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ECG Predictors of Appropriate therapy in ICD Implanted Patients for Primary Prevention: A Retrospective Study

Chitresh Chahar[1], Dr Hemlata Sharma[2], Dr Mayank Sarawag[3], Dr Himanshu Mahla[4], Dr Anoop Jain[5] , Dr Varun Kumar Saini[6*]

[1]Consultant Cardiologist, EHCC Hospital, Jaipur, Rajasthan

[2]Associate Professor, Department of Anatomy, Jhalawar Medical College and Attached Hospitals, Jhalawar, Rajasthan

[3]Professor, Department of Medicine, Jhalawar Medical College and Attached Hospitals, Jhalawar, Rajasthan

[4]Assistant Professor, Department of Cardiology, SMS Medical College and Attached Hospitals, Jaipur, Rajasthan

[5]Professor, Department of Cardiology, SMS Medical College and Attached Hospitals, Jaipur,

[6]Associate Professor, Department of Anaesthesiology, RUHS CMS, Jaipur,

Corresponding Author: Varun Kumar Saini, E-mail: docvar4u@gmail.com

Abstract

Purpose: Current ICD recommendations are based on studies which were concluded decades ago. Meanwhile, significant changes have occurred in medical therapy, ICD programming and concomitant comorbidities. As a result incidence of ICD therapies and sudden cardiac death have decreased and significant number of patients undergoing ICD never any appropriate therapy discharged. This study was planned to look for prevalence of appropriate therapy and its predictors.

Methods: Study was cross-sectional with retrospective collection of clinical, ECG and echocardiographic parameters from ICD implanted patients for primary prevention at the time of interrogation, which had to be at least of 12 months from device insertion. Appropriate ICD therapies were ascertained. Patients with indications for CRT, pacing and wide QRS patients as well as the familial cardiomyopathies and channelopathies were excluded. Resting ECG parameters analyzed included QTc, Tpeak-Tend, QRSd, fQRS, early repolarization pattern. To predict appropriate ICD therapies multivariate logistic regression analysis was carried out with p value <0.05 considered significant.

Results: 64 patients were enrolled. 12 patients experienced appropriate therapy while 5 had adverse events related to ICD. QTc, TpTe and fQRS proved to be statistically significant predictors in univariate analysis (p value of 0.04, 0.005, 0.009 respectively). Multivariate analysis yield only 2 significant predictors including fQRS with odds ratio of 5.5 (95% CI 1.4-24, p=0.006) and every 10ms increase in TpTe had odds ratio of 1.74 (95% CI 1.21-11.3, p=0.01). ROC curve analysis yielded a cut-off of 103.5ms for optimal prediction of 75% sensitivity and 73% specificity of appropriate therapy by TpTe.

Conclusion: Overall, difference between benefit versus risk in a contemporary ICD cohort was narrow. Amongst the various parameters studied only TpTe and fQRS proved to be valuable. Larger prospective cohorts need to be studied for better understanding of variables predicting net ICD benefit.

Key words: ICD, primary prevention, SCD, $T_{peak}T_{end}$, fragmented QRS.

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Introduction

Currently guidelines [1,2] recommend ICD insertion for primary prevention in a large population of patients based primarily on the left ventricular ejection fraction. However, ejection fraction has been proved to be both insensitive, as majority of the SCD happen in the persons without low LVEF [3], and non-specific marker of sudden cardiac death, as it also a predictor of total mortality [4,5]. Moreover, in the last two decade the overall mortality as well as SCD in low EF population has decreased significantly as a result of improvement of overall medical care with pharmacotherapies and better awareness playing a significant part [6]. As a result, appropriate shock therapies have decreased from 5.1% shocks per year in the SCD-HEFT trial [7] to 3.6% shocks and ATP per year in the DANISH trial [8]. Overall the story of the primary prevention of SCD has been one of diminishing returns with cost-effectiveness and number needed to treat rising to a point where they can no longer be ignored. Although there have been quite a number of impressive attempts [9, 10] to evaluate the predictors of SCD in general population, none have reached the stage of clinical implication in daily practice, still they have contributed a lot to increase the overall knowledge with regards to the enigma of predicting SCD. We planned this study to retrospectively look for the predictors of appropriate therapy (ATP and shocks) in patients who underwent ICD implantation for primary prevention.

Methods

All the patients who underwent ICD implantation for primary prevention, as dictated by guidelines, and were being followed-up at the cardiology department, SMS medical college were included in the study. Only patients with either ischemic cause or no cause identified during routine evaluation prior to ICD implantation were included for study. Patients with baseline QRS ≥120ms as well as paced rhythm including CRT were excluded, as were the patients with familial cardiomyopathies including arrhythmogenic and hypertrophic cardiomyopathies as well as channelopathies such as brugada, long QT syndrome. The reason for former being non-standardization in ascertaining various ECG parameters versus the focused approach for individual disease being already well established for the latter entities. Also, patients with less than 12 months of duration from ICD implantation to interrogation were not included in the current analysis so as to minimize the bias due to very small period to interrogation in recently implanted patients which included patients with replaced defibrillator due to battery depletion.

The study design was cross-sectional in nature with data pertaining to general clinical characteristics, ECG and echo parameters retrospectively collected during a routine follow-up visit along with device interrogation for presence of therapy discharged including ATP. Inappropriate therapy was not included. Patients who did not have ECG of analyzable quality of the time of implantation one done at later point of time were accepted. Clinical data gathered included demographics, etiology of heart failure, comorbidities, LVEF. Ischemic cardiomyopathy was denoted for patients with low EF (<35%) who either had prior history of MI or underwent prior PCI. Diabetes was defined as patient having already being diagnosed as diabetic and were either on lifestyle modification or medical therapy. Atrial fibrillation was said to be present if the patient had any standard 12 lead resting ECG during follow-up showing atrial fibrillation or being diagnosed with it during follow-up.

Resting ECG parameters analyzed included QTc, Tpeak-Tend, QRSd, fQRS, early repolarization pattern. U waves present after the T wave returned to baseline were not included. Bazette's method was used to correct for rate. Tail method for TpTe duration was default, whereby actual end of the wave is used for calculating duration. Resting ECGs with rates in between 60 and 90 were considered for analysis. fQRs was defined according to

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criteria by Das [11] as the presence of an additional R wave (R') (Fig 1) or notching in the nadir of the S wave, or the presence of 1 R' (fragmentation) in 2 contiguous leads, corresponding to a major coronary artery territory and early repolarization pattern by the consensus paper [12]. Standard 12 lead ECG were examined with digital calipers. Measurements were performed by 2 cardiologists. Inappropriate therapies were not included. All patients in follow-up were prescribed guideline directed medical therapy with Beta-blocker, ACE inhibitor/Angiotensin receptor blocker/ARNI, aldosterone receptor antagonist, as is done under usual care. Compliance evaluation for medications was not undertaken. All patients provided written informed clinical consent and approval from institutional ethics committee was obtained.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median [quartile 1; quartile 3] if not normally distributed. Categorical variables were expressed as absolute numbers with percentage. Normality of the data was assessed with Shapiro-Wilk test. Comparison of continuous variables among groups were done by independent samples t-test if normally distributed and by Mann–Whitney U test if not and categorical variables by Chi-square tests and fisher exact test.

To identify predictors of appropriate ICD therapies univariate logistic regression analysis of clinical data were performed and later multivariate logistic regression analysis was carried out to determine independent predictor variables. Variables were selected by stepwise method from parameters with p values <0.05 in the univariate analysis. Receiver operating characteristic (ROC) curves were constructed to assess cut-off for significant ECG continuous variables to predict optimally the presence of appropriate events in ICD interrogation. A p value <0.05 was considered as significant.

Results

The study population comprised of 64 patients who underwent ICD implantation between the period of January 2014 to March 2019 and met the inclusion criteria. The mean time from ICD implantation to follow-up study visit was 3.8 years. Baseline clinical characteristics are presented in table 1. Briefly, the mean age was 54 years with 17% being females. Study population was approximately equally distributed amongst NYHA class II and III. 58% of the heart failure patients had ischemic etiology. 31% of the population had diabetes mellitus and 14% had documented atrial fibrillation. 12 patients experienced appropriate ICD therapy either in form of ATP or shock, out of these 4 happened in the dilated cardiomyopathy group. Mean age of the group experiencing ICD therapy was approximately 2 years younger than those who did not however the difference was not statistically significant (Table 1). Similarly, mean ejection fraction of the patients who had ICD therapy discharges was 2 points lower but it was too not statistically significant. Both the groups had similar proportion of patient distribution between NYHA II and NYHA III, with no statistical difference. Similarly, etiology of heart failure being non-statistically different between 2 study groups. No statistical difference was observed pertaining to the comorbidities and medications. Amongst the electrocardiogram parameters QRS duration was slightly more prolonged in the event group, however not statistically different. Significant differences were seen only in QTc and TpTe, with both parameters being larger in duration in event group. The mean QTc was 448 in the outcome group compared to 432 in non-therapy group, similar values for TpTe were 112 and 98ms. Fragmented QRS was highly statistically prevalent in the ICD therapy group. Amongst the total 14 patients who had fragmented QRS 4 were in the non-ischemic group. There was no statistically significant difference in prevalence of early repolarization

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variant in the two groups. Next, the parameters which were statistically significant parameters in univariate analysis were analyzed by multivariate logistic regression. Only two parameters of TpTe and fQRS remained of significance in the model (Table 2). QTc became statistically non-significant with odds ratio for the variable ranging from 1 to 1.056 with p value of 0.053. The odds ratio for fQRS predicting appropriate ICD therapy was 5.5 with 95% confidence intervals (CI) ranging from 1.4 to 24 due to the small sample size. While, the odds ratio for every 10ms increase in TpTe variable were 1.74 with 95% CI from 1.21 to 11.30. Next, ROC curve for TpTe was construed (Figure 2). The AUC for the same was 0.768 with p value of 0.004. The best cut-off calculated by Youden's index was 103.5ms with sensitivity of 75% and specificity of 73%. Due to low number of patients and events between the two different heart failure etiology group statistical comparisons were futile and hence were not carried out. Five patients in our cohort experienced side-effects from ICD; one had lead dislocation and another developed local site complication and 3 experienced non-appropriate ICD therapy.

Table 1: Patient groups baseline characteristics who experienced appropriated ICD therapy compared with those who did not.

Parameter	Appropriate ICD therapy		Total	P value
	Yes (n=12)	No (n=52)		
Age	52.6±4.8	54.4±5.6	54±6	0.35
Female sex	2(17%)	9(17%)	11 (17%)	0.66
EF	26±3.4	28±3.8	27±3.7%	0.10
NYHA class Class II Class III	 7(58%) 5(42%)	 27(52%) 25(48%)	 34(53%) 30(47%)	 0.68
Heart failure aetiology Ischemic	 8(66%)	 29(56%)	 37 (58%)	 0.49
Time to interrogation(yrs)	4±1.7	3.7±1.6	3.8±1.6	0.47
Diabetes	2(17%)	18(35%)	20(31%)	0.31
Medications ACEi/ARB/ARNI Beta-blocker MRA	 12(100%) 12(100%) 8(67%)	 50(96%) 49(94%) 31(60%)	 *62(97%)* *61(95%)* *39(61%)*	 0.41 0.21 0.65
Atrial fibrillation	1(8%)	8(15%)	9(14%)	0.46
QRSd	108±7	105±7	106±7	0.30
QTc	448±23	432±26	435±26	0.04
Tp-Te	112±14	98±14	100±15	0.005
fQRS	6(50%)	8(15%)	14(22%)	0.009
J wave	2(17%)	3(6%)	5(8%)	0.23

Table 2: Multivariate logistic regression analysis of covariates to predict the occurrence of appropriate ICD therapy discharge.

Parameter	OR	95% CI	P value
fQRS	5.5	1.4-24	0.006
Tp-Te (every 10ms increase)	1.74	1.21-11.30	0.010

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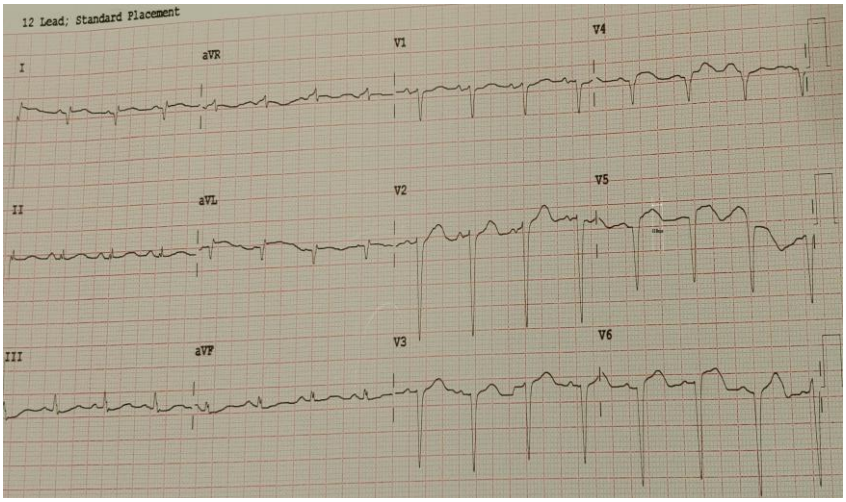

Figure 1: Figure showing fQRS in leads II, III and aVF in a patient with multiple appropriate ICD discharge. This patient had a TpTe duration of 118ms.

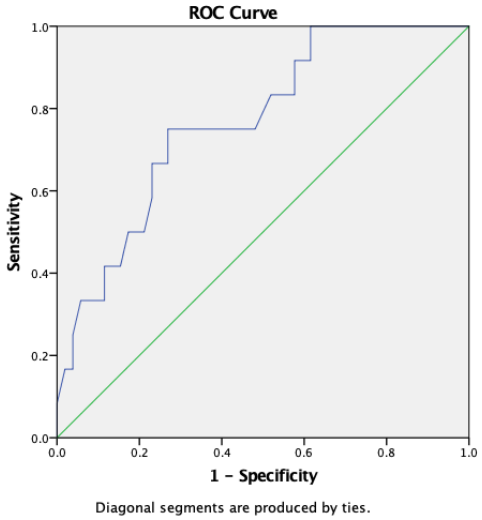

Figure 2: ROC curve for TpTe to predict appropriate ICD therapy discharge.

Table 3:

	AUC	P value	Cut-off	Youden's index	Sensitivity	Specificity
TpTe	0.768(0.629-0.906)	0.004	103.5	0.481	75%	73%

Discussion

We observed, in our study of 64 patients who had undergone ICD implantation for primary prevention, that the overall rate of appropriate therapies provided by ICD in such population group was quite low. We witnessed that in our patient group with time to interrogation from implant ranging from one to six years only 12 had appropriate utilization of their ICD out of which 8 happened in ischemic cardiomyopathy group. In an attempt to look for the predictors of successful VT-VF occurrence only two proved significant in a multivariate model i.e. presence of fragmented QRS and TpTe interval. Other variables like QTc, demographics, comorbidities were not significant predictors in our study group.

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Current primary prevention recommendations for ICD are based mainly on MADIT-II trial [13] which included CAD patients and SCD-HeFT trial [7] which included mixed patient population. These trials concluded in 2002 and 2005 respectively with recruitment happening at an even earlier period of time. The major concern with these is as the subsequent years showed phenomenal improvement in medical therapy and overall care of such patients group, mortality rates and appropriate ICD therapy rates have drastically gone down [6], to an extent that there have been widespread attempts to question the current overall cost-effective of these therapies. Even the patient population has changed with increasing extent of comorbidities being present in the patient population today which have an effect on the proportional benefit from ICD on total mortality. In addition, the programming of ICD has also undergone massive changes with improvement in reduction of inappropriate shocks and improvement in mortality as shown in MADIT-RIT trial [14], none of which was deployed in the landmark trials. The most recent trial, DANISH trial [8], concluded in 2016, evaluating the effect of ICD in non-ischemic cardiomyopathies found no overall benefit of ICD on all-cause mortality. This trial had one of the longest follow-ups of 8 years amongst the landmark trials. There have been attempts to generate risk scores to predict sudden arrhythmic deaths in general population [9,10]. We utilized a different approach as we tried to analyze the factors which predict appropriate ICD therapies in patients who underwent device implantation according to current guidelines as quite a significant number of patients in primary prevention trial never had their ICD provide a therapy. We attempted to look for factors under 4 broad category i.e the demographics, heart failure stage, comorbidities and ECG parameters. Surprisingly, the two groups did not differ statistically with regards to etiology of heart failure although numerically two thirds of the events happened in ischemic group. D. S. Lee et al [15] analyzing the appropriate shocks and deaths in a large ICD implanted population developed a point score, in which lower age, male sex and presence of atrial fibrillation predicted higher incidence of shock. They observed incidence for shock decreased the farther the QRS duration got from 130ms, both below and above. Teodorescu et al [16] showed that prolonged depolarization predicted SCD in CAD patients independent of the effects of QTc. We on the contrary did not find any significant correlation of ICD therapies with QRSd, nor with regards to age, sex and atrial fibrillation. This difference may have been due to our relatively younger overall population and very less numbers of patients belonging to female sex. Also, our decision to exclude patient with wider QRS and CRT, so as to study purely the benefit accrued from ICD, might have played a role in us observing no difference as pertaining to the QRS duration. Zareba et al [17] studying the MADIT II population showed that NYHA class 2 and 3 as well as the subgroups division by EF below 30% had similar incidence of appropriate shocks. We too saw same relationship with approximately equal distribution of ICD therapies amongst the 2 classes of NYHA as well no correlation with EF. Ruwald et al [18] examining the Danish nationwide clinical registers observed that incidence of appropriate ICD therapy remained approximately same no matter the number of comorbidities including atrial fibrillation, diabetes afflicting the patient. We too observed similar findings. Watanabe et al [19] determined in their study the importance of TpTe as a marker of transmural dispersion of repolarization in a group of heart disease patients. They studied patients who could be induced VT-VF in lab and further followed them up. However, they employed correction of TpTe similar to Bazette's hence our results cannot be compared directly. Panikkath et al [20] retrospectively analyzing available ECG in a large group of persons in general population who died with SCD demonstrated that TpTe was an independent predictor and superior to the QTc. The cases in their study had mean of 89 and control 76ms. Also, odds ratio for SCD for every 12ms increase came in their study to be in-between to 2 to 6 times. Aro et al [21] combined all the above ECG risk markers into an ECG risk score which included heart rate >75, LVH, delayed QRS transition, wide frontal QRS-T

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angle >90, prolonged QTc >450 and prolonged TpTe >89ms. They externally validated it in ARIC study and was shown to be particularly effective for LVEF > 35%. We hypothesize that because we were studying a sicker population of lower EF and multiple comorbidities our cutoff for TpTe was observed to be higher. Apiyasawat et al [22] followed a cohort of 107 ICD implanted patients for approximately 2 years and demonstrated fQRS to be a significant predictor for appropriate therapy with hazard ratio of 5.3. The overall prevalence of fQRS in their study was 39% compared to 22% in ours. However, they included patients with wide QRS. Das et al [23] too found fQRS to be significant predictor of events and time to event with prevalence of 23% in their study. Both the groups studied ICD implanted patients regardless of indications. Forleo et al [24] studied only primary prophylaxis patients and reached to a different conclusion of non-significance of fQRS. fQRS has been shown to correlate with presence of fibrosis hence tying up with the SCD mechanistically [11]. Das et al even found the sensitivity of fQRS to be better than that of q waves for detecting scar and the importance is even magnified considering that timely treatment and increased uptake of primary PCI has reduced incidence of q waves to all time low. Regarding ERP, we did not find any correlation with ICD therapy, which is not surprising considering the small number with such pattern in our study. Moreover, consensus on how to define ERP so as to encapsulate the group with highest risk has not born to fruition as of yet, with a carefully conducted cohort study showing large number of healthy adults showing features overlapping with ones which over the years were thought to associated with malignant form, namely the amplitude of J wave and the straight or descending type of ST elevation [25].

Limitations

Current study was a single center based observational study carried out with limited number of eligible patients. Patient who underwent procedure at the institute but were not in follow-up here could not be included. Furthermore, active attempts for the same could not be pursued due to limited nature of information recording done at the time of procedure. Also due to time duration over which ICD implanted patients were included in study, there was variable time duration from implantation to interrogation for individual patients. We also did not include in our study methodology advanced T wave analysis such as micro T wave alternans or periodic repolarization dynamics and hence the autonomic system involvement in causing sudden cardiac arrhythmic deaths. Despite the favorable research results by various groups these specialized analysis techniques are not available commonly. Also due to retrospective nature of our study we were unable to study the impact of PVC burden on Holter as well as advanced imaging technologies such as late gadolinium enhancement on appropriate ICD therapy discharge prediction. Finally, even able to successfully predict ICD appropriate therapy does not translate to automatic proven clinical benefit of ICD, as the DANISH trial despite showing significantly lower sudden arrhythmic cardiac death was unable to show any impact on overall mortality, which conceivably depends on relative balance of non-cardiac death or cardiac sudden death due to non-shockable rhythm versus sudden cardiac death due to arrhythmia which can be treated by ICD, latter contributing to just a part of the multiple competing risks.

Conclusion

In a contemporary group of 64 ICD implanted patients for primary prevention followed up for mean 3.4 years up to the time of interrogation we observed rates of appropriate ICD therapy to be approximately 19% with only significant predictors being TpTe interval and fQRS. Prospective trial involving large number of patients need to be carried out to further ascertain the relative importance of these two factors.

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