Predictors of appropriate and inappropriate Therapies in Patients with implantable cardioverter-defibrillator and Structural Heart Disease

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Beschluss über die Verleihung des Doktorgrades vom: 26.01.2016
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\* Implantable Cardioverter-Defibrillator  
\** Ventricular Tachycardia  
\¶ Cardiac Resynchronization Therapy
Identifying factors associated with appropriate and inappropriate therapies in patients with implantable cardioverter-defibrillator (ICD) could help to identify those at risk and reduce the incidence of this emergency situation which has detrimental effect on mortality and morbidity in patients with ICD. These studies were designed to find the prevalence and factors associated with appropriate and inappropriate therapies in patients with ICD.

* Impact Points of 2013 as stated on official website of the Journals
Introduction (Einführung):

There is no controversy that implantable cardioverter-defibrillator (ICD) in selected patients reduces the long term mortality. [1] However, in patients with ICD appropriate and/or inappropriate shocks are associated with increased mortality and morbidity. A recent meta-analysis showed a significant association between appropriate and inappropriate ICD shocks and mortality, with a stronger association for appropriate shocks. [1] In a recent study a total of 1398 consecutive patients of the ICD-registry Ludwigshafen who had an ICD implanted between 1992 and 2008 for primary or secondary prevention of sudden cardiac death were studied. [2] During the median follow-up time of 6 years, 749 (54%) patients experienced 17827 episodes of ventricular tachycardia (VT) or fibrillation (VF) which were terminated by anti-tachycardia pacing (ATP) in 74% and by shock in 26% of patients. [2]

In 321 of those patients with VT/VF, the first episode was terminated by ATP. [2] In a multivariable analysis, the occurrence of first ATP therapy was associated with a higher mortality rate [hazard ratio (HR) 2.60, 95% confidence interval (CI) 2.02-3.35]. When excluding all patients with appropriate ICD shocks first ATP therapy still associated with a worse prognosis (HR 1.92, 95% CI 1.38-2.67). [2] Therefore not only ICD shocks but also ATPs are associated with increased mortality.

Identifying the predictors of ICD therapies could help to identify those at risk and reduce the incidence of these therapies which has detrimental effect on mortality and morbidity in patients with ICD. Identifying these patients is very important as prophylactic catheter ablation of VT can reduce the incidence of ICD therapies and therefore may improve the long term survival. [3] In SMASH-VT study 128 patients were randomly assigned to ICD implantation alone or with adjunctive prophylactic
catheter ablation. [3] Ablation was performed with the use of a substrate guided approach in which the myocardial scar is mapped and ablated while the heart remains predominantly in sinus rhythm. [3] During the follow up period of 22.5±5.5 months 21(33%) and 7(12%) patients received appropriate ICD shocks in ICD alone and ICD plus adjunctive catheter ablation groups, respectively (hazard ratio in the ablation group, 0.35; 95% confidence interval, 0.15 to 0.78, \( P = 0.007 \)). [3]

In addition early referral for catheter ablation of ventricular arrhythmias in these patients is associated with improved acute and long-term outcomes. [4] We studied recently 300 patients with sustained VT who underwent catheter ablation. [4] Catheter ablation was performed within 30 days after the first documented VT in 75 (25%) patients (group 1), between 1 month and 1 year in 84 (28%) patients (group 2), and >1 year after the first VT occurrence in 141 (47%) patients (group 3). Recurrence-free survival was higher in group 1, as compared with group 2 (hazard ratio [HR], 1.85; \( P=0.009 \)) and group 3 (HR, 2.04; \( P=0.001 \)). VT recurrence (HR, 1.91; \( P=0.037 \)) predicted cardiac mortality. These results showed that catheter ablation of scar-related VT performed within 30 days after the first documented VT was associated with improved acute and long-term outcome. [4]

In the first manuscript (Part 1) we sought to find the prevalence and predictors of the electrical storm, defined as occurrence of \( \geq 3 \) episodes of ventricular tachycardia and/or fibrillation in a one day period, in patients with ICD. Electrical storm severely impairs the quality of life and associated with increased mortality.

One hundred sixty two patients with ICD were included in this study and were followed for a mean of 14.3±10 months. After ICD implantation the patients were
followed on a regular basis (3 months) and upon receiving high voltage therapy in our outpatient ICD clinic. The devices were interrogated at each session and the complete set of data (including intra-cardiac electrograms) was recorded.

The algorithms that should discriminate VT or VF from less lethal supra-ventricular arrhythmias do not always work perfectly. As many as one-third of the patients who have an ICD implanted, receive inappropriate ICD shocks. [1] Inappropriate shocks occur when the device delivers a high-voltage discharge for a reason other than a ventricular arrhythmia. As stated above not only appropriate but also inappropriate ICD shocks are associated with increased mortality. [1] Patients describe an ICD shock as “an earthquake,” or “being hit by a truck”. [1, 5] Given the traumatic nature of ICD shocks, it would be ideal if the ICD could always successfully distinguish ventricular arrhythmias from non–life-threatening tachyarrhythmias and administer only appropriate shocks for VT or VT. [6]

Several studies have suggested that quality of life is influenced adversely in patients who experience appropriate and/or inappropriate ICD shocks. [1] For example, in the SCD-HeFT study patients who received shocks within one month of a scheduled assessment had substantially worse quality of life compared to those without ICD shocks. [7]

Several factors influence the incidence and prevalence of inappropriate ICD shocks. Every ICD manufacturer uses a different discrimination protocol and therefore the rate of inappropriate ICD therapies might be different among various ICD models. However, at the time of our second study to the best of our knowledge no study assessed the rate of inappropriate ICD shocks between different ICD manufacturers.
This was a single centre study to analyze and compare the probability of ≥1 inappropriate ICD therapies between the two manufacturers after trans-venous ICD implantation. To prevent disclosure of data on the two ICD manufacturers we named them as manufacturer “A” (n=113) and “B” (n=49) and did not mention the ICD models and detailed programming variables. Immediately after implantation the detection and discrimination criteria were activated with the *nominal* values. We used the nominal values after implantation for comparison of discriminatory protocols of the two manufacturers under default settings. During all initial programming in all the devices we defined ventricular fibrillation zone (300 ms) plus one ventricular tachycardia zone (400 ms). If the patient had an episode of spontaneous or induced sustained monomorphic ventricular tachycardia slower than 370 ms (5 patients, three received manufacturer A’s and 2 Manufacturer B’s ICDs) we extended the ventricular tachycardia zone to the arrhythmia cycle length plus 40 ms.

After first inappropriate ICD therapy if deemed necessary, the attending physicians were able to modify ICD programming and optimize medical treatment in order to decrease the rate of inappropriate ICD therapy. Therefore, we just compared the occurrence of ≥ 1 appropriate ICD therapy between these two groups rather than total number of inappropriate ICD therapies. The results of this study are presented in Part 2 of this dissertation.

In the third part of this dissertation we assessed the role of first VT cycle length on subsequent incidence and prevalence of ventricular arrhythmias in patients with ICD. As stated in part 3 several studies assessed the effect of hemodynamic stability of the VTs on subsequent mortality and recurrence of VT.
Sarter et al. have suggested a better prognosis for hemodynamically tolerated VT but other showed that the risk is similar to patients with more severely symptomatic VT. Raitt et al. in a subgroup analysis of AVID registry showed that the absence of symptoms with sustained VT does not predict a benign prognosis. Olson et al. assessed the predictors of sudden cardiac death in 122 patients and showed that the rate of sudden cardiac death is not affected by presence or absence of symptoms during sustained monomorphous VT. [8, 9]

Bocker and colleagues studied the natural course of 50 patients with hemodynamically tolerated VT who received ICD. They showed that during mean follow up of 17 months, 33 patients (66%) had 3861 episodes of VTs. Eleven patients (22%) had episodes of potentially life-threatening fast VT (CL<250 ms) during follow up period. Had the ICD not been implanted in the Bocker study, their patients would have had at least the same mortality as patients in AVID registry. [8, 10]

The effect of first VT cycle length on the subsequent VT recurrence is largely unknown. We sought to assess the effect of cycle length of first VT episode (as the index arrhythmia) on total number of subsequent appropriate ICD therapies as a surrogate for total ventricular arrhythmia burden in a cohort of patients with ICD. We hypothesized that the first VT cycle lengths do not influence the total sustained ventricular arrhythmia burden, and therefore, the slow and fast VTs should be treated similar in these patients as our recent data have also shown. [4]

One hundred ninety five patients (75% male) with structural heart disease who underwent ICD implantation were included in this study. Among these 45 patients with sustained monomorphous VT as the first arrhythmia requiring ICD therapy were included
in this study. The subgroups of arrhythmia cycle length are chosen based on the median values in the study population (Table 2, Part 3). During follow up 22% (n=5) and 19% (n=4) of the ICD recipients with initial fast and slow VT experiences at least one episode of potentially life threatening fast VT, defined as VT with cycle length ≤ 250 ms, respectively (P = 0.853). [10] Further results and detailed analyses are presented in the third part of this dissertation.

In the final part of this dissertation we tried to answer the question if cardiac resynchronization therapy (CRT) affects the prevalence of ventricular arrhythmias. Cardiac resynchronization therapy is an established mode of therapy in selected symptomatic patients with heart failure due to systolic dysfunction. The published large scale clinical trials of CRT confirmed the favorable effects of CRT on symptoms, the quality of life, ventricular function, and blood pressure and showed that CRT significantly reduces the risk of mortality. Calculations based on data from Cardiac Resynchronization — Heart Failure trial depicted that, for every nine biventricular pacemaker implanted, one death and three hospitalizations for major cardiovascular events were prevented. The reduction in mortality by CRT is at least in some part is related to homodynamic improvement. [11-14]

We conducted a retrospective case-control study to assess the effect of CRT on incidence of appropriate therapy, as a surrogate for sustained ventricular arrhythmias, in patients with ICD. Thirty one patients with biventricular ICD implantation were included in this study. All these patients had QRS width ≥ 120 ms and standard indication for CRT and ICD implantation. During the same period 68 patients with structural heart disease received dual chamber ICD. To provide an adequate comparable control group, among these 68 patients we selected all the patients with QRS duration ≥
120 ms (n=34) as the control group. The detailed results of this study which showed that CRT decreased the rate of appropriate ICD therapy by suppressing the occurrence of sustained ventricular arrhythmias requiring ICD therapy are presented in part 4. During follow up period patients with biventricular ICD received 66% less appropriate ICD therapy compared to those with dual chamber ICD.
References:


Predictors of Electrical Storm and Appropriate Therapy in Patients with ICD and Structural Heart Disease

eingereicht von: Arash Arya
angefertigt am Herzzentrum Universität Leipzig
Betreut von Prof. Dr. med. Gerhard Hindricks

Abstract (Part 1)*

Identifying predictors of electrical storm in patients with implantable cardioverter-defibrillator (ICD) could help to identify those at risk and reduce the incidence of this emergency situation which has detrimental effect on mortality and morbidity in patients with ICD. In this retrospective study we sought to find the prevalence and predictors of electrical storm in patients with ICD.

One hundred sixty two patients (126 men, mean age 58±13 years) who received ICD between January 2001 and 2005 were included in the study. Clinical, electrocardiographic, and ICD stored data and electrograms were collected and analyzed. Twenty-two patients (14%) developed electrical storm during mean follow up of 14.3±10 months. Using Cox multiple regression analysis we found that ejection fraction < 25% (P=0.007), QRS width ≥ 120 ms (P=0.002), and lack of adjunctive angiotensin converting enzyme inhibitor and beta-blocker therapy (both P < 0.001) were correlated with higher probability of electrical storm. Adjunctive amiodarone and digoxin therapy, indication of ICD implantation, and age were not correlated with occurrence of electrical storm during the follow up (all P=NS).

In conclusion, electrical storm is not uncommon among patients with ICD. Optimum medical therapy with beta-blockers and angiotensin converting enzyme inhibitors could reduce the occurrence of electrical storm and this especially should be persuaded among those who are at higher risk of this complication (i.e. those with left ventricular ejection fraction < 25% and QRS width ≥ 120 ms).

Introduction:

Patients with an implantable cardioverter-defibrillator (ICD) can develop electrical storm, defined as occurrence of ≥ 3 episodes of ventricular tachycardia and/or fibrillation in a one day period. These patients frequently receive multiple ICD shocks, which severely impair quality of life. Although both ventricular tachycardia and fibrillation could be responsible for electrical storm, ventricular tachycardia is the most common cause. Several studies have assessed the prevalence, and possible predictors of electrical storm in patients with ICD. In this study we assess the prevalence and predictors of electrical storm in a group of patients with ICD.

Methods:

Patients Population: Between January 2001 and January 2005, 196 patients with coronary artery disease or dilated cardiomyopathy underwent ICD implantation at our centre. We excluded patients with biventricular ICDs from our study (n=34). We included all the other patients (n=162) who received single or dual chamber ICD during the same period. All the patients gave written informed consent for the procedure of ICD implantation.

Implanted ICDs: The implanted devices were manufactured by Medtronic ([GEM-VR, GEM-DR, GEM-II-VR, GEM-II-DR, GEM-III-VR, GEM-III-DR, Marquis-VR, Marquis-DR] Medtronic Inc., Minneapolis, MN, USA, n=113) and St. Jude ([Photon-VR, Photon-DR, Photon-μ-VR, Photon-μ-DR, Atlas-VR, Atlas-DR, Epic-VR, and Epic-DR] St. Jude Medical Inc. Sylmar, CA, USA, n=49). Single and dual chamber ICDs were implanted in 107 and 55 patients, respectively.

ICD Data Storage and Retrieval: After ICD implantation the patients were followed on a regular basis (3 months) and upon receiving high voltage therapy in our outpatient ICD clinic. The devices were interrogated at each session and the complete set of data (including
intra-cardiac electrograms) was recorded on floppy diskettes. The floppy diskettes were used to retrieve all sustained arrhythmia episodes resulted in ICD therapy.

**Definitions:** Electrical storm was defined as ≥ 3 episodes of ventricular tachycardia and/or fibrillation requiring ICD therapy in a one day period. 3 Indication of ICD implantation was defined as secondary prevention (n=113) in patients who had experienced aborted sudden cardiac death, sustained ventricular arrhythmia, or syncope (whose electrophysiological study showed inducible sustained hemodynamically unstable ventricular arrhythmias). The indication of ICD implantation in all the other patients (23 patients with coronary artery disease without history of syncope who had left ventricular ejection fraction < 40%, nonsustained ventricular tachycardia on Holter monitoring, and inducible sustained hemodynamically unstable ventricular arrhythmia during electrophysiologic study; and 26 asymptomatic patients with dilated cardiomyopathy with nonsustained ventricular tachycardia during Holter monitoring who had inducible sustained hemodynamically unstable ventricular arrhythmia during electrophysiologic study) was categorized as primary prevention. 10

**Statistics:** Variables are expressed as mean ± SD, and percentage. Differences in frequency of characteristics were assessed by independent sample student’s t-test for continuous variables. Chi-square statistics (or fisher’s exact test if applicable) used for discrete variables. We used Cox regression analysis with forward selection method (likelihood ratio) to find the potential predictors of electrical storm after device implantation. Probability of electrical storm based on the time (month) to electrical storm after ICD implantation between different groups determined by the Kaplan-Meier analysis (with Mantel-Cox test) and the time to electrical storm plotted according to the Kaplan-Meier method. A two-tailed p-value < 0.05 was considered statistically significant. We used SPSS® 13.0 (SPSS Inc. Chicago, IL, USA) for data storage and analysis.
Results:

**Baseline Characteristics:** One hundred sixty two patients with ICD were followed for a mean of 14.3±10 months. We compared baseline patients’ characteristics between patients with (n=22) and without (n=140) electrical storm during follow up (Table 1).

**Table 1:** Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Electrical Storm</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=22)</td>
<td>No (n=140)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>53±19</td>
<td>58±12</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (95%)</td>
<td>105 (75%)</td>
</tr>
<tr>
<td>Female</td>
<td>1 (5%)</td>
<td>35 (25%)</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>9 (41%)</td>
<td>98 (70%)</td>
</tr>
<tr>
<td><strong>Dilated cardiomyopathy</strong></td>
<td>13 (59%)</td>
<td>42 (30%)</td>
</tr>
<tr>
<td><strong>Left ventricular ejection fraction (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>19 (86%)</td>
<td>83 (59%)</td>
</tr>
<tr>
<td>≥ 25</td>
<td>3 (14%)</td>
<td>57 (41%)</td>
</tr>
<tr>
<td><strong>QRS duration (ms)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120</td>
<td>5 (23%)</td>
<td>89 (64%)</td>
</tr>
<tr>
<td>≥ 120</td>
<td>17 (77%)</td>
<td>51 (36%)</td>
</tr>
<tr>
<td><strong>JT interval (ms)</strong></td>
<td>353±58</td>
<td>350±46</td>
</tr>
<tr>
<td><strong>Type of ICD:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-VR</td>
<td>17 (77%)</td>
<td>90 (64%)</td>
</tr>
<tr>
<td>ICD-DR</td>
<td>5 (23%)</td>
<td>50 (36%)</td>
</tr>
<tr>
<td><strong>Indication of ICD implantation:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>9 (41%)</td>
<td>40 (29%)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>13 (59%)</td>
<td>100 (71%)</td>
</tr>
<tr>
<td><strong>β-blocker therapy</strong></td>
<td>13 (60%)</td>
<td>109 (78%)</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
<td>17 (77%)</td>
<td>129 (92%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>9 (41%)</td>
<td>60 (43%)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>14 (64%)</td>
<td>97 (69%)</td>
</tr>
</tbody>
</table>

* A two tailed P-value < 0.05 is considered significant.

The subgroups of left ventricular ejection fraction and QRS duration are chosen based on the median value in study population.
Number of Appropriate ICD therapies: During our follow up period the patients received mean number of 17±29 (range 1 – 132) appropriate ICD therapy. Among these the number of appropriate ATP was 11.9±28 (range 0 – 131) and the number of appropriate shock therapy was 5.1±9.9 (range 1 – 56). The success rate of ATP therapy among the episodes in the VT detection zone was 88%.

Predictors of electrical storm: Predictors of electrical storm were found by Cox regression. In the model ejection fraction < 25% (P=0.007), QRS width ≥ 120 ms (P=0.002), and lack of adjunctive beta-blocker and angiotensin-converting enzyme inhibitors (both P < 0.001) were correlated with the higher probability of electrical storm during the follow up period. In our model underlying heart disease (0.391), age (P=0.348), indication of ICD implantation (P=0.296), and adjunctive amiodarone and digoxin therapy (P=0.238 and P=0.407, respectively) were not correlated with higher probability of electrical storm in our patients. Table 2 shows the odds ratios and 95% confidence interval for predictors of electrical storm in our patients.

Table 2: Predictors of electrical storm

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS width ≥ 120 ms</td>
<td>5.87</td>
<td>2.0 – 16.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Ejection fraction &lt; 25%</td>
<td>4.0</td>
<td>1.2 – 14.5</td>
<td>0.038</td>
</tr>
<tr>
<td>Lack of beta-blocker therapy*</td>
<td>6.0</td>
<td>1.75 – 21.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Lack of ACE‡ inhibitor therapy*</td>
<td>6.12</td>
<td>1.47 – 25.5</td>
<td>0.017</td>
</tr>
</tbody>
</table>

* These analyses were stratified for ejection fraction and QRS duration. The subgroups of left ventricular ejection fraction and QRS duration are chosen based on the median values in the study population.

** The Mantel-Haenszel P-value is reported for these analyses.

‡ Angiotensin converting enzyme inhibitor.

Discussion

This study showed that (1) electrical storm occurs in a significant minority of patients with ICD; (2) patients left ventricular ejection fraction < 25% and/or QRS duration ≥ 120 ms...
are especially at greater risk of electrical storm (Figure 1); and (3) optimum medical therapy with beta-blockers and angiotensin-converting enzyme inhibitors could reduce the incidence of this devastating complication in patients with ICD.

Studies have shown that up to 50%-70% of the patients received appropriate ICD therapy within the first two years of follow up. 1,11 In addition 10 to 20% of ICD patients experience electrical storm during a follow up of three years. 3 In our study during mean follow up of 14.3±10 month 22 (13.6%) of patients had electrical storm. The difference in the rate of electrical storm in various studies probably reflects difference in patient population and follow up period.

Six clinical trials have been published hitherto studying the possible effect of electrical storm on mortality in patients with ICD. 1,2,4-6,9 Among these, four reports 4-6,9 showed that electrical storm was an independent predictor of increased mortality. Therefore, development of electrical storm identifies patients with ICD who are at increased risk of mortality and this warrants closer medical follow up. 6 Currently we do not know whether electrical storm plays a contributing or bystander role in the observed excess mortality. 6 However, other studies have shown that the independent predictors of electrical storm in our study are independent predictors of mortality in comparable patients’ population. 12-16

Clinical profile of patients with electrical storm: Gatzoulis et al. have recently shown that the underlying heart disease did not predict electrical storm in patients with ICD. 4 Verma et al. demonstrated that coronary artery disease as the underlying heart disease was an independent predictor of electrical storm among 2028 patients with ICD. 5 The prevalence of electrical storm in our patients was equal in patients who received ICD for primary versus secondary prevention of sudden cardiac death (Table 1). However, Gatzoulis et al. stated that among their patients in whom the ICD was implanted for primary prevention of sudden cardiac death (n=18) none experienced electrical storm during the follow up period. 4 These
differences could be explained by different patients’ population and characteristics (see definition). Left ventricular ejection fraction < 25% and QRS width ≥ 120 ms were independent predictors of electrical storm in our ICD patients (Figure 1). Low ejection fraction and wide QRS complexes are well known predictors of mortality in similar patients’ population. These simple risk predictors could help to select ICD patients who are at increased risk of electrical storm and mortality. The concomitant medical therapy should be optimized in ICD patients (and especially in this high risk subgroup) to reduce the risk of electrical storm. The antiarrhythmic effects of beta-blocker and angiotensin converting enzyme inhibitor and their favourable effect on mortality now are well known. Therefore, especial attention should be paid to adjunctive medical therapy in ICD patients as this could decrease the risk of electrical storm and mortality (in addition to effect of ICD). Finally, newer treatment options could also be useful in the management of patients with electrical storm.  

Kaplan–Meier plot of the time to the first electrical storm according to subgroups of left ventricular ejection fraction (A) and QRS duration (B). The subgroups of left ventricular ejection fraction and QRS duration are chosen based on the median values in the study population. We used Log-Rank (Mantel-Cox) test to generate the P-value.
References:

10. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E, Della Bella P, Hindricks G, Jaïs P, Josephson ME, Kautzner J, Kay GN, Kuck KH, Lerman BB, Marchlinski F, Reddy V, Schalij MJ, Schilling R, Soejima K, Wilber D; European Heart Rhythm Association (EHRA); Registered Branch of the European Society of Cardiology (ESC); Heart Rhythm Society (HRS); American College of Cardiology (ACC); American Heart Association (AHA). EHRA/HRS Expert Consensus on Catheter Ablation of Ventricular Arrhythmias: developed in a partnership with the European Heart Rhythm Association (EHRA), a Registered Branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society (HRS); in collaboration with the American College of Cardiology (ACC) and the American Heart Association (AHA). Heart Rhythm. 2009;6:886-933.
Abstract (Part 2)*

This study was conducted to compare the rate of ≥1 inappropriate therapy between ICDs from two manufacturers which use different discriminatory protocols.

One hundred sixty two patients (mean age 58±13 years, 126 male) who received ICDs between January 2001 and 2005 were included in the study. Clinical, electrocardiographic, and ICD stored data and electrograms were collected and analyzed. Immediately after implantation all the detection and discrimination criteria were activated with the nominal values in order to compare the two discriminatory protocols under the default manufacturer’s settings. During the follow up period of 14.3±10 months, 49 (30%) patients received ≥1 inappropriate ICD therapy. The rate of ≥1 inappropriate ICD therapy in manufacturer A and B ICDs was 26% (n=29) and 41% (n=20), respectively. Comparing the rate of ≥1 inappropriate ICD therapy between the two groups by Kaplan-Meier analysis and the log rank test resulted in P =0.04.

Having all discriminatory variables activated with the nominal values, discriminatory performance differs between the two manufacturers. Further larger-scale studies are warranted to prospectively compare the performance of various available ICDs’ discriminatory protocols, and define the optimum combination of discriminators in each ICD to decrease the rate of inappropriate therapy.

Introduction:

A major issue in patients with implantable cardioverter-defibrillator (ICD) is inappropriate therapies, which have a major impact on morbidity and quality of life.\textsuperscript{1-2} To the best of our knowledge no study has assessed the rate of inappropriate therapy between ICDs from different manufacturers which use different discriminatory protocols. This is a single centre study to analyze and compare the probability of $\geq 1$ inappropriate ICD therapies between the two manufacturers after trans-venous ICD implantation.

Methods

Patient population: (see section one, above for the patients’ population) Table 1 shows the baseline characteristics of the patients.

Implanted ICDs and programming: To prevent disclosure of data on the two ICD manufacturers we named them as manufacturer “A” (n=113) and “B” (n=49) and did not mention the ICD models and detailed programming variables. The devices from these manufacturers comprise 95\% of the ICDs which are implanted at our centre. Immediately after implantation all the detection and discrimination criteria were activated with the nominal values. We used the nominal values after implantation for comparison of discriminatory protocols of the two manufacturers under default settings. During all initial programming in all the devices we defined ventricular fibrillation zone (300 ms) plus one ventricular tachycardia zone (400 ms). If the patient had an episode of spontaneous or induced sustained monomorphic ventricular tachycardia slower than 370 ms (5 patients, three received manufacturer A’s and 2 Manufacturer B’s ICDs) we extended the ventricular tachycardia zone to the arrhythmia cycle length plus 40 ms. After first inappropriate ICD therapy if deemed necessary, the attending physicians were able to modify ICD programming and optimize medical treatment in order to decrease the rate of inappropriate ICD therapy.
Therefore, we just compared the occurrence of ≥ 1 appropriate ICD therapy between these two groups rather than total number of inappropriate ICD therapies.

**Table 1: Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Manufacturer A</th>
<th>Manufacturer B</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>113 (66%)</td>
<td>49 (34%)</td>
<td>--</td>
</tr>
<tr>
<td>Rate of ≥ 1 inappropriate ICD therapy</td>
<td>29 (26%)</td>
<td>20 (41%)</td>
<td>0.045 *</td>
</tr>
<tr>
<td>Reasons of 1st inappropriate ICD therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>16 (55%)</td>
<td>4 (20%)</td>
<td></td>
</tr>
<tr>
<td>Atrial tachycardia/fibrillation</td>
<td>9 (31%)</td>
<td>5 (25%)</td>
<td>0.003 *</td>
</tr>
<tr>
<td>MTD † / High rate time out</td>
<td>0 (0%)</td>
<td>7 (35%)</td>
<td></td>
</tr>
<tr>
<td>Over-sensing ¶</td>
<td>4 (14%)</td>
<td>4 (20%)</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>58±13</td>
<td>57.5±15</td>
<td>0.92</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>92 (81%)</td>
<td>34 (70%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Female</td>
<td>21 (19%)</td>
<td>15 (30%)</td>
<td></td>
</tr>
<tr>
<td>Underlying heart disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>79 (70%)</td>
<td>28 (57%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>34 (30%)</td>
<td>21 (43%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>29±10</td>
<td>31±10</td>
<td>0.14</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>108±30</td>
<td>108±36</td>
<td>0.93</td>
</tr>
<tr>
<td>JT interval (ms)</td>
<td>351±52</td>
<td>351±37</td>
<td>0.91</td>
</tr>
<tr>
<td>Type of ICD:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single chamber ICD</td>
<td>79 (70%)</td>
<td>28 (57%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Dual chamber ICD</td>
<td>34 (30%)</td>
<td>21 (43%)</td>
<td></td>
</tr>
<tr>
<td>Indication of ICD implantation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>37 (33%)</td>
<td>12 (25%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>76 (67%)</td>
<td>37 (75%)</td>
<td></td>
</tr>
<tr>
<td>β-blocker therapy</td>
<td>80 (71%)</td>
<td>32 (65%)</td>
<td>0.57</td>
</tr>
<tr>
<td>ACE ‡ Inhibitors</td>
<td>102 (90%)</td>
<td>44 (89%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Digoxin</td>
<td>51 (45%)</td>
<td>18 (37%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>80 (70%)</td>
<td>31 (63%)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* Unadjusted P value by chi-square statistics
** Upper time limit to diagnosis and therapy by ICDs: We use this generic name to prevent disclosure of the Manufacturers. The nominal value was “off” in manufacturer A and “on” in the manufacturer B.
† Angiotensin converting enzyme
ICD Data Storage and Retrieval: After ICD implantation the patients were followed every three months and upon receiving high voltage therapy in our outpatient ICD clinic. The devices were interrogated at each session and the complete set of data (including intra-cardiac electrograms) was recorded on floppy diskettes. The floppy diskettes were used to retrieve all episodes of ICD therapy. All the episodes resulted in ICD therapy, studied independently by two electrophysiologists to define the diagnosis. In case of discrepancy in diagnosis the final analysis of the arrhythmia episode was made by a consensus of three electrophysiologists.

Definitions: Inappropriate ICD therapy was defined as an anti-tachycardia pacing or shock therapy for any rhythm and/or arrhythmia other than ventricular tachycardia or fibrillation. Indication of ICD implantation was defined as secondary prevention (n=113) in patients who had experienced aborted sudden cardiac death, sustained ventricular arrhythmia, or syncope (whose electrophysiologic study [using three basic drive cycle lengths of 600, 500 and 400 with up to three premature extra-stimuli from right ventricular apex and/or outflow tract] showed inducible sustained hemodynamically unstable ventricular arrhythmias). The indication of ICD implantation in all the other patients (23 patients with coronary artery disease and 26 patients with dilated cardiomyopathy) was categorized as primary prevention.

Statistics: (please also see section one; appropriate ICD therapy) We compared the probability of ≥1 inappropriate ICD therapy based on the time to first inappropriate therapy between the two groups by the Kaplan-Meier analysis and used log-rank test to generate the P-value. A two-tailed p-value < 0.05 was considered statistically significant.

Results:

Incidence and reason of inappropriate ICD therapy: Table 1 (see above) shows the patients’ baseline characteristics. During the follow up period of 14.3±10 months, 49 (30%) patients received ≥1 inappropriate ICD therapy. The rate of ≥1 inappropriate ICD
therapy in manufacturer A and B ICDs was 26% (n=29) and 41% (n=20), respectively. Higher number of women received ICD from manufacturer B and there was a trend toward higher prevalence of dilated cardiomyopathy in this group however both failed to reach to statistical significance (Table1). Our data showed that the cumulative hazard (Figure1) and reason (Table1) of first inappropriate ICD therapy was different between the two manufacturers. The probability of ≥1 inappropriate ICD therapy was comparable between the two groups of primary and secondary prevention (Figure3, Log-Rank P = 0.279).

Figure 1: Kaplan–Meier plot of the cumulative hazard of ≥1 inappropriate ICD therapy according to the manufacturer of the ICD
As it is shown in table 1, the major difference in the rate of inappropriate ICD therapy arise from the “upper time limit to diagnosis and therapy” parameter. While this parameter is set off by default in manufacturer A’s ICDs, it is programmed on in the basal default settings in the ICDs from the manufacturer B. Excluding the patients with ICDs from manufacturer B who received inappropriate ICD therapy due to maximum time to diagnosis results in comparable rate of inappropriate ICD therapy (Figure 2).

Figure 2: Kaplan–Meier plot of the cumulative hazard of ≥1 inappropriate ICD therapy according to the manufacturer of the ICD after exclusion of the cases of inappropriate ICD therapy due to “upper time limit to diagnosis and therapy”
Our data also showed that the cumulative hazard on inappropriate therapy was comparable between single and dual chamber ICDs (Figure 3). But why our data and the other trials have shown this finding? Ventricular tachycardias can be easily diagnosed in case of ventricular rate > atrial rate. This occurs in 80-90% of Ventricular tachycardias which occurs in the Ventricular tachycardia zone of dual-chamber ICDs. Hence, additional dual chamber discriminators actually apply to only 10-20% of Ventricular tachycardias. Improvement in current algorithms in field of tachycardias with 1:1 association and management of atrial blanking period in the atrial channel of dual chamber ICDs can influence the rate of inappropriate ICD therapy. 

**Figure 3:** Kaplan–Meier plot of the cumulative hazard of ≥1 inappropriate ICD therapy according to the type of the ICD.
Discussion

Although arrhythmia detection enhancements compared to rate-only detection decrease the rate of inappropriate ICD therapy without compromising the ICD’s safety the rate of inappropriate therapy remains high. 3-5 We showed that having all discrimination protocols activated with the nominal values, the rate (figure 1) and the reason of (Table 1) first inappropriate ICD therapy differs between the two manufacturers. The difference in the reasons of the first inappropriate ICD therapy also supports our finding that the different devices’ discriminatory algorithm(s) may work differently under default settings. Our data showed that the “upper time limit to diagnosis and therapy” parameter was the major reason for the difference in the rate of inappropriate ICD therapy. Although excluding this parameter could have resulted in the same rate of inappropriate ICD therapy, the reason for these therapies remains different between the two manufacturers (Table 1).

Although to the best of our knowledge there has been no prospective comparison between different discrimination protocols, Glikson et al. 6 have recently shown that in a dual chamber ICD various combinations of arrhythmia discriminators influences the performance of ICD with respect to arrhythmia diagnosis and inappropriate ICD therapy. Therefore, as it is suggested by our findings it could be assumed that the discriminatory performance of various ICDs might be different as they use different protocols and approaches for arrhythmia diagnosis and classification. 7 However, further studies are needed to better clarify this issue.

In addition in each ICD the optimum combination(s) of discriminatory parameters can influence the performance and specificity of the ICD systems. 6 Several investigators have shown that optimal dual chamber ICD programming reduces the inappropriate detection of supraventricular tachycardia as ventricular tachycardia, 8-10 In the future, as the reason of inappropriate ICD therapies can be different from patient to patient, in addition to newer more accurate discriminatory protocols we would also need ICDs with the ability of customized
software installation for different patients and arrhythmic circumstances. This would help to reduce the rate of inappropriate ICD therapies. 8

**In conclusion** having all discrimination protocols activated with the nominal values, the rate of ≥1 inappropriate ICD therapy (discriminatory performance) differs between the two manufacturers. The “upper time limit to diagnosis and therapy” algorithm was the major reason in this observed difference in the rate of inappropriate ICD therapy. However, our study included a relatively small number of patients. Therefore further larger-scale studies are warranted to prospectively compare the performance of various available ICDs’ discriminatory protocols, and define the optimum combination of discriminators in each ICD to decrease the rate of inappropriate therapy.
References:


Effect of Ventricular Tachycardia Cycle Length on Rate of Ventricular Arrhythmia Recurrence in Patients with ICD

Abstract (Part 3)*

Some controversies exist regarding the proper treatment of hemodynamically tolerated and slow ventricular tachycardia (VT). We intended to assess the effect of cycle length of first VT episode on total ventricular arrhythmia burden in a cohort of patients with implanted cardioverter-defibrillator (ICD).

Between March 2000 and March 2005, 195 patients underwent ICD implantation at our centre. We included 158 patients (mean age 58.3±12.9 year) with follow up ≥ 3 months in this study. Clinical, electrocardiographic, and ICD stored data and electrograms were collected and analyzed. During the follow up of 16.7±10.6 months, 45 (28.5%), and 20 (12.6%) patients received first appropriate ICD therapy for VT and ventricular fibrillation, respectively. We divided the 45 patients with VT (based on the median value of VT cycle length) into two groups. Although patients with VT cycle length < 350 had higher total mean number of appropriate ICD therapy (25 versus 6.3, P=0.023), during multivariate regression analysis only left ventricular ejection fraction (LVEF) <25% (P=0.020) was correlated with total number of appropriate ICD therapy. First VT cycle length (P=0.341), QRS duration (P=0.126), age (P=0.405), underlying heart disease (P=0.310), indication of ICD implantation (P=0.113), and gender (P=0.886) were failed to predict the total burden of ventricular arrhythmia during the follow up period.

After adjustment for LVEF slower initial VT cycle length per se did not confer a lower risk of subsequent ventricular arrhythmia recurrence compared to those with faster VT. LVEF<25% was correlated with higher ventricular arrhythmia burden in patients with ICD.

Introduction:

Some controversies exist regarding the proper treatment of hemodynamically tolerated and slow ventricular tachycardia (VT). AHA/ACC guideline has given ICD a class I indication with level of evidence: B in patients with spontaneous sustained VT (irrespective of hemodynamic status during arrhythmia) in association with structural heart disease \(^1\)-\(^3\). While there is a consensus on treatment of hemodynamically unstable sustained VT, some controversies exist regarding the proper treatment of hemodynamically tolerated ventricular tachycardia \(^1\),\(^3\),\(^4\).

Several studies hitherto have assessed the effect of hemodynamic status of VT on mortality. \(^5\)-\(^11\) However, to the best of our knowledge the effect of cycle length of initial sustained monomorphic VT (regardless of its hemodynamic status) on the cumulative rate of subsequent VT recurrence has not been studied so far. We hereby sough to assess the effect of cycle length of first VT episode (as the index arrhythmia) on total number of subsequent appropriate ICD therapies as a surrogate for total ventricular arrhythmia burden in a cohort of patients with ICD. We hypothesized that the first VT cycle lengths do not influence the total sustained ventricular arrhythmia burden.

Methods:

Patients Population: Between March 2000 and March 2005, 195 patients (75\% male) with coronary artery disease (CAD) and dilated cardiomyopathy (DCM) underwent ICD implantation at our centre. Among these 158 patients had follow up period \(\geq\) 3 months. Among these 45 patients with sustained monomorphic VT as the first arrhythmia requiring ICD therapy were included in this study. All the patients gave written informed consent for the procedure of ICD implantation. The mean age was 58.3±12.9 years.
ICD Data Retrieval: After ICD implantation the patients were followed at three months interval and upon receiving high voltage therapy in our outpatient ICD clinic. The devices were interrogated at each session and the complete set of data (including intracardiac electrograms) was recorded on floppy diskettes. The floppy diskettes were used in this study to retrieve all sustained arrhythmia episodes. Each episode studied by two independent electrophysiologists to define the diagnosis. In case of discrepancy in diagnosis the final analysis of the arrhythmia episode was made by a consensus of three electrophysiologists. Beside from diagnosis, the time of arrhythmia after implantation and the mode of therapy were recorded.

Implanted ICDs and programming: The implanted devices were manufactured by Medtronic (n=115, [GEM-VR, GEM-DR, GEM-II-VR, GEM-II-DR, GEM-III-VR, GEM-III-DR, Marquis-VR, Marquis-DR] Medtronic Inc., Minneapolis, MN, USA) and St. Jude (n=43, [Photon-VR, Photon-DR, Photon-µ-VR, Photon-µ-DR, Atlas-VR, Atlas-DR, Epic-VR, and Epic-DR] St. Jude Medical Inc. Sylmar, CA, USA). In all the devices we defined ventricular fibrillation zone (300 ms) plus one VT zone (400 ms). If the patient had an episode of spontaneous or induced sustained monomorphic VT slower than 370 ms we extended the VT zone to VT cycle length+40 msec.

Definitions: Appropriate ICD therapy was defined as an anti-tachycardia pacing or shock therapy for ventricular tachycardia or fibrillation. First therapy in the VT zone was programmed as three sequences of anti-tachycardia pacing. The initial episode consisted of 8 beats with cycle length of 88% of VT cycle length, and shortest interval of 200 msec. If the initial episode failed to terminate VT, the subsequent episode’s cycle length was reduced by 20 msec. Second to sixth therapies were programmed as Cardioversion. Diagnosis of monomorphic VT was defined as a regular tachycardia with monomorphic intra-cardiac ventricular electrogram in the VT detection zone with the change in the morphology of the
recorded intra-cardiac electrogram from baseline rhythm confirmed by visual inspection (see above).  

**Statistics:** Variables are expressed as mean ± SD, and percentage. Differences in frequency of characteristics were assessed by independent sample student’s *t*-test between two groups and analysis of variance for comparison between three groups for continuous variables. Chi-square statistics (or fisher’s exact test if applicable) used for discrete variables. A two-tailed *p*-value < 0.05 was considered statistically significant. We used SPSS® 13.0 (SPSS Inc. Chicago, USA) for data storage and analysis.

**Results:**

**Baseline Characteristics:** One hundred fifty eight patients with ICD were followed for a mean of 16.7±10.6 months. The mean follow up time after first ICD therapy for monomorphic ventricular tachycardia was 11.2 ± 8.9 months. Table 1 shows the basic characteristics of the patients based on the status of appropriate ICD therapy during the follow up period. We selected the 45 patients with sustained monomorphic VT as the first ventricular arrhythmia requiring therapy after ICD implantation to assess the effect of its cycle length on total number of appropriate ICD therapy as a surrogate for total ventricular arrhythmia burden.
Table 1: Baseline Patients’ Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>VT‡</th>
<th>VF†</th>
<th>No VA¶</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>45</td>
<td>20</td>
<td>93</td>
<td>--</td>
</tr>
<tr>
<td>Age (year)</td>
<td>58±14</td>
<td>57.6±12.5</td>
<td>58±13.5</td>
<td>0.886</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (80%)</td>
<td>18 (90%)</td>
<td>65 (70%)</td>
<td>0.115</td>
</tr>
<tr>
<td>Female</td>
<td>9 (20%)</td>
<td>2 (10%)</td>
<td>28 (30%)</td>
<td></td>
</tr>
<tr>
<td>Underlying heart disease:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>19 (42%)</td>
<td>12 (60%)</td>
<td>65 (70%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>26 (58%)</td>
<td>8 (40%)</td>
<td>28 (30%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25%</td>
<td>25 (56%)</td>
<td>12 (60%)</td>
<td>41 (44%)</td>
<td>0.242**</td>
</tr>
<tr>
<td>≥ 25%</td>
<td>20 (44%)</td>
<td>8 (40%)</td>
<td>52 (56%)</td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120</td>
<td>15 (33%)</td>
<td>6 (30%)</td>
<td>53 (57%)</td>
<td>0.007</td>
</tr>
<tr>
<td>≥ 120</td>
<td>30 (67%)</td>
<td>14 (70%)</td>
<td>40 (43%)</td>
<td></td>
</tr>
<tr>
<td>Mean number of appropriate ICD therapy</td>
<td>16±28</td>
<td>7±9</td>
<td>--</td>
<td>0.0001</td>
</tr>
<tr>
<td>Indication of ICD implantation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>23 (51%)</td>
<td>3 (15%)</td>
<td>21 (23%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>22 (49%)</td>
<td>17 (85%)</td>
<td>72 (77%)</td>
<td></td>
</tr>
<tr>
<td>B-blocker therapy</td>
<td>22 (49%)</td>
<td>14 (70%)</td>
<td>56 (60%)</td>
<td>0.234</td>
</tr>
<tr>
<td>Angiotensin converting enzyme Inhibitors</td>
<td>42 (93%)</td>
<td>17 (85%)</td>
<td>80 (86%)</td>
<td>0.422</td>
</tr>
<tr>
<td>Digoxin</td>
<td>18 (40%)</td>
<td>10 (50%)</td>
<td>41 (44%)</td>
<td>0.749</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>32 (71%)</td>
<td>11 (55%)</td>
<td>57 (62%)</td>
<td>0.407</td>
</tr>
</tbody>
</table>

* The subgroups of left ventricular ejection fraction and QRS duration are chosen based on the median values in the study population. ** Left ventricular ejection fraction was significantly correlated with total number of appropriate ICD therapy during the follow up period (P<0.005). ‡ Patients with sustained monomorphic ventricular tachycardia requiring ICD therapy. These comprise our study population. † Patients with ventricular fibrillation requiring ICD therapy. ¶ Ventricular arrhythmia.

Number of appropriate ICD therapy based on initial VT cycle length: Table 2 depicts the baseline characteristics of patients with sustained monomorphic ventricular tachycardia as the index arrhythmia according to its cycle length. Patients with initial VT cycle length < 350 ms were younger, had higher prevalence of DCM as the underlying heart disease, had lower left ventricular EF, and had higher mean number appropriate ICD therapy.
**Predictors of ICD Therapies**

**Table 2:** Baseline characteristics of patients with sustained monomorphic ventricular tachycardia as the reason for first appropriate therapy *

<table>
<thead>
<tr>
<th>Variables</th>
<th>ACL**&lt;350ms</th>
<th>ACL≥350 ms</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>22</td>
<td>--</td>
</tr>
<tr>
<td>Age (year)</td>
<td>53±17</td>
<td>63±9</td>
<td>0.026</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (83%)</td>
<td>17 (77%)</td>
<td>0.470</td>
</tr>
<tr>
<td>Female</td>
<td>4 (17%)</td>
<td>5 (23%)</td>
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</tr>
<tr>
<td>Underlying heart disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7 (30%)</td>
<td>12 (55%)</td>
<td>0.136</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>16 (70%)</td>
<td>10 (45%)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>18 (78%)</td>
<td>7 (32%)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥ 25</td>
<td>5 (22%)</td>
<td>14 (68%)</td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120</td>
<td>16 (70%)</td>
<td>13 (59%)</td>
<td>0.542</td>
</tr>
<tr>
<td>≥ 120</td>
<td>7 (30%)</td>
<td>9 (41%)</td>
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<tr>
<td>Indication of ICD implantation:</td>
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<td></td>
</tr>
<tr>
<td>Primary prevention</td>
<td>10 (43%)</td>
<td>10 (45%)</td>
<td>0.350</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>13 (57%)</td>
<td>11 (55%)</td>
<td></td>
</tr>
<tr>
<td>β-blocker therapy</td>
<td>12 (52%)</td>
<td>10 (45%)</td>
<td>0.652</td>
</tr>
<tr>
<td>Angiotensin converting enzyme Inhibitors</td>
<td>21 (91%)</td>
<td>21 (95%)</td>
<td>0.537</td>
</tr>
<tr>
<td>Digoxin</td>
<td>12 (52%)</td>
<td>6 (27%)</td>
<td>0.088†</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>16 (70%)</td>
<td>16 (72%)</td>
<td>0.815</td>
</tr>
<tr>
<td>Mean† number of appropriate ICD therapy</td>
<td>25±7.7</td>
<td>6.3±1.3</td>
<td>0.023§</td>
</tr>
<tr>
<td>First arrhythmia cycle length (ms)</td>
<td>310±23</td>
<td>380±16</td>
<td>0.0001</td>
</tr>
<tr>
<td>(270 – 345)</td>
<td>(350 – 420)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia cycle length during follow up (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>322±25</td>
<td>354±26</td>
<td>0.001</td>
</tr>
<tr>
<td>Shortest (range)</td>
<td>258±30</td>
<td>274±45</td>
<td>0.235</td>
</tr>
<tr>
<td>(190-290)</td>
<td>(210-340)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longest (range)</td>
<td>384±33</td>
<td>428±15</td>
<td>0.001</td>
</tr>
<tr>
<td>(340-460)</td>
<td>(410-460)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The subgroups of arrhythmia cycle length, left ventricular ejection fraction, and QRS duration are chosen based on the median values in the study population.

** Arrhythmia cycle length. † Mantel-Haenszel P value for re-analysis stratified for ejection fraction = 0.095.

§ Expressed as mean ± standard error of mean. § During multiple regression analysis presenting VT cycle length failed to correlate with total number of appropriate ICD therapy as a surrogate for total arrhythmia burden (P=0.341). The medications are based on the medical history at the time of first appropriate ICD therapy.

We hypothesized that other confounding variable(s) might have resulted in the observed difference of mean number of appropriate ICD therapy between subgroups of VT cycle length. We used multiple regression analysis to find the predictors of total number of appropriate ICD therapy among patients with sustained monomorphous VT. Left ventricular EF < 25% was the only variable correlated with the total number of appropriate ICD therapy in
these patients (P=0.020). In addition, presenting VT cycle length (P=0.341), QRS duration (P=0.126), age (P=0.405), underlying heart disease (P=0.310), indication of ICD implantation (P=0.113), and gender (P=0.886) were failed to predict the total number of appropriate ICD therapy during the follow up period.

**First and subsequent ventricular arrhythmia cycle lengths:** Table 2 (see above) shows first VT cycle length in each group. Although the mean longest arrhythmia cycle length during follow up was different among the two groups (P = 0.001), the shortest tachycardia cycle length was comparable between the two groups (P = 0.235). In addition during follow up 22% (n=5) and 19% (n=4) of the ICD recipients with initial fast and slow VT experiences at least one episode of potentially life threatening fast VT, defined as VT with cycle length ≤ 250 ms, respectively (P = 0.853).

**Discussion:**

We showed that (1) Among our ICD patients who had sustained monomorphic VT as the first arrhythmia after ICD implantation the LVEF < 25% correlated with the total number of appropriate ICD therapy as a surrogate for total ventricular arrhythmia burden; (2) After adjustment for left ventricular EF, initial VT cycle length did not correlate with the total number of appropriate ICD therapy during multivariate regression analysis (P=0.341); (3) The frequency of potentially life threatening fast VT and the mean shortest VT cycle length after first VT were comparable between the two groups.

To the best of our knowledge this is the first study assessing the effect of VT cycle length on subsequent VT recurrence. The initial VT cycle length did not correlate with VT recurrence during the follow up. In addition the mean shortest VT cycle length and the occurrence of potentially lethal fast VT were comparable between the two groups. There might be an association between VT cycle length and symptoms. Therefore, one could
suggest that the slower VT might have been associated with more benign symptoms compared to faster VTs.  

Several studies have evaluated the effect of hemodynamic status and concomitant symptoms on long term outcome of patients with sustained monomorphic VT. Sarter et al. have suggested a better prognosis for hemodynamically tolerated VT (however, some debates exist on their data) but other showed that the risk is similar to patients with more severely symptomatic VT. Raitt et al. in a subgroup analysis of AVID registry showed that the absence of symptoms with sustained VT does not predict a benign prognosis. Olson et al. assessed the predictors of sudden cardiac death in 122 patient and showed that the rate of sudden cardiac death is not affected by presence or absence of symptoms during sustained monomorphic VT.

Bocker et al. studied the natural course of 50 patients (82%, CAD) with hemodynamically tolerated VT who received ICD. They showed that during mean follow up of 17 months, 33 patients (66%) had 3861 episodes of ventricular tachycardia which is comparable to other studies. Eleven patients (22%) had episodes of potentially life-threatening fast VT (CL<250 ms) during follow up period. Had the ICD not been implanted in the Bocker study, their patients would have had at least the same mortality as patients in AVID registry.

We found that EF < 25% define a subgroup of patients with ICD who are at higher risk of subsequent ICD therapy after initial VT. Freedberg et al. followed 125 patients with ICD for 408±321 days and found that first appropriate ICD therapy which occurred in 46% of patients, tends to occur in patients presenting with sustained monomorphic VT and left ventricular EF <25%.
Finally, Sadoul et al. have recently showed that slow VT (defined as VT < 148 beat per minute) occurs in 30% of ICD recipients without prior history of symptomatic or ECG documented slow VT exhibited slow VT during a 1-year follow-up. However, they did not assess the effect of slow VT on the rate of recurrence, cycle length, and hemodynamic status of subsequent sustained arrhythmic episodes.

**In conclusion:** After adjustment for left ventricular EF, initial VT cycle length did not predict subsequent VT recurrence in our patients with ICD. In addition mean shortest VT cycle length and prevalence of potentially lethal fast VT was comparable between the two groups. Using multiple regression analysis, only left ventricular EF < 25% defined a subgroup of patients who are higher risk appropriate ICD therapy due to VT recurrence after initial ICD therapy. This may (at least partially) explain the discrepancy between various studies conducted on effect of slow VT on prognosis. Further prospective studies are warranted to clarify this issue.
References:

Effect of Cardiac Resynchronization Therapy on Incidence of Ventricular Arrhythmias in Patients with ICD

eingereicht von: Arash Arya
angefertigt am Herzzentrum Universität Leipzig
Betreut von Prof. Dr. med. Gerhard Hindricks

Abstract (Teil 4)*

Cardiac resynchronization therapy (CRT) reduces the mortality in selected patients with heart failure. However this may not be entirely related to its beneficial hemodynamic effects. We assessed retrospectively the effect of CRT on incidence of appropriate therapy in patients with implantable cardioverter-defibrillator (ICD).

Sixty five patients (mean age 58±13 years, 48 male) with ICD (31 with biventricular ICD and 34 with dual chamber ICD) were included in the study. Clinical, electrocardiographic, and ICD stored data and electrograms were collected. Biventricular and dual chamber ICDs were implanted in 31 and 34 patients respectively, who had either ischemic (n=36) or dilated cardiomyopathy (n=29). Thirty two (49%) patients received ≥ 1 appropriate ICD therapy during follow up period of 11±8 months. Thirty-five percent and 62% of patients with biventricular (n=11) and dual chamber ICDs (n=21), respectively, received appropriate ICD therapy during follow up period (odds ratio = 0.340, P=0.048). Stratifying the patients according to underlying heart disease and ejection fraction resulted in adjusted odds ratio = 0.239, P=0.029). We compared the rate of ≥ 1 appropriate ICD therapy between the two groups by Kaplan-Meier analysis and the Log-Rank test which resulted in P = 0.027.

In this retrospective analysis, biventricular pacing was associated with a decrease in the incidence of sustained ventricular arrhythmias requiring ICD therapy. The antiarrhythmic effect of biventricular pacing could contribute to reduction of mortality shown in recent large scale clinical trials on CRT. However, further prospective studies are warranted to clarify this issue.

Introduction:

Cardiac resynchronization therapy is an established mode of therapy in selected symptomatic patients with heart failure due to systolic dysfunction. Recently published large scale clinical trials of CRT confirmed the favorable effects of CRT on symptoms, the quality of life, ventricular function, and blood pressure and showed that CRT significantly reduces the risk of mortality. Calculations based on data from Cardiac Resynchronization — Heart Failure trial depicted that, for every nine biventricular pacemaker implanted, one death and three hospitalizations for major cardiovascular events were prevented. The reduction in mortality by CRT is at least in some part is related to homodynamic improvement.

Some experimental studies have suggested that epicardial pacing of left ventricle in CRT prolongs QT interval and increases the transmural dispersion of refractoriness. In addition some cases of increase in ventricular arrhythmias following CRT have been reported in the literature. Contrary to these, several clinical studies have suggested the opposite and showed that the CRT could also reduce the mortality by decreasing the incidence of lethal ventricular arrhythmias. We hereby conducted a retrospective case-control study to assess the effect of CRT on incidence of appropriate therapy, as a surrogate for sustained ventricular arrhythmias (see definitions), in patients with implantable cardioverter-defibrillator (ICD).

Methods:

Patients Population: Between December 2002 and February 2005, 31 patients underwent transvenous biventricular ICD implantation at our centre. In two patients the left ventricular lead was implanted via thoracotomy. All these patients had QRS width ≥ 120 ms and standard indication for CRT and ICD implantation (see definitions). During the same period 68 patients with coronary artery disease (CAD) or dilated cardiomyopathy (DCM) received dual chamber ICD at our centre. To provide an adequate comparable control group, among these 68 patients we selected all the patients with QRS duration ≥ 120 ms (n=34) as
the control group. The bradycardia pacing of dual chamber ICDs were programmed to VVI with the rate of 40 beats per minute to prevent unnecessary ventricular pacing, except in patients with an established indications for cardiac pacing (n=5). All the patients gave written informed consent for the procedure of ICD implantation. The mean age was 58±13 years. Table 1 shows the basic characteristics of the patients.

**Table 1:** Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>ICD-DR†</th>
<th>CRT-D¶</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>34</td>
<td>31</td>
<td>--</td>
</tr>
<tr>
<td>Follow up period</td>
<td>11±8</td>
<td>10.3±6</td>
<td>0.455</td>
</tr>
<tr>
<td>Age (year)</td>
<td>57±13</td>
<td>58±12</td>
<td>0.849</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td>0.614</td>
</tr>
<tr>
<td>Male</td>
<td>26 (76%)</td>
<td>22 (71%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (34%)</td>
<td>9 (29%)</td>
<td></td>
</tr>
<tr>
<td>Underlying heart disease:</td>
<td></td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>24 (70%)</td>
<td>12 (39%)</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>10 (30%)</td>
<td>19 (61%)</td>
<td></td>
</tr>
<tr>
<td>LVEF * (%)</td>
<td>26±8</td>
<td>22±6</td>
<td>0.013</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>146±30</td>
<td>149±25</td>
<td>0.711</td>
</tr>
<tr>
<td>Corrected QT interval (ms)</td>
<td>480±58</td>
<td>473±68</td>
<td>0.631</td>
</tr>
<tr>
<td>Indication of ICD implantation (n):</td>
<td></td>
<td></td>
<td>0.484</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>23</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker therapy (%)</td>
<td>53%</td>
<td>40%</td>
<td>0.250</td>
</tr>
<tr>
<td>ACE ** Inhibitors</td>
<td>88%</td>
<td>83%</td>
<td>0.371</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>62%</td>
<td>53%</td>
<td>0.409</td>
</tr>
</tbody>
</table>

* Left ventricular ejection fraction.
** Angiotensin converting enzyme.
† Dual chamber implantable cardioverter-defibrillator.
¶ Implantable cardioverter-defibrillator with biventricular pacing option.

**ICD Data Storage and Retrieval:** After ICD implantation the patients were followed on a regular basis (3 months) and upon receiving high voltage therapy in our outpatient ICD clinic. The devices were interrogated at each session and the complete set of data (including intracardiac electrograms) was recorded on floppy diskettes. The summary of the episodes
were also recorded in the patient’s file. The floppy diskettes were used in this study to retrieve all sustained arrhythmia episodes. Each episode studied by two independent electrophysiologists (AA and MRD) to define the diagnosis. In case of discrepancy in diagnosis the final analysis of the arrhythmia episode was made by a consensus of three electrophysiologists (AA, MRD, and MH). Beside from diagnosis, the time of arrhythmia after implantation and the mode of therapy were recorded.

**Definitions:** Appropriate ICD therapy was defined as an antitachycardia pacing or shock therapy for ventricular tachycardia or fibrillation. All the patients who received biventricular ICD had standard indications for ICD implantation. \(^{16}\) Indication of ICD implantation was defined as secondary prevention \((n=44)\) in patients who had experienced aborted sudden cardiac death, sustained ventricular arrhythmia, or syncope \((n=9, \text{ with structural heart disease whose electrophysiologic study showed inducible sustained hemodynamically unstable ventricular arrhythmias})\). The indication of ICD implantation in all the other patients \((n=21 \text{ with MADIT, MUSTT like indications in those with CAD } [n=10] \text{ and asymptomatic patients with DCM } [n=11] \text{ with nonsustained VT during Holter monitoring who had inducible sustained hemodynamically unstable ventricular arrhythmia during electrophysiologic study})\) was categorized as primary prevention. \(^{16}\)

**Statistics:** Variables are expressed as mean ± SD, and percentage. Differences in frequency of characteristics were assessed by independent sample student’s \(t\)-test for continuous variables. Chi-square statistics (or fisher’s exact test if applicable) used for discrete variables. Probability of \(\geq 1\) appropriate ICD therapy based on the time to first appropriate ICD therapy between the two groups determined by the Kaplan-Meier analysis with Mantel-Cox (Log-Rank) test. The time to first appropriate ICD therapy plotted according to the Kaplan-Meier method. We used Mantel-Haenszel test to generate P value for the
reported odds ratios. A two-tailed p-value < 0.05 was considered statistically significant. We used SPSS® 13.0 (SPSS Inc. Chicago, USA) for data storage and analysis.

Results:

Baseline Characteristics: Sixty five patients with biventricular and dual chamber ICD were followed for a mean of 11±8 months. Biventricular and dual chamber ICDs were implanted in 31 and 34 patients, respectively. We compared patients’ characteristics between two types of ICD (Table 1, see above). Patients with biventricular ICD had lower left ventricular EF (22±6 versus 26±8, P=0.013); and higher prevalence of DCM as underlying heart disease (61% versus 30%, P=0.013). Other variables were comparable between two groups.

Appropriate ICD therapy: Thirty two (49%) patients received ≥ 1 appropriate ICD therapy during the follow up period. Ventricular tachycardia and fibrillation (based on detection zones) were responsible for first appropriate ICD therapy in 20 (62.5%) and 12 (27.5%) patients, respectively. The proportion and cycle length of these ventricular arrhythmias were comparable between the two groups (all P = NS).

Thirty five percent and 62% of patients with biventricular (n=11) and dual chamber ICD (n=21), respectively, received appropriate ICD therapy during the follow up period (Odds ratio = 0.340, 95% confidence interval = 0.125 – 0.935, P=0.048). The mean number of appropriate ICD therapies in patients with dual chamber and biventricular ICDs were 13±32 (range: 0-132) and 1.3±2.5 (range: 0-9), respectively (P=0.047).

Interaction between type of ICD and probability of ≥ 1 appropriate ICD therapy: Figure 1 shows the comparison of the differences in ≥ 1 appropriate ICD therapy using Kaplan-Meier survival curves for the two device groups, with application of Mantel-Cox (Log-Rank) test (P = 0.027). Among 34 and 31 patients with dual chamber and biventricular
ICDs, 62% and 35% received appropriate ICD therapy, respectively (Odds ratio = 0.340, 95% confidence interval = 0.125 – 0.935, \( P=0.048 \)). We repeated the analysis by stratifying the patients according to underlying heart disease and left ventricular EF. The subgroups of left ventricular EF was divided based on the median value (25%) in the study population. The adjusted odds ratio was 0.239 (95% confidence interval = 0.1 to 0.84, \( P=0.029 \)).

**Figure 1:** Kaplan–Meier plot of the Time to the first inappropriate therapy according to types of ICD. We used Log-Rank (Mantel-Cox) test to generate the P-value.

**ICD-DR:** Dual chamber ICD. **CRT-D:** Biventricular ICD.

**Prevalence and number of nonsustained VTs:** Forty eight (74%) patients had nonsustained VT during the follow up period. Although there was a trend toward higher prevalence of NSVT in patients with dual chamber ICDs compared to those with biventricular ICDs (80% versus 68%), it failed to reach to statistical significance (\( P = 0.258 \)). Although there was also a trend toward the higher mean number of nonsustained VTs in patients with
dual chamber ICDs (155±394 [range: 1 – 1642] versus 33±95 [range: 1 – 436]), it failed to reach to statistical significance (P = 0.113).

Discussion:

**Main finding:** Biventricular pacing decreased the rate of appropriate ICD therapy (including both antitachycardia pacing and shock) by suppressing the occurrence of sustained ventricular arrhythmias requiring ICD therapy. During follow up period patients with biventricular ICD received 66% less appropriate ICD therapy compared to those with dual chamber ICD (figure 1 and 2).

![Figure 2](image.png)

**Figure 2:** Effect of biventricular pacing on the incidence of appropriate ICD therapy. Unadjusted odds ratios and 95% confidence intervals are shown. The subgroups of age, ejection fraction, and QRS width are divided based on the median values of the study population. **ICD-DR:** Dual chamber ICD. **CRT-D:** Biventricular ICD.

The recent clinical trials on CRT confirmed that it significantly reduces the risk of death. However the reduction in mortality by CRT may not be related entirely to its favourable homodynamic effects. Several potential mechanisms may explain the observed antiarrhythmic effect of CRT.
Although we did not assess the hemodynamic response to the CRT in our study, improvement in left ventricular performance could partly explain the decreased incidence of appropriate ICD therapy in patients with biventricular ICDs. The hemodynamic improvement following CRT could decrease the stretch on myocardium and modulate the autonomic nervous system activity and these in turn would reduce the incidence of lethal ventricular arrhythmias. Several studies have shown that biventricular pacing decreases the frequency of ventricular ectopy. Reducing the ventricular ectopy which can trigger sustained ventricular arrhythmias could decrease the incidence of sustained ventricular arrhythmias and appropriate ICD therapy.

Several studies have shown that biventricular pacing reduces the inducibility of ventricular tachycardia. Kowal et al. in a prospective randomized study evaluated the acute electrophysiologic effects of biventricular pacing. They showed that biventricular compared to right ventricular programmed electrical stimulation significantly reduces the induction of ventricular tachycardia (but not ventricular fibrillation) and hypothesized that the mechanism of arrhythmia suppression by biventricular pacing is due to preexcitation of the area of slow conduction responsible for re-entrant arrhythmias and significant increase in the local left ventricular coupling interval.

Experimental studies have suggested that epicardial left ventricular pacing increases the transmural dispersion of refractoriness and hence biventricular pacing may potentially cause proarrhythmia in selected patients with CRT. Berger et al. have recently assessed the effect of biventricular pacing on ECG markers of ventricular repolarization in patients with congestive heart failure and showed that using a high resolution surface ECG, biventricular pacing actually significantly reduced ECG markers of ventricular dispersion of repolarization which could further contribute to the antiarrhythmic effects of CRT.

Higgins et al. in a similar study to ours showed that in patients with standard indications for ICD, appropriate ICD therapy was less common with biventricular ICDs.
However, several points merit consideration. In their study all the left ventricular leads were placed via thoracotomy while left ventricular leads where positioned via coronary sinus in all but two of our patients. In Higgins’ study only 32 of 54 (59%) patients were suitable for the final paired analysis; and duration of observation in each mode of pacing was only three months. 17 Our study with a larger patient population confirmed the beneficial effect of biventricular pacing on reduction of appropriate ICD therapy in a longer follow up duration. However, ICD therapy should not be equated with reduction in sudden cardiac death, therefore larger prospective studies with cardiac and all cause mortality as the endpoints are warranted to clarify this issue.

While the bulk of evidences are in favour of antiarrhythmic effects of CRT, 7-14 several case reports have shown the increased occurrence of ventricular arrhythmia following biventricular pacing or ICD implantation. 5, 6 In addition, in Cardiac Resynchronization — Heart Failure study, despite statistically significant lower absolute number of deaths classified as sudden in CRT group compared to control group, the proportion of deaths which were classified as sudden cardiac death were comparable between the two groups. The mode of death was classified as sudden in 38 of the 120 patients who died in the medical therapy group (32 percent) and in 29 of the 82 patients who died in the CRT group (35 percent). 2

Although the underlying mechanism(s) in the above mentioned case reports were not exactly clear, physicians should be aware of occasional proarrhythmic effects of CRT. The biventricular pacing induced ventricular tachycardia is one of the study endpoints of PACMAN trial – pacing for cardiomyopathies, a prospective single blinded study ongoing in Europe. This would help to find the incidence of biventricular pacing induced ventricular tachycardia. 6
**Conclusion:** in selected patients with heart failure who had accepted indications for ICD implantation biventricular pacing reduced the incidence of appropriate ICD therapy, as a surrogate for sustained ventricular arrhythmias. Further large scale prospective studies are warranted to assess the potential antiarrhythmic effects of CRT.

**Implication:** The antiarrhythmic effect of biventricular pacing could contribute to reduction of mortality seen in CRT patients.
References:


Summary (Zusammenfassung)

Dissertation zur Erlangung des akademischen Grades Dr. med.
an der medizinischen Fakultät der Universität Leipzig

Titel: Predictors of appropriate and inappropriate Therapies in Patients with implantable cardioverter-defibrillator and Structural Heart Disease

Eingereicht von: Arash Arya

Angefertigt am Herzzentrum Universität Leipzig

Betreut von: Professor Dr. med. Gerhard Hindricks

Eingereicht: April 2015

There is no controversy that ICD in selected patients reduces the long term mortality. However, appropriate and/or inappropriate shocks in patients with ICD are associated with increased mortality and morbidity. Identifying the predictors of ICD therapies could help to identify those at risk and reduce the incidence of these therapies through appropriate measures and therapies which may improve mortality and morbidity in patients with ICD. I hereby summarize my four published studies on predictors of appropriate and inappropriate ICD therapies.

In the first study we assess the prevalence and predictors of electrical storm in 162 patients with ICD who were followed for a mean of 14.3±10 months. Electrical storm was defined as ≥ 3 episodes of ventricular tachycardia and/or fibrillation requiring ICD therapy in a one day period. During our follow up period the patients received mean number of 17±29 (range 1 – 132) appropriate ICD therapy. Among these the number of appropriate ATP was 11.9±28 (range 0 – 131) and the number of appropriate shock therapy was 5.1±9.9 (range 1 – 56). The success rate of ATP therapy among the episodes in the VT detection zone was 88%. Predictors of electrical storm were found by Cox regression. In the Cox-regression model...
ejection fraction < 25% (P=0.007), QRS width ≥ 120 ms (P=0.002), and lack of adjunctive beta-blocker and angiotensin-converting enzyme inhibitors (both P < 0.001) were correlated with the higher probability of electrical storm during the follow up period.

Therefore this study showed that optimum medical therapy with beta-blockers and angiotensin-converting enzyme inhibitors could reduce the incidence of this devastating complication in patients with ICD. In addition low left ventricular ejection fraction (< 25%) and wide QRS complex (≥ 120 ms) identify patients who are at higher risk of appropriate ICD therapies and therefore may profit more from prophylactic catheter ablation of ventricular arrhythmias.

The algorithms that should discriminate VT or VF from less lethal supra-ventricular arrhythmias do not always work perfectly. As many as one-third of the patients who have an ICD implanted, receive inappropriate ICD shocks. Inappropriate shocks occur when the device delivers a shock for a reason other than a ventricular arrhythmia. Inappropriate ICD shocks are also associated with increased mortality. Given the traumatic nature of ICD shocks, it would be ideal if the ICD could always successfully distinguish ventricular arrhythmias from non–life-threatening tachyarrhythmias and administer only appropriate shocks for VT or VT. Several factors influence the incidence and prevalence of inappropriate ICD shocks. Every ICD manufacturer uses a different discrimination protocol and therefore the rate of inappropriate ICD therapies might be different among various ICD models. However, at the time of our second study to the best of our knowledge no study assessed the rate of inappropriate ICD shocks between different ICD manufacturers.

In the second study immediately after ICD implantation in 162 patients all the detection and discrimination criteria were activated with the nominal values. We used the nominal values after implantation for comparison of discriminatory protocols of the two manufacturers under default settings. After first inappropriate ICD therapy if deemed
necessary, the attending physicians were able to modify ICD programming and optimize medical treatment in order to decrease the rate of inappropriate ICD therapy. During the follow up period of 14.3±10 months, 49 (30%) patients received ≥1 inappropriate ICD therapy. The rate of ≥1 inappropriate ICD therapy in manufacturer A and B ICDs was 26% (n=29) and 41% (n=20), respectively (P<0.05). The rate of inappropriate ICD therapies was comparable between patients with single and two chamber ICDs (P=0.85).

Therefore, having all discrimination protocols activated with the *nominal* values, the rate of ≥1 inappropriate ICD therapy (discriminatory performance) differs between the two manufacturers. The “upper time limit to diagnosis and therapy” algorithm was the major reason in this observed difference in the *rate* of inappropriate ICD therapy. Therefore, optimal ICD programming based on ICD model and manufacturer may help reducing the rate of inappropriate ICD therapies.

Some controversies exist regarding the proper treatment of *hemodynamically tolerated* and *slow* ventricular tachycardia (VT). In the third part of the manuscript we sought to assess the effect of cycle length of first VT episode (as the index arrhythmia) on total number of subsequent appropriate ICD therapies as a surrogate for total ventricular arrhythmia burden in a cohort of patients with ICD. We hypothesized that the first VT cycle lengths do not influence the total sustained ventricular arrhythmia burden.

One hundred fifty eight patients with ICD were followed for a mean of 16.7±10.6 months. We showed that: (1) after adjustment for left ventricular ejection fraction, initial VT cycle length did not correlate with the total number of appropriate ICD therapy (P=0.341) (2) the frequency of potentially life threatening fast VT (i.e. cycle length ≤ 250 ms) and the mean shortest VT cycle length after first VT were comparable between the two groups with initial fast and slow VTs, respectively. Therefore, patients with slower VTs were at the same risk.
compared to those with faster VTs, with respect to total ventricular arrhythmia burden and the frequency of subsequent fast VTs.

In the forth manuscript we conducted a retrospective case-control study to assess the effect of cardiac resynchronization therapy (CRT) on incidence of appropriate therapies, as a surrogate for sustained ventricular arrhythmias, in patients with ICD. Sixty five patients with biventricular (n=31) and dual chamber ICD (n=34) were followed for a mean of 11±8 months. Thirty two (49%) patients received ≥ 1 appropriate ICD therapy during the follow up period. Ventricular tachycardia and fibrillation (based on detection zones) were responsible for first appropriate ICD therapy in 20 (62.5%) and 12 (27.5%) patients, respectively. Thirty five percent and 62% of patients with biventricular (n=11) and dual chamber ICD (n=21), respectively, received appropriate ICD therapy during the follow up period (Odds ratio = 0.340, 95% confidence interval = 0.125 – 0.935, P=0.048). The mean number of appropriate ICD therapies in patients with dual chamber and biventricular ICDs were 13±32 (range: 0-132) and 1.3±2.5 (range: 0-9), respectively (P=0.047).

In conclusion in our case-control study in selected patients with heart failure who had accepted indications for ICD implantation, CRT reduced the incidence of appropriate ICD therapy, as a surrogate for sustained ventricular arrhythmias.
Erklärung über die eigenständige Abfassung der Arbeit


Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren.

..................................................
Datum

..................................................
Unterschrift
Lebenslauf

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### Publikationen

**Artikel auf Englisch, internationale Zeitschriften, gelistet in PubMed**
(132 Artikels, einschließlich 44 als erster oder letzter Autor)


Predictors of ICD Therapies

Arash Arya


Piorkowski C, Bollmann A, Platonov PG. Effects of baseline P-wave duration and choice of atrial septal pacing site on shortening atrial activation time during pacing. Europace. 2012 Sep;14(9):1294-301.


Predictors of ICD Therapies

Arash Arya


Predictors of ICD Therapies

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Gutachtertätigkeiten für die folgenden Zeitschriften

Gutachtertätigkeiten für die folgenden Zeitschriften

Journal of Cardiovascular Electrophysiology
European Journal of Heart Failure
Pacing and Clinical Electrophysiology
International Journal of Cardiology
American Journal of Cardiology
Iranian Heart Journal
Journal of Interventional Electrophysiology
Heart Rhythm
Journal of Electrocardiology (Editorial Board)
Europace
European Heart Journal

Mitgliedschaft

Deutsche Gesellschaft für Kardiologie (DE)
Iranian Heart Association (IRAN)
European Heart Rhythm Association (EU)
Heart Rhythm Society (US)
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