208 cases.

The number (percentage) of ICD patients with appropriately treated overall ventricular episodes (including single episodes and clustered shocks) was 158 (63%) among secondary prevention patients, 123 (40%) among primary prevention patients. In the CRT-D group single tachycardia episodes were detected in 23 (49%) secondary prevention patients, 57 (47%) among primary prevention patients (Fig. 3).

Electrical storm was more frequent in patients with devices for secondary prevention (25 patients, 63%) compared to the incidence of

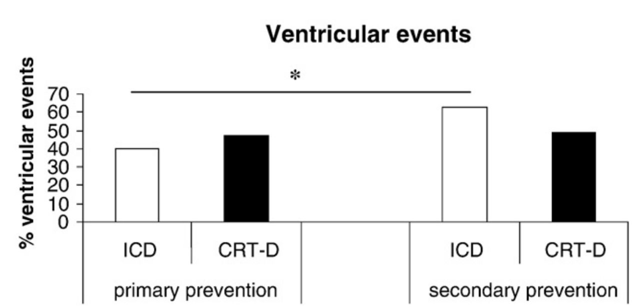

Fig. 3. Correlation of primary vs. secondary prevention with the occurrence of ventricular events. * indicates significance ($p<0.05$).

multiple clustered shocks in patients that received their devices for primary prevention (15 patients, 37.5%, $p<0.05$) (Table 2). The patient with CRT-D that experienced electrical storm received his device for primary prevention.

3.4. Electrical storm and predisposing factors

We assessed factors which can induce electrical storm. A reduction in left ventricular ejection fraction clearly increased the risk for electrical storm (Table 2). In contrast, NYHA class was not significantly correlated to recurrent tachycardias. From the 39 ICD patients presenting with ES 9 patients were NYHA class I, 13 were NYHA class II, 10 were NYHA class III, and 7 were NYHA class IV. The CRT-D patient with ES was NYHA class III.

Mean ejection fraction of all ICD recipients was 34±15%. From the 39 patients that experienced electrical storm mean EF was 25±11% ($p<0.05$). In the CRT-D group mean EF was 21.7±11%. The CRT-D patient that experienced ES had an EF of 18%.

We further assessed ventricular function and electrical storm in the disease group with the highest number of electrical storms: patients with coronary artery disease (Table 2). Mean ejection fraction in CAD patients was 38±9% (range 17% to 72%). Mean EF in CAD patients with recurrent episodes of VT/VF was 34±7 ($p<0.05$). 18 of the CAD patients with electrical storm (78%) had an EF<30%. However, coronary artery disease alone did not increase the risk for electrical storm significantly, but only if there was a history of previous myocardial infarction we observed a significantly elevated risk for recurrent VT's ($p<0.05$) (Table 2).

5 patients (13%) had electrical storm as the primary tachyarrhythmic episode resulting in ICD therapy. The remaining 34 patients (87%) had ventricular tachycardia or fibrillation before electrical storm. There was no correlation between the total number of VT/VF episodes and the development of electrical storm.

Furthermore, there was no correlation between electrical storm and current medication, or acute decompensation of congestive heart failure, respectively.

In summary, patients with lower EF (<30%), secondary prevention and previous myocardial infarction had a significantly increased risk for electrical storm.

Table 2
Characteristics of patients with or without electrical storm.

	Electrical storm	No electrical storm	p value
Patients	40	689	n.s.
Age	62±17	66±19	n.s.
Gender			
Male	31 (77.5%)	452 (65.6%)	n.s.
Female	9 (22.5%)	237 (34.4%)	n.s.
Disease			
CAD	33 (82.5%)	578 (83.9%)	n.s.
Previous MI	29 (72.5%)	407 (59.1%)	<0.05
NICM	7 (17.5%)	111 (16.1%)	n.s.
LVEF	25±11	37±14	<0.01
CRT-D	1 (2.5%)	167 (24.2%)	<0.05
Medication			
β-blocker	36 (90%)	632 (91.7%)	n.s.
Amiodarone	6 (15%)	89 (12.9%)	n.s.
Class I	1 (2.5%)	12 (1.7%)	n.s.
Primary prevention	15 (37.5%)	416 (60.4%)	<0.01
Secondary prevention	25 (62.5%)	273 (39.6%)	<0.01
Previous NSVT	10 (25%)	198 (28.7%)	n.s.
Functional class			
NYHA I–II	22 (55%)	392 (57%)	n.s.
NYHA III–IV	18 (45%)	297 (43%)	n.s.

Data are given as mean±SD. p values are from univariate analysis.

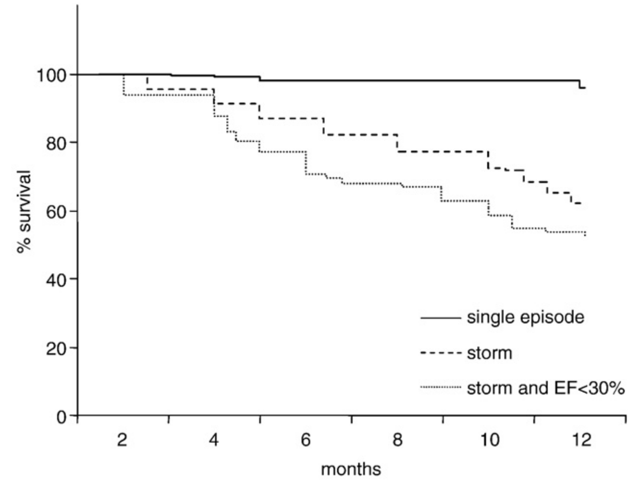

Fig. 4. One year survival of patients after VT/VF. 96% of patients that experienced a single therapy (for VT or VF) were alive after one year. From all patients that had electrical storm 67% were alive after the first year after the episode. In patients that had an EF<30% at the time of electrical storm only 54% survived the first year after the recurrent episodes.

3.5. Prognosis

We assessed prognosis of patients with electrical storm and patients with only single shocks or without shock in the ICD group. 13 patients (33%) with electrical storm died, all within the first year following the electrical storm episode. 5 patients (13%) of all patients with electrical storm died related to the acute episodes. From the 281 patients (50% of all ICD patients) that experienced at least one appropriate therapy, 12 patients (2%, $p<0.05$) died during follow-up (4% within the first year after the arrhythmic episode).

Out of the patient group with electrical storm, there were only four patients (10%) with recurrent episodes of electrical storm. In 2 of these patients these episodes could be terminated successfully. From the patients with fatal events four patients had CAD (2% of all CAD patients) and two patients had non-ischemic cardiomyopathy (NICM) (1% of all NICM patients). In four patients with death related to electrical storm, EF was <30%. One patient had an EF of 40% at the time of the event. The CRT-D patient with ES died within 5 days of that event. The survival rates are condensed in Fig. 4.

4. Discussion

Cardiac resynchronization therapy (CRT) is an established therapy in the treatment of heart failure. Multiple studies have demonstrated the benefit of biventricular pacing on hemodynamics, quality of life, morbidity, and mortality [4,5,7,8,19–21]. Nevertheless, electrophysiologic effects of CRT are still poorly understood. Some studies demonstrated a decreased incidence of ventricular tachycardias (VTs) after CRT [9,10,22–27]. In line with these findings, no significant proarrhythmic effects have been discovered in large-scale trials of CRT [4–8,19,20,28].

Despite these latter studies there is currently a continuing debate on the antiarrhythmic or proarrhythmic properties of biventricular pacing. Evidence reported in the literature suggests that pacing itself might provoke arrhythmias, and proarrhythmic effects of RV apical pacing have been described [29]. Furthermore, there are now several case reports of occurrence of ventricular tachycardia, ventricular fibrillation, and even electrical storm after biventricular pacing [11–13].

The occurrence of multiple clustered episodes of VT/VF referred to as electrical storm not only represents a traumatic situation for patients, at least if accompanied by multiple shock deliveries, but is also accompanied with an especially poor outcome. Therefore, understanding the (anti-) arrhythmic effects of biventricular pacing is crucial.

Subgroup analysis from the MADIT II trial [30] and COMPANION trial [31] demonstrated that sudden cardiac death risk is associated with higher New York Heart Association class and especially with QRS duration >160 ms. From this data it is clear that the patient population that was eligible for a CRT-D device was at particularly high risk for sudden cardiac death, compared to the mere ICD population.

In this study we investigated incidence of electrical instability in our ICD and CRT-D patients and in this context it is most notable that electrical storm was significantly more frequent in our ICD patients than in patients that received a CRT-D device. In a total of 168 CRT-D patients included in the current study only one experienced electrical storm, even though this patient group had a particularly low ejection fraction which has been shown to highly increase risk for ventricular arrhythmia and sudden cardiac death. In the current study, we also noticed an explicit increase in single ventricular tachycardia episodes and clustered shocks in patients with an ejection fraction below 30%, both in ICD and in CRT-D patients. There was no significant difference in the time to development of tachycardia events in ICD vs. CRT-D patients.

Regarding ventricular function and the probability of electrical storm there are conflicting results. Some studies in the past [1,2,32] found no significant differences in EF in patients that developed multiple shocks compared to patients with only single shocks. This is in contradiction to our results. We found that the risk for clustered shocks was clearly elevated for ICD patients which had concomitant severe heart failure (EF<30%). This risk was not elevated when patients were treated with CRT-D. Similarly, the TOVA trial [33] found that class III CHF is an important predictor, along with LVEF, of appropriate device discharges in ICD patients.

In general, CRT improves hemodynamics by reducing ventricular dysynchronicity. This usually results in an improvement of ejection fraction and functional capacity. This was also apparent in the CRT-D patients of the current study. In turn, some studies on the incidence of recurrent ventricular tachycardias indeed demonstrated a close correlation between low ejection fraction and the occurrence of electrical storm [34–36]. Therefore, improving ventricular output by CRT might be one mechanism that contributes to the reduced arrhythmia burden.

A different mechanism for potential arrhythmia suppression was suggested by Kowal et al. [25]. He hypothesized that the mechanism of arrhythmia suppression under biventricular pacing is due to preexcitation of the area of slow conduction responsible for the reentrant arrhythmia. From these considerations it is clear that the pacing site plays an important role in the development of VT [37] in these anecdotal reports.

Non sustained ventricular tachycardia (NSVT) did not give any information on the subsequent development of electrical storm. This also in line with previous studies since the presence of NSVT is common in heart failure patients and does not necessarily predict sudden cardiac death [38]. The presence of NSVT in these patients is rather a marker of worse prognosis related to poor left ventricular function than an indication for sudden cardiac death. The MADIT II trial demonstrated a 31% reduction in all-cause mortality for post-myocardial infarction patients with LVEF ≤ 30%, even without NSVT [30]. Wilkoff et al. recently reviewed the difference in VT burden between primary and secondary prophylaxes in patients with resynchronization therapy [39]. Patients with a primary prophylaxis were much less likely to develop ventricular tachyarrhythmias. This could be confirmed in our ICD and CRT populations. Patients that received their device for secondary prevention (after survived sudden cardiac death or sustained VT that required intervention) had a significantly increased risk to experience electrical storm compared to the primary prevention patients.

4.1. Limitations

Analysis of predisposing factors for electrical storm in our patient population demonstrated that cardiac resynchronization therapy significantly decreased the risk for electrical storm. This however, despite the encouraging result, has to be taken carefully since the population of ICD and CRT-D patients was different. Nevertheless, this observational study did not confirm the hypothesis that CRT carries an increased risk of proarrhythmia in a large population of patients.

5. Conclusions

In summary, the present analysis provides new insight into the incidence of electrical storm in CAD and NICM patients. We showed that electrical storm occurs frequently in ICD recipients and is a predictor for/accompanied with a high mortality rate. The risk for electrical storm is highest in patients with coronary artery disease, previous myocardial infarction, and an ejection fraction below 30%. Also, secondary prevention as cause for device implantation indicated an increased risk for electrical storm. Electrical storm appeared significantly less often in the patients supplied with a CRT-D device, even though a lower EF was found in these patients compared to the ICD recipients.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [40].

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