Latent Clinical Outcomes of Appropriate and Inappropriate ICD Shocks

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ABSTRACT

Introduction: Despite the proven survival benefits, implantable cardioverter defibrillator (ICD) therapy has still some drawbacks. It is clearly known that inappropriate shocks increase mortality however, randomized controlled trials showed that appropriate shocks might also increase mortality. Left untreated, ventricular arrhythmias are known to be fatal and in this case ICD shock therapy is life-saving so it is appropriate to assess the effects of antitachycardial pacing (ATP) therapy and shock therapy separately. The aim of our study is to determine the clinical effects of inappropriate and appropriate shocks in a population of ICD implanted patients.
Patients and Methods: We retrospectively screened ICD implanted patients between January 2003 and December 2013 in our clinic. Additionally, patients were called by telephone and parameters such as survival and rehospitalization were updated. During the retrospective follow-up, the occurrence of inappropriate-appropriate ICD shocks and mortality causes were noted. Characteristics of patients suffering from shocks were also investigated.
Results: A total of 260 ICD implanted patients were included in the study. Forty of them experienced inappropriate shocks (defined as at least one inappropriate shock, without any appropriate shocks). Sixty nine patients experienced appropriate shocks (defined as at least one appropriate shock, without any inoppropriate shocks). Retrospective mean follow up period was 49 months, minimum follow up period was 6 months. Among 40 patients experiencing inappropriate shocks 13 deaths (32.5%) occured (p=0.039). Among 69 patients experiencing appropriate shocks 24 deaths (34.8%) occured (p=0.001).
Conclusion: In a large cohort of ICD implanted patients, inappropriate and appropriate shocks were common. The most important finding was the association between appropriate shocks and mortality.
Key Words: Implantable cardioverter-defibrillators; heart failure; cardiac arrhythmias

Uygun ve Uygunsuz ICD Şoklamalarının Latent Klinik Sonuçları

ÖZET

Giriş: Kanıtlanmış faydalarına rağmen, implantable cardioverter defibrillator (ICD) tedavisinin halen bazı dezavantajları bulunmaktadır. Net olarak bilinmektedir ki, uygunsuz ICD şoklamaları mortaliteyi arttırmaktadır ancak randomize kontrollü klinik çalışmalar bize aynı zamanda uygun şoklamaların da mortaliteyi arttırabildiğini göstermiştir. Tedavi edilmediği takdirde ventriküler aritmiler ölümcüldür ve bu durumda ICD tedavisinin yaşam kurtarıcı olduğu bilinmektedir. Bu nedenle Antitachycardial Pacing (ATP) ve şoklama terapilerinin etkilerini ayrı ayrı değerlendirmek uygun olacaktır. Çalışmamızın amacı ICD implante edilmiş olan bir grup hastada uygun ve uygunsuz ICD şoklamalarının oluşturdukları klinik sonuçların saptanmasıdır.
Hastalar ve Yöntem: Retrospektif olarak kliniğimizde Ocak 2003 ve Aralık 2013 tarihleri arasında ICD implante edilmiş olan hastaları tarandı. Ek olarak, bahsi geçen hastalar telefon ile arandı ve sağkalım, tekrarlayan hastaneye yatış gibi parametreler güncellendi. Retrospektif tarama sırasında uygun-uygunsuz şoklamaların varlığı ve mortalite nedenleri not edildi. Şoklama yaşayan hastaların özellikleri dikkatli bir şekilde araştırıldı.
Bulgular: Çalışmaya toplamda 260 hasta dahil edildi. Kırk tanesinde uygunsuz şoklama (uygun şoklama olmaksızın en az bir adet uygunsuz şoklama) ve 69 tanesinde uygun şoklama (uygunsuz şoklama olmaksızın en az bir adet uygun şoklama) saptandı. Retrospektif ortalama takip süresi 49 ay, minimum takip süresi 6 ay idi. Uygunsuz şoklama yaşayan 40 hastadan 13 tanesi (%32,5) exitus oldu (p=0,039). Uygun şoklama yaşayan 69 hastadan 24 tanesi (%34,8) exitus oldu (p=0,001).
Sonuç: Geniş bir ICD implante edilmiş hasta serisinde, uygun ve uygunsuz ICD şoklamaları yaygın olarak izlendi. En önemli bulgu uygun şoklamalar ve mortalite arasında izlenen kuvvetli ilişki idi.
Anahtar Kelimeler: İmplante edilebilir kardiovertör-defibrilatörler; kalp yetmezliği; kardiak aritmiler

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INTRODUCTION

Implantable cardioverter defibrillators (ICDs) are first preferred method of treatment in patients who have risk of sudden cardiac death due to ventricular arrhythmias. Per year in the U.S. alone more than 100.000 ICD implantations are performed[1]. First ICD implantation in man was performed in 1980 by Mirowski et al., since then following the generator and the electrode wire technology innovation, ICD treatment evolved through several development stages[2]. Various primary and secondary prevention trials showed that the life saving effect of ICDs was evident especially in patients suffering from coronary artery disease[3-7]. Despite the clear benefits, ICDs have many disadvantages such as inappropriate shocks, electrode breakage, subsequent technical manufacturing defects and excessive cost.

Despite the proven survival benefits, ICD therapy has still some drawbacks. One of these important drawbacks is the application of shocks to other arrhythmias instead of life-threatening ventricular tachycardia (VT) or ventricular fibrillation (VF). These inappropriate shocks are painful, psychologically disturbing and potentially arrhythmogenic. Recently concerns raised on the relationship between inappropriate ICD shocks and mortality because of the published study of van Rees et al.[3]. The other drawback is that data from SCD-Heft trial and MADIT II trial showed us appropriate shocks are also increasing mortality (respectively HR: 5.68 $p<0.001$ and HR: 3.4 $p<0.001$)[8,9]. Sweeney et al. established that based on their analysis, appropriate shocks also increase heart failure and mortality rates[10]. Left untreated, ventricular arrhythmias are known to be fatal and in this case ICD shock therapy is life-saving so it is appropriate to assess the effects of ATP therapy and shock separately.

The aim of our study is to establish the effects of inappropriate and appropriate shocks in a population of ICD implanted patients. Inappropriate and appropriate shocks were assessed by examining intracardiac electrogram signal frequency, amplitude, electrogram width, auto-gain, auto-threshold analysis, sudden onset, cycle length variability and changes in electrogram morphology. Post mortem analysis was performed if necessary.

PATIENTS and METHODS

Study Design

A retrospective study was designed.

Study Population and Study Protocol

In our research we used patient files from hospital archieve and epicrisis information on Probel® system. The study protocol was approved by local non-invasive ethics committee (2011/35-13). In addition, after retrospective research, patients were called by telephone and 188 of them were able to be reached. Parameters such as survival and rehospitalization were updated with information obtained from themselves or their relatives. Death events were classified into cardiac death (death from sudden arrythmia, progressive heart failure or other cardiac causes) and non-cardiac death (death except from described as cardiac death). We screened 284 patients who had ICD implantation according to the guideline recommendation between January 2003 and December 2013 in our clinic. Among 284 patients screened, we reached 272 patients whose personal and hospital data was sufficient. Twelve of these patients experienced both appropriate and inappropriate shocks, therefore they have been excluded from the study in order to evaluate the effects of appropriate shock or inappropriate shock separately. Remaining 260 patients were included in the study.

Study Variables and Definitions

In our clinic we programmed most of the defibrillators as follows: Ventricular arrhythmias faster than 150 beats/min were initially attempted to be terminated with 2 bursts of anti-tachycardia pacing and, after continuation of the arrhythmia, with defibrillator shocks (zone 1). Ventricular arrhythmias faster than 188 beats/min were initially attempted to be terminated with 3 bursts of anti-tachycardia pacing and, after continuation of the arrhythmia, with defibrillator shocks (zone 2). In the case of a ventricular arrhythmia faster than 210 beats/min, device shocks were the initial therapy (zone 3). Furthermore, atrial arrhythmia detection was set to 150 beats/min with supraventricular tachycardia discriminators enabled. In all devices, stability and sudden onset algorithms were activated to reduce the occurrence of inappropriate shocks. Moreover, additional discriminators were activated in dual-chamber ICDs and cardiac resynchronization therapy defibrillators. During the retrospective follow-up, individual therapy resettings according to the patients' need were established. All defibrillator systems were implanted in the pectoral region.

Among 260 patients, 40 of them experienced inappropriate shocks (defined as at least one inappropriate shock, not any appropriate shocks). Sixty-nine patients experienced appropriate shock (defined as at least one appropriate shock, not any inoppropriate shocks). Retrospective mean follow-up period was 49 months, minimum follow-up period was 6 months. Among aforementioned 260 ICD devices 205 of them were manufactured by St. JUDE (St. Jude Medical; Minnesota, USA) (78.8%), 29 of them were manufactured by BIOTRONIK (BIOTRONIK SE & Co.KG; Berlin, Germany) (11.2%), 13 of them were manufactured by MEDTRONIC (Medtronic; Minnesota, USA) (5%) and 13 of them were manufactured by GUIDANT (Boston Scientific; Massachusetts, USA) (5%). Among 205 St. JUDE® devices, 38 of them had RIATA® lead system (18.6%) and 167 (81.4%) were from another lead series. Hundred eighty eight devices were one-chambered (72.3%), 27 devices were dual-chambered (10.4%) and 45 devices were cardiac resynchronization therapy (CRT) (17.3%) device.

Statistical Analysis

Data obtained from this study was entered into SPSS® (Statistical Package for Social Sciences) 15.0 and statistical

analysis was performed with the same program. Standard deviation, median, minimal and maximal values, class variables, frequencies and percentages were presented. Compliance with the normal distribution of continuous variables was investigated. Independent group comprasions were performed with a non-parametric method, Mann-Whitney U test. Cross tabulations were created and statistical comparisons were performed with the Chi-Square test method. All tests were two-sided, 95% confidence level was performed, identified as alpha error of 0.05. P-value smaller than 0.05 was considered to indicate a statistical significant difference between the groups.

RESULTS

Inappropriate Shock

As can be seen in Table 1, among 260 patients in the research group 40 of them tended to experience inappropriate shock. Among 40 patients experiencing inappropriate shock, 33 of them were male (82.5%) and 7 of them were female (17.5%) (p=0.557). Mean age of the study population 66.3±14.2, mean ejection fraction (EF) value was 35.5±13.5% and mean QRS duration was 117.2±27.3 miliseconds (ms). There was not a significant relationship between inappropriate shock and age, EF and QRS duration (respectively p=0.201, p=0.769, p=0.162). The reason of ICD implantation was secondary prevention in 28 patients (70.0%) and primary prevention in 55 patients (30.0%).

Table 1. Demographic findings of inappropriate shock group analysed with Mann Whitney U and Chi-square test

	Inappropriate Shock (n=40) (%)	p value
Age	66.3±14.2	0.201
Female	17.5	0.557
Diabetes mellitus	20.0	0.379
LVEF	35.5±13.5	0.769
Smoking	42.5	0.818
MI history	60.0	0.434
CABG history	27.5	1.00
QRS duration (msn)	117.2±25.3	0.162
Previous NYHA 3-4	17.5	0.022
History of AF	65.0	<0.001

LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, CABG: Coronary artery bypass grafting, NYHA: New York Heart Association, AF: Atrial fibrillation

As can be seen in Table 2, among 40 patients experiencing inappropriate shocks 13 deaths (32.5%) occured (p=0.039). Among 13 patients who experienced inappropriate shocks and died, 3 patients (23.1%) died due to non-cardiac causes. There was not a statistical significant relationship between inappropriate shocks and exitus cause (p=0.852). Among 40 patients experiencing inappropriate shocks, 7 of them (17.5%) tended to have a previous NYHA class 3-4 history (p=0.022). Among 40 patients experiencing inappropriate shocks, 26 of them (65.0%) tended to have an atrial fibrillation history whereas 14 (35.0%) did not (p<0.001) (Table 1). Previous appropriate shocks also tended to increase the risk of suffering from inappropriate shocks; among 40 patients experiencing inappropriate shocks, 16 of them (60.0%) had a previous appropriate shock history while 24 (40.0%) did not have (p=0.036). Hospitalization due to cardiac causes and all causes increased after experiencing inappropriate shocks (respectively p=0.04 and p<0.001).

Appropriate Shock

As can be seen in Table 3, among 260 patients in the research group 69 of them tended to experience appropriate shocks. Among 69 patients experiencing appropriate shocks 58 of them were male (84.1%) and 11 of them were female (15.9%) (p=0.189). The mean age of these patients was 67.2±15.8, mean ejection fraction (EF) value was 34.5±12.1% ve mean QRS duration was 112.3±24.4 miliseconds (ms). There was not a significant association between inappropriate shock and EF, QRS duration (respectively p=0.819, p=0.699). However, the relationship between appropriate shock and age was significant (p=0.011). The reason of ICD implantation was secondary prevention in 14 patients (20.3%) and primary prevention in 55 patients (79.7%). During a mean follow-up of 49 months, appropriate ICD shock occured in 11.1% and 41.0% of ICD patients in primary and secondary prevention, respectively (p<0.001).

As can be seen in Table 2, among 69 patients experiencing appropriate shocks 24 deaths (34.8%) occured (p=0.001). Among 24 patients who experienced appropriate shocks and died, 5 patients (20.8%) died due to non-cardiac causes. There was not a statistical significant relationship between appropriate shock and exitus cause (p=0.748). Hospitalization due to cardiac causes and all causes increased after experiencing appropriate shock (respectively p=0.003 and p<0.001).

DISCUSSION

One of the wide range analyses in this field was MADIT II trial. Inappropriate shock predictors in MADIT II trial

Table 2. The relationship between exitus, hospitalization causes and shock types analysed with Chi-square test

	Exitus Due to All-Cause (n=53)	Exitus Due to Cardiac Cause (n=39)	Hospitalization Due to all-Cause (n=139)	Hospitalization Due to Cardiac Cause (n=78)
Appropriate Shock (n=69)	p=0.001 (34.7%)	p=0.748 n=19 (27.5%)	p<0.001 n=56 (81.1%)	p=0.003 n=42 (60.8%)
Inappropriate Shock (n=40)	p=0.039 n=13 (32.5%)	p=0.852 n=10 (25.0%)	p<0.001 n=33 (82.5%)	p=0.04 n=28 (70.0%)

were atrial fibrillation history (p<0.01), history of smoking (p=0.03), and history of a previous appropriate shock (p=0.03). A meta-analysis published in 2011 about 1544 ICD implanted patients showed that inappropriate shock predictors were atrial fibrillation history (p<0.01), age <70 (p<0.01), history of a previous appropriate shock (p=0.04), not statin use (p=0.03) and history of a non-ischemic heart disease (p=0.04). Even one inappropriate shock was related to all-cause mortality (p=0.01) [3]. In our study, previous high NYHA class (p=0.005), previous appropriate shock (p=0.036) and atrial fibrillation history (p<0.001) were found as inappropriate shock predictors. Both previous appropriate shock and atrial fibrillation history increasing inappropriate shock rates were similar with findings from MADIT II study. As shown in Table 3, rehospitalization due to cardiac cause tended to increase in patients suffering from inappropriate shock in our study (p=0.003).

MADIT-CRT trial which was published in 2012 demonstrated that patients who experienced appropriate shock were found to have increased risk of mortality compared to patients who never experienced shock (p<0.001), but the same result could not be applied to patients who experienced inappropriate shock[11,12]. The explanation of this situation was the possible increase of abnormal myocardium and subsequent increased risk of mortality. Shock only was not to be accused of mortality. On the other hand, SCD-HeFT trial exhibited that patients experiencing any type of shock (appropriate or inappropriate) had increased all-cause mortality rates than patients experiencing none of these shocks. We also observed that both appropriate and inappropriate shocks were related with increased mortality risk in our retrospective search. Progression of the underlying disease may worsen clinical status and may increase the frequency of appropriate or inappropriate shocks however, we believe that only shocks themselves may deteriorate myocardial functions even when they are appropriate.

In 2010, Sweeney et al. performed a retrospective pool analysis of PainFREE 1-2, EMPIRIC and PREPARE trials. They revealed that ATP therapies did not increase all-cause or cardiac mortality but shocks did increase all-cause mortality. ATP treated fast VT did not increase mortality risk but shock treated VT did. According to Sweeney et al. reducing the number of shocks and treating patients with optimal treatment was essential because these two seemed to reduce mortality risk[4]. Patients who experienced appropriate shock had also increased risk of all-cause mortality in DINAMIT and IRIS trials.

Table 3. Demographic findings of appropriate shock group analysed with Mann Whitney U and Chi-square test

	Appropriate Shock (n=69) (%)	p Value
Age	67.2±15.8	0.011
Female	15.9	0.189
Diabetes mellitus	34.8	0.119
EF value (%)	34.5±12.1	0.819
Smoking	47.8	0.104
MI history	60.9	0.130
CABG history	29.0	0.902
QRS duration (msn)	112.3±24.4	0.699
Previous NYHA 3-4	24.6	0.042

EF: Ejection fraction, MI: Myocardial infarction, CABG: Coronary artery bypass grafting, NYHA: New York Heart Association

Our study revealed that consistent with literatue findings, patients who experienced appropriate shock had increased risk of all-cause mortality. Age and previous NYHA 3-4 history were the predictors of appropriate shocks (respectively p=0.011 and p=0.042). As shown in Table 2, hospitalization due to cardiac cause and all-cause tended to increase in patients suffering from appropriate shock (respectively p=0.003 and p<0.001). It is possible that damaging effect on the myocardium increases as the shock treatment gets stronger. When the shock force becomes less on myocardial cells, the oxidative metabolism and hemodynamic performance are preserved, reducing the possibility of mechanical dysfunction. Experimental studies show that as a result of disruption of mitochondrial function after defibrillation, oxidative metabolism temporarily stops. Free oxygen radicals in the cell come into existence afterwards. By time these free radicals disrupt the balance of ions within the cell then the cell membrane degrades. For this reason unlike expected benefits, shock therapies may not offer real biological benefits in the long term. This is particularly important in patients with severe left ventricular dysfunction. Thus programming ATP levels and shock therapies at lower joules might decrease the potential harms in certain groups of patients and is considered to have a positive impact on endpoints.

Consistent with literature, our study revealed that both inappropriate shocks and appropriate shocks increased all-cause mortality. Comorbidities such as diabetes mellitus, anemia, chronic kidney failure were common in our aged study population and this is the possible reason why all-cause mortality rate in our population was found higher than cardiac mortality rate. We conclude that attention should be paid on the relationship between both types of shocks and mortality risk, regardless of whether it is a consequence of shocks or associated with the progression of underlying disease.

We suggest that ATP therapy should be the first preferred treatment in all patients suffering from ventricular arrhythmia (except ventricular fibrillation which must be terminated by applying shock) especially who have comorbities such as diabetes mellitus, anemia, chronic kidney failure and chronic obstructive pulmonary disease. We also suggest that arrangements of ICD therapy zones and treatment options should be made individually to avoid inappropriate shocks.

Study Limitations

There are some potential limitations of the present study. First of all, retrospectively analized ICD devices were programmed standard initially, but individual settings were established when necessary. The second limitation is that retrospectively analized ICD devices were in different trademarks, thus lead types and software programmes were not standardized. The third limitation is that because of conducting this study in one center, we were not able to reach more number of patients to assess the difference between shock effect and ATP effect seperately.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

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