

## Associated factors with the occurrence of inappropriate shocks among admitted patients with ischemic cardiomyopathy

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### Original Article

#### Abstract

**BACKGROUND:** It has been previously shown that Implantable Cardioverter-Defibrillator (ICD) shocks are associated with subsequent increased mortality risk in patients with heart failure. We designed this study to assess the factors related to ICD shocks in patients with ischemic cardiomyopathy (ICM).

**METHODS:** Eighty consecutive patients with ICM underwent primary or secondary preventive ICD implantation, and experienced shocks were recruited in this cross-sectional study between March 2018 and March 2019. Patients were grouped based on the presence of appropriate or inappropriate ICD therapy. Data on demographic, clinical, laboratory and medications of eligible patients were assessed to identify ICD shocks related factors with univariate and multiple adjusted models.

**RESULTS:** The mean age of the total population was  $65.4 \pm 9.8$  years (males: 86.3%). Eleven patients (13.7%) experienced inappropriate shocks. The presence of sinus tachycardia was 7.38 (95% confidence interval (CI): 1.78-30.56,  $P= 0.006$ ), which was associated with higher likelihood of inappropriate shock occurrence. Moreover, patients with atrial fibrillation (AF) had significantly elevated odds of inappropriate shock frequency (odds ratio (OR): 4.32, 95% CI: 1.15-16.13,  $P= 0.02$ ).

**CONCLUSION:** Our findings indicate that the presence of sinus tachycardia and prior AF could significantly increase the likelihood of inappropriate shock frequency among patients with ICM using ICDs. Further large-scale studies are required to prove our outcomes.

**Keywords:** Defibrillators; Implantable; Myocardial Ischemia; Inappropriate Shocks; Appropriate Shocks

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#### List of abbreviations

- ICM: Ischemic Cardiomyopathy
- ICD: Implantable Cardioverter-Defibrillators
- AF: Atrial Fibrillation
- NYHA: New York Heart Association
- LVEF: Left Ventricular Ejection Fraction
- SCD: Sudden Cardiac Death
- VT: Ventricular Tachycardia
- VF: Ventricular Fibrillation
- BMI: Body Mass Index
- HTN: Hypertension
- DM: Diabetes Mellitus
- ACEIs: Angiotensin-Converting Enzyme Inhibitors
- ARBs: Angiotensin Receptor Blockers
- HR: Heart Rate
- GFR: Glomerular Filtration Rates
- ECG: Electrocardiogram
- bpm: beats per minute

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- OR: Odds Ratio
- IUMS: Isfahan University of Medical Sciences
- SPSS: Statistical Package for Social Sciences
- ATP: Anti-Tachycardia Pacing
- CI: Confidence Interval
- MADIT-II: Multicenter Automatic Defibrillator Implantation Trial
- MADIT RIT: Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy
- NSR: Normal Sinus Rhythm
- AV: Atrioventricular
- CKD: Chronic Kidney Disease

## Introduction

Patients suffering from ischemic cardiomyopathy (ICM) are at increased risk of developing ventricular arrhythmias.<sup>1</sup> Implantable cardioverter-defibrillators (ICDs) have been announced to be effective for treatment and recommended by both U.S and European guidelines as the first modality to reduce the risk of sudden cardiac death and all-cause mortality in patients with either ischemic or non-ischemic heart failure with more substantial evidence for the former.<sup>2-4</sup> Several underlying factors have been proposed to cause inappropriate shocks among individuals with ICDs, including rapid supraventricular tachycardia, atrial fibrillation (AF) and abnormal sensing.<sup>5</sup> Previous studies have shown that ICD shocks, regardless of whether shocks are appropriate or inappropriate, are associated with higher mortality risk in the long term.<sup>6-7</sup> Besides, ICD shocks can cause significant psychological effects such as anxiety or depression, which can worsen patients' quality of life.<sup>8</sup> It has been reported that approximately one-third of patients would receive a shock from their ICDs within five years of implantation, and 18% of these are categorized as inappropriate ones.<sup>9</sup> Therefore, proper management of ICD shocks and maximal effort to prevent ventricular or supraventricular tachyarrhythmia could be essential in managing these patients. Previous studies revealed that numerous parameters such as gender, New York Heart Association (NYHA) class, renal diseases, beta-blocker or antiarrhythmic drug usages, electrolyte imbalance and left ventricular ejection fraction (LVEF) were predictors of ICD shocks with controversial results.<sup>8</sup> Thus, better identification of probable factors associated with ICD shocks seems necessary to reduce their occurrence.

In the present study, we aimed to assess the factors associated with the frequency of inappropriate shock among Iranian patients suffering from ICM.

## Materials and Methods

This observational cross-sectional single-center study was done from March 2018 to March 2019 in a public tertiary heart center located in Isfahan, Iran (Chamran hospital). Any individuals aged at least 18 years suffering from ICM with reduced LVEF irrespective of NYHA class with implantation of ICD for either primary or secondary sudden cardiac death (SCD) who experienced either appropriate or inappropriate shocks during the study period were eligible for recruitment in this study. ICM was defined as a reduced LVEF associated with at least one of the followings: more than 70% stenosis in one or more of the major epicardial coronary vessels, a history of coronary intervention including angioplasty and/or bypass surgery, stress-induced perfusion abnormalities detected by nuclear scintigraphy indicating myocardial ischemia or a history of transmural myocardial infarction.<sup>11</sup> Patients with heart failure caused by myocarditis, primary valvular disease, restrictive or hypertrophic cardiomyopathies and other non-ischemic cardiomyopathies were excluded from our study.

The primary endpoint ICD therapy was defined as an appropriate or inappropriate shock occurrence, and we included those with these aforementioned shock types. An appropriate one was considered according to the cardiac electrophysiologist's decision based on the analysis of intra-cardiac electrograms and the shock itself. All patients were evaluated after the occurrence of the shocks, regardless of their types. In terms of inappropriate shock incidence, device alteration, including complete device analysis and morphology template assessment, and device parameter alteration for ventricular tachycardia (VT) or ventricular fibrillation (VF) detection was performed by a skillful electrophysiologist for prevention of further attacks accordingly. Moreover, any other previously approved effective clinical or para-clinical factors on inappropriate shock incidence were corrected individually or with either medical or ablation methods.

Data on demographic features, including age, gender (male/female), smoking history and body mass index (BMI), were assessed from the questionnaire. The patients were also assessed for the previous history of hypertension (HTN), diabetes mellitus (DM) and persistent AF. We collected further information on drug usages, including amiodarone, mexiletine, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Laboratory data, including sodium, potassium, magnesium, calcium and albumin, were obtained at the admission time. We further assessed

**Table 1.** General and laboratory characteristics of the study population according to shock types

Variables	Total (n=80)	Shock type		P *
		Appropriate (n=69)	Inappropriate (n=11)	
Age(years)	65.4±9.7	65.5±9.9	64.7±8.7	0.79
Males (%)	69(86.3)	60(87)	9(81.8)	0.64
BMI(kg/m <sup>2</sup> )	25.86±3.53	26.06±3.55	24.64±3.26	0.21
Heart rate (beats per minute)	80.81±22.48	78.12±20.37	97.73±28.45	0.006
Sinus tachycardia (%)	12(15)	7(10.1)	5(45.5)	0.002
Prior Atrial fibrillation (%)	21(26.3)	15(21.7)	6(54.5)	0.02
Diabetes mellitus (%)	14(17.5)	12(17.4)	2(18.2)	0.94
Hypertension (%)	41(51.3)	35(50.7)	6(54.5)	0.81
Smoking status (%)	22(27.5)	18(26.1)	4(36.4)	0.47
Mexiletine usage (%)	10(12.5)	10(14.5)	0(0)	0.17
Amiodarone usage (%)	27(33.8)	24(34.8)	3(27.3)	0.62
Beta blocker usage (%)	51(63.8)	46(66.7)	5(45.5)	0.17
ACEI/ARB usage (%)	48(60)	41(59.4)	7(63.6)	0.79
GFR (ml/min/1.73m <sup>2</sup> )	57.45±16.97	57.33±17.33	58.18±15.19	0.87
Left ventricular ejection fraction (%)	20.25±6.41	19.93±6.28	22.27±7.19	0.26
Sodium (mEq/l)	137.58±3.66	137.61±3.63	137.36±4	0.83
Potassium (mEq/l)	4.09±0.51	4.06±0.53	4.24±0.40	0.28
Magnesium (mg/dl)	2.08±0.27	2.09±0.28	2.03±0.20	0.51
Calcium (mg/dl)	9.25±0.71	9.21±0.65	9.45±1.02	0.30
Albumin (g/dl)	4.02±0.44	3.99±0.46	4.20±0.30	0.15
QRS duration (msec)	129.13±29.04	130.29±29.80	121.82±23.58	0.37
Abnormal QRS duration (%)	57(71.3)	51(73.9)	6 (54.5)	0.18

BMI: body mass index, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, GFR: glomerular filtration rate

\*: P-values resulted from chi-square test and independent t test for categorical and continuous variables, respectively.

data on heart rate (HR), LVEF and glomerular filtration rates (GFR) at admission. QRS duration details were gathered from surface electrocardiogram (ECG) (< 120 msec or ≥ 120 msec).<sup>12</sup>

**Statistical analysis:** Continuous and categorical variables were reported as mean ± standard deviation or frequency (percentage). Independent t-test and chi-square test were used for evaluating the differences between shock types based on numerical and nominal variables, respectively. The researchers calculated the odds ratio (OR) of inappropriate shock incidence with pre-defined variables. The study protocol was approved by the Institutional Review Board of Isfahan University of Medical Sciences (IUMS) (IR.MUI.MED.REC.1397.034). All the patients were informed about study objects, and written informed consent was signed by all of them. The Statistical Package for Social Sciences (SPSS Inc., version 22.0, Chicago, IL, USA) was used to compile and analyze data. The results were

considered statistically significant when P-values were less than 0.05.

## Results

The study population consisted of 80 patients with ICM who received the ICD shock during the study. The mean age of the total population was 65.4 ± 9.8 years, and 86.3% were males. The prevalence of inappropriate shocks was 13.7%, and paroxysmal supraventricular tachycardia (36.4%), AF (36.4%), and atrial tachycardia (27.2%) were the culprits for the occurrence of this shock type. Medtronic and St Jude Medical devices were the models of ICDs in admitted patients. In addition, 46 (57.5%) and 34 (42.5%) of participants had single and dual chambers ICDs, respectively. Different discrimination algorithms were used based on the presence/absence of single or dual-chamber ICDs, including interval stability, the suddenness of onset, electrogram morphology, P: R pattern, AV association and atrial and ventricular

**Table 2.** Odds ratio of inappropriate shock incidence among study population

Variables	Odds ratio	95% confidence interval	P
Age	1.009	0.94-1.07	0.79
Males	1.48	0.27-7.98	0.64
BMI	1.12	0.93-1.36	0.21
Heart rate	0.96	0.94-0.99	0.01
Sinus tachycardia	7.38	1.78-30.56	0.006
Prior Atrial fibrillation	4.32	1.15-16.13	0.02
Diabetes mellitus	1.05	0.20-5.51	0.94
Hypertension	1.16	0.32-4.18	0.81
Smoking status	1.61	0.42-6.18	0.48
Amiodarone usage	0.70	0.17-2.89	0.62
Beta blocker usage	2.40	0.66-8.70	0.18
ACEI/ARB usage	0.83	0.22-3.12	0.79
GFR	0.99	0.96-1.03	0.87
Left ventricular ejection fraction	0.94	0.85-1.04	0.26
Sodium	1.01	0.85-1.21	0.83
Potassium	0.49	0.13-1.78	0.28
Magnesium	2.19	0.21-22.48	0.50
Calcium	0.63	0.26-1.51	0.30
Albumin	0.30	0.06-1.53	0.15
QRS duration	0.42	0.11-1.55	0.19

BMI: body mass index, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, GFR: glomerular filtration rate

rates comparison. Most patients' programming details were the followings: VT zone: 170-200 bpm, VF zone:  $\geq 200$  bpm, detection duration: 9-12 seconds (30-40 intervals), and VT detection  $>12$  seconds. Anti-tachycardia pacing (ATP) for both VT and VF zone were the followings: VT zone: 2 ATP burst, 20 msec scan, 8 pulses, 85-88% RR interval, VF zone: during the charge or before charging, 8 pulses, 85-88% RR interval.

Table 1 showed the general characteristics, laboratory profile, and medication history of participants. The patients who experienced inappropriate shock had significantly higher mean HR than individuals with appropriate shocks ( $97.73 \pm 28.45$  vs.  $78.12 \pm 20.37$  beats per minute,  $P= 0.006$ ). Individuals experienced inappropriate shocks had higher prevalence of sinus tachycardia in comparison to those with appropriate ones (45.5% vs. 10.1%,  $P= 0.002$ ). Twenty-one (26.3%) patients had a history of prior AF, in which most of them were attributed to an inappropriate shock group (54.5% vs. 21.7%,  $P= 0.02$ ). There was no significant difference between groups regarding other pre-defined variables, including medication consumption, electrolyte levels or QRS duration.

Table 2 represented OR of inappropriate shock occurrence. Our findings revealed that in comparison

to patients with no prior AF history, individuals with this disorder had 4.32 (95% confidence interval (CI): 1.15-16.13,  $P= 0.02$ ) times increased likelihood of experiencing an inappropriate shock. Participants with sinus tachycardia had 7.38 (95% CI: 1.78-30.56,  $P= 0.006$ ) times higher likelihood of inappropriate shock occurrence rather than subjects with normal HRs.

## Discussion

In the present study, patients with ICM were assessed to identify factors associated with the occurrence of inappropriate ICD shocks. Our findings revealed that 86.3% of the patients experienced appropriate shocks, and 13.7% of them had inappropriate shocks. Device setting for proper noise detection due to aberrant signals originating from external environment done by VF therapeutic shock delivery for up to 45 seconds and automatic algorithm resulted in long VF detection to 30/40 intervals explain this lower percentage of inappropriate shock occurrence. However, some other factors, including rapid ventricular response and aberrancy during AF leading to morphology alteration, might be considered some discriminators failure for appropriate rhythm diagnosis. Our findings showed that the presence of prior AF and sinus tachycardia



was significantly associated with the occurrence of inappropriate shocks.

AF is a frequently found supraventricular arrhythmia in patients with ICDs. Some studies have shown that AF independently increases the risk of inappropriate shocks in these patients.<sup>7,12,13</sup> AF was the more common cause of inappropriate shock therapy in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial).<sup>14</sup> On the other hand, the MADIT RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy) trial showed a reduction in all-cause mortality and inappropriate shocks by programming ICD shocks for HRs of at least 200 beats per minute.<sup>15</sup> However, in a subgroup of the MADIT RIT, the inappropriate shocks were still significantly higher in patients with atrial arrhythmias than patients with normal sinus rhythm (NSR).<sup>16</sup> It has been reported that in a cohort of 73 patients with ICDs undergoing AF ablation, the incidence of inappropriate shocks was significantly lower after the procedure.<sup>17</sup> However, whether the benefits of ICD in patients with AF would be similar to those with NSR is not well established. Further studies are needed to clarify the possible mechanisms underlying the harmful effects of AF in these patients.

Controlled resting heart rate ranges from 60 bpm to 80 bpm have been recommended for patients with heart failure.<sup>18</sup> A slower ventricular rate may have a lower risk of reaching the ICD therapy zone.<sup>19</sup> Our study showed that the mean of HRs in patients with inappropriate shocks was significantly higher than those of patients with appropriate ones. We found that inappropriate shocks' incidences increased significantly with raised HR (OR: 7.38, 95% CI: 1.78-30.56, P= 0.006). It has been shown that increased HR could be considered as a risk factor for cardiovascular death in patients with chronic heart failure treated with standard treatment.<sup>20</sup> Therefore, medications helping HR control, including beta-blockers, might be positively influential in improving survival in patients with chronic heart failure.

Besides, drug therapy can decrease the risk of inappropriate shock incidences. Beta-blockers can decrease the ventricular rates in AF and reducing the risk of HR rising into the ICD therapy zone. Similarly, these drugs reduce the maximum sinus rates leading to risk reduction of ICDs shocks by sinus tachycardia. Finally, beta-blockers may prevent supraventricular tachycardia such as atrioventricular (AV) node reentry tachycardia, and ectopic atrial tachycardia reduces the risk.<sup>21</sup> Our study showed there was not a significant association between beta-blockers consumption and inappropriate shock frequency. Moreover, beta-blockers and ACEIs/

ARBs were used by only 63.8% and 60% of the patients, respectively, which were lower than current recommendations for treating patients with heart failure.<sup>22</sup>

In the era of QRS duration, GFR, LVEF, potassium, and magnesium level, our study failed to demonstrate any statistically significant difference between appropriate and inappropriate ICD shocks. Our study was in accordance with the study done by *Ghanbarabadi et al.* They found that QRS duration was not a predictor for increased risk of inappropriate shocks.<sup>23</sup> Furthermore, *Bansal et al.* evaluated the associations between chronic kidney disease (CKD) and device shock therapy (inappropriate versus appropriate). They reported no significant association between kidney function and appropriateness of ICD shocks.<sup>24</sup> Potential triggering factors such as electrolyte abnormalities are rare causes of inappropriate ICD shocks and might play roles to provoke arrhythmic activities.<sup>25</sup> In our study, no statistically significant association was found between potassium and magnesium levels and ICD shocks' appropriateness. Some limitations are attributed to the current study. The main one is the study's design, which disables us for investigating the cause-and-effect relation between variables, and the expansion of data should be done with caution. We did not collect data of patients with ICDs who experienced no shocks, and consequently, we were not able to calculate the incidence of either appropriate or inappropriate shocks. Due to the quite low sample size, we were unable to use multivariable adjusted models and the generalizability of our outcomes might be negatively affected. The low prevalence of beta-blocker usage might play a role in our deductions from the outcomes. Furthermore, we did not follow patients for the probable further occurrence of shocks and analyzing the data.

## Conclusion

Our findings indicate that the presence of prior AF and sinus tachycardia could significantly increase the likelihood of inappropriate shock incidence among patients with ICM using ICDs. Further large-scale studies are required to prove our outcomes.

## Declarations

*Ethical approval and consent to participate:* All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (IR.MUI.MED.REC.1397.034).

### Consent for publication

Informed consent had been obtained from each patient to publish this material.

### Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available due to confidential issues but are available from the corresponding author on reasonable request.

### Competing interests

None of the authors had any personal or financial conflicts of interest.

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### Authors contribution

M. M., D. S., J. S.: Study concept and design. M. M., D. S.: Acquisition of data. M. V.: Analysis and interpretation of data. D. S., M. V., M. M., J. S.: Drafting of the manuscript. M. V., D. S.: Critical revision of the manuscript for valuable intellectual content. M. V.: Statistical analysis. M. M., D. S.: Administrative, technical, and material support. D. S., J. S.: Supervision.

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