Original Research

Inducibility of Ventricular Arrhythmia and Tachyarrhythmia Recurrences in Patients with Implantable Defibrillator

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Introduction: We evaluated the potential ability of the electrophysiological (EP) inducibility of ventricular arrhythmias to predict the likelihood of appropriate ICD intervention over the long-term in ischemic and non-ischemic patients with current primary prevention indications for ICD implantation.

Methods: Between 2006 and 2008, 206 consecutive heart failure patients who were candidates for ICD implantation for the primary prevention of sudden cardiac death according to standard indications underwent EP testing, usually on ICD implantation.

Results: On EP testing, 15 (7%) patients had inducible monomorphic ventricular tachycardia (VT) and 14 (7%) ventricular fibrillation (VF). Over 24 months, 64 (31%) patients received appropriate ICD therapies: 51 (25%) for VT and 16 (8%) for VF. The time to the first appropriate ICD therapy trended to be shorter in the group of patients who were inducible on EP testing (p=0.072). Among patients receiving appropriate therapies, the median number of arrhythmic episodes was 2, and the proportion of patients with ≥2 treated arrhythmic episodes was higher in the group of inducible patients (34% versus 14%, p=0.005). On multivariate analysis, inducibility proved to be an independent predictor of frequent (≥2) arrhythmic episodes, as did a history of coronary artery bypass grafting. Moreover, patients with ≥2 treated arrhythmic episodes showed higher mortality (log-rank test, p=0.042).

Conclusion: Patients with inducibility of VT or VF are more likely to experience frequent appropriate ICD therapies during follow up.

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Several studies of the primary prevention of sudden cardiac death (SCD) have confirmed that implantable cardioverter defibrillators (ICD) improve the survival of patients with ischemic and non-ischemic dilated cardiomyopathy, showing a 23-59% reduction in the risk of death in ICD recipients.[1-5]

Electrophysiological (EP) testing has been evaluated in ischemic cardiomyopathy and was found to be predictive of arrhythmic events.[6,7] However, prior studies in patients with non-ischemic cardiomyopathy have suggested that EP inducibility may be of limited value in identifying patients at increased risk of arrhythmic events.[8,9]

In this study, we sought to evaluate the potential ability of EP inducibility of ventricular arrhythmias to predict the likelihood of appropriate ICD intervention over the long term in ischemic and non-ischemic patients with current primary prevention indications for ICD implantation.

Methods

Study population

From 2006 to 2008, this prospective multicenter study enrolled consecutive adult patients with heart failure who presented at the participating centers for ICD implantation for the primary prevention of SCD according to standard indications.[10] Informed consent was obtained from all patients. The principles outlined in the Declaration of Helsinki were followed.

Baseline evaluation included demographics and medical history, clinical examination, 12-lead electrocardiogram, estimation of New York Heart Association (NYHA) functional class and assessment of left ventricular ejection fraction (LVEF).

Defibrillator implantation and device programming

Devices and pacing leads (Boston Scientific Inc., Natick, MA, USA) were implanted using standard techniques. All devices were programmed with two arrhythmia detection zones: ventricular tachycardia (VT) (160-200 beats/min) and ventricular fibrillation (VF) (>200 beats/min). An arrhythmic episode was detected when 8 of the last 10 intervals fell within the detection zone. An additional period of 5 seconds in the VT zone and 1 second in the VF zone was programmed for confirmation of the detection before therapy delivery. Non-sustained VT was defined as ventricular arrhythmia lasting 3 beats or more and terminating before the delivery of device therapy. Defibrillators were programmed to deliver anti-tachycardia pacing (3 bursts of 8-9-10 pulses coupling at 81% of the tachycardia cycle, with a decrement of 8 ms) for VT termination,[10] possibly followed by a 17 J shock and then 4 shocks at 31 J. In the VF zone, 8 shocks at 31 J were programmed.

EP Testing for Inducibility

On implantation, patients underwent noninvasive EP testing. The stimulation protocol, delivered at one right ventricular site through the ICD, entailed pacing cycle trains of 600 ms and 400 ms followed by up to three extra stimuli at coupling intervals not less than 200 ms. A sustained arrhythmia was defined *a priori* as one treated by the device. The EP study endpoints were induction of one episode of sustained ventricular arrhythmia or completion of the protocol. On completion of the EP study, a defibrillation threshold test was performed. VF induced for the purpose of defibrillation threshold testing did not meet the definition of inducibility.

Follow up

Pharmacological treatments were based on clinical evaluation by the attending physicians.

We collected and evaluated arrhythmias and device therapies for at least 24 months and recorded survival status for more than 2 years. The information from the ICD was downloaded at the time of implantation, every 6 months thereafter, and after ICD shocks were delivered. All electrograms showing non-sustained VT or events that triggered ICD therapies were assigned to two blinded independent expert electrophysiologists, who classified the events according to predetermined diagnostic criteria for cardiac rhythms. To discriminate ventricular from supraventricular rhythms, we analyzed onset characteristics, electrograms recorded before detection of the arrhythmia and after delivery of the shock, and plots of RR intervals. Therapies were considered to be appropriate if the triggering rhythm was determined to be VF or VT. Mortality data were obtained by means of hospital file review or direct telephone contact.

Statistical analysis

Continuous data are expressed as mean ± standard deviation. Categorical data are expressed as percentages. Differences between mean data were compared by means of a t-test for Gaussian variables, and by the Mann–Whitney non-parametric test for non-Gaussian variables. Differences in proportions were compared by means of chi-square analysis or Fisher's exact test, as appropriate. Arrhythmia and mortality rates were summarized by constructing Kaplan–Meier curves, and the distributions of the groups were compared by means of a log-rank test. Univariate binary logistic regression analysis was used to analyze possible predictors of arrhythmia recurrence. All variables associated with a p-value <0.20 were considered for multivariate binary logistic regression analysis. A p-value <0.05 was considered significant for all tests. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Study population and electrophysiological inducibility. A total of 206 consecutive heart failure patients

with an indication for ICD were scheduled for implantation, and were enrolled in the present study. On EP testing, 15 (7%) patients had inducible monomorphic VT, 14 (7%) had inducible VF, and 18 (9%) were induced into non-sustained VT which did not require ICD therapies. Table 1 shows the baseline clinical variables of inducible and non-inducible patients. Only the prevalence of ischemic heart disease was significantly higher in patients with arrhythmia inducibility during EP testing.

Follow up

Over 24 months, 64 (31%) patients received appropriate ICD therapies and 27 (13%) inappropriate therapies. Among patients receiving appropriate therapies, 51 (25%) had VT and 16 (8%) VF. Among patients receiving inappropriate therapies, 22 (11%) received anti-tachycardia pacing and 16 (8%) received a shock. In addition, the ICD detected non-sustained VT in 157 (76%) patients. The Kaplan–Meier analysis showed a trend toward shorter time to first appropriate ICD therapy (p=0.072) in the group of patients inducible on EP testing (Figure 1). The numbers of patients who received one or more device therapies for VT or VF, grouped by inducibility on EP testing, are presented in Figure 2. Among patients receiving appropriate therapies, the median number of arrhythmic episodes was 2 (25th-75th percentile: 1-4). The proportion of patients with 2 or more treated arrhythmic episodes during follow up was significantly higher in the group of inducible patients (10 out of 29) than among non-inducible patients on EP testing (24 out of 177; 34% versus 14%, p=0.005).

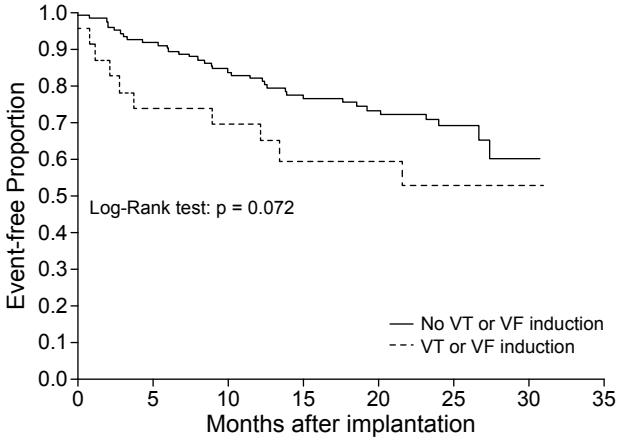

Figure 1. Kaplan–Meier estimates of time to first appropriate ICD therapy.

Baseline parameters were evaluated for their

Table 1. Demographics and baseline clinical parameters of the study population.

Parameter	All (n=206)	Inducible patients (n=29)	Non-inducible patients (n=177)	p-value
Male sex, n (%)	158 (77)	24 (83)	134 (76)	0.405
Age, years	68 ± 10	66 ± 9	68 ± 10	0.202
Ischemic etiology, n (%)	135 (66)	24 (83)	111 (63)	0.035
NYHA, n (%):				0.841
Class I	2 (1)	0 (0)	2 (1)	
Class II	91 (44)	13 (45)	78 (44)	
Class III	110 (53)	16 (55)	94 (53)	
Class IV	3 (1)	0 (0)	3 (2)	
LV ejection fraction, %	28 ± 5	29 ± 5	28 ± 5	0.664
QRS duration, ms	113 ± 30	105 ± 30	115 ± 30	0.126
Left bundle branch block, n (%)	79 (38)	7 (24)	72 (41)	0.090
Permanent atrial fibrillation, n (%)	46 (22)	5 (17)	41 (23)	0.456
Myocardial infarction, n (%)	126 (61)	22 (76)	104 (59)	0.087
Previous CABG, n (%)	45 (22)	8 (28)	37 (21)	0.418
Previous angioplasty, n (%)	51 (25)	6 (21)	45 (25)	0.663
Hypertension, n (%)	119 (58)	16 (56)	103 (58)	0.844
Diabetes, n (%)	58 (28)	9 (31)	48 (27)	0.649
Type of defibrillator, n (%):				0.251
Single-chamber	82 (40)	11 (40)	71 (40)	
Dual-chamber	50 (26)	11 (38)	43 (24)	
Biventricular	70 (34)	7 (24)	63 (36)	

NYHA – New York Heart Association; LV – left ventricular; CABG – coronary artery bypass grafting.

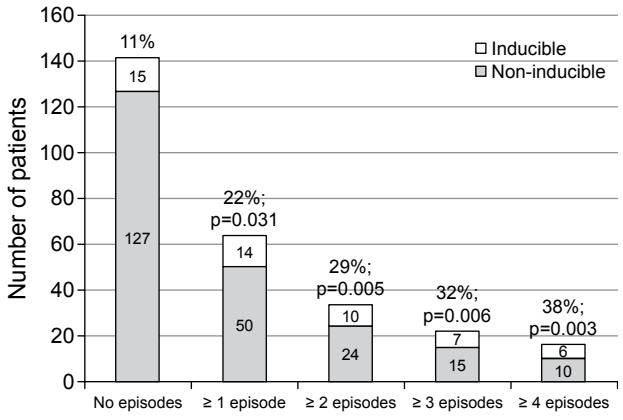

Figure 2. Numbers of patients who received one or more device therapies for VT or VF. Proportions of inducible patients on electrophysiological testing compared with "No episodes" group.

ability to predict frequent (i.e. ≥2) arrhythmic episodes during follow up (Table 2). On multivariate analysis, inducibility on EP testing proved to be an independent predictor of frequent arrhythmic episodes, as did a history of coronary artery bypass grafting.

During a follow up of 37 ± 15 months, 30 patients died. Inducibility on EP testing was not associated with higher mortality (log-rank test, p=0.311). However, patients with 2 or more treated arrhythmic episodes during follow up showed substantially higher mortality. Figure 3 shows the survival curves for all-cause mortality obtained by means of Kaplan–Meier analysis (log-rank test, p=0.042).

Discussion

Our study showed a weak association between arrhythmia inducibility by programmed stimulation and appropriate ICD intervention during follow up in patients with either ischemic or non-ischemic cardiomyopathy who received an ICD for the primary prevention of SCD. Only a trend towards a shorter time to the first tachyarrhythmia recurrence requiring ICD intervention was observed in patients with ventricular arrhythmia inducibility during the EP study. However, the proportion of patients with frequent (≥2 episodes) arrhythmias was higher among inducible patients, and inducibility turned out to be an independent predictor of multiple ICD interventions during follow up.

Inducibility of ventricular arrhythmias in heart failure patients

The predictive value of EP testing for stratifying patients in terms of the risk of life-threatening arrhythmias has been evaluated in ischemic[6] and non-ischemic[8,9] cardiomyopathy, and conflicting results have been reported. Large randomized studies have recently demonstrated the beneficial role of ICD in the primary prevention of SCD, regardless of the underlying heart disease and without inducibility as a requirement for implantation.[5,12] Nonetheless, the role of programmed stimulation in the risk stratification of ICD recipients has continued to be investigated.[13-15]

Table 2. Univariate and multivariate analyses of factors predicting frequent (≥2) arrhythmic episodes during follow up.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Male sex	2.01	0.6–7.1	0.278	-	-	-
Age (>70 years)	1.37	0.6–3.4	0.499	-	-	-
Ischemic etiology	1.08	0.4–2.8	0.870	-	-	-
Myocardial infarction	1.03	0.4–2.7	0.936	-	-	-
Previous CABG	2.34	0.8–6.6	0.108	5.15	1.5–18.3	0.011
Previous angioplasty	0.39	0.1–1.8	0.229	-	-	-
QRS duration	1.01	0.98–1.02	0.928	-	-	-
NYHA class I/II	1.57	0.6–4.1	0.353	-	-	-
LV ejection fraction (<25%)	1.94	0.8–4.8	0.153	1.90	0.4–6.0	0.459
Hypertension	0.95	0.4–2.5	0.922	-	-	-
Diabetes	0.67	0.2–2.1	0.499	-	-	-
Inducibility on EP testing	3.47	1.2–10.5	0.027	6.59	1.8–24.4	0.005
Permanent atrial fibrillation	1.63	0.6–4.3	0.329	-	-	-
Biventricular defibrillator	0.86	0.3–2.2	0.749	-	-	-

For QRS duration, 10 ms increments were considered. OR – odds ratio; CI – confidence interval; CABG – coronary artery bypass grafting; NYHA – New York Heart Association; LV – left ventricular; EP – electrophysiological.

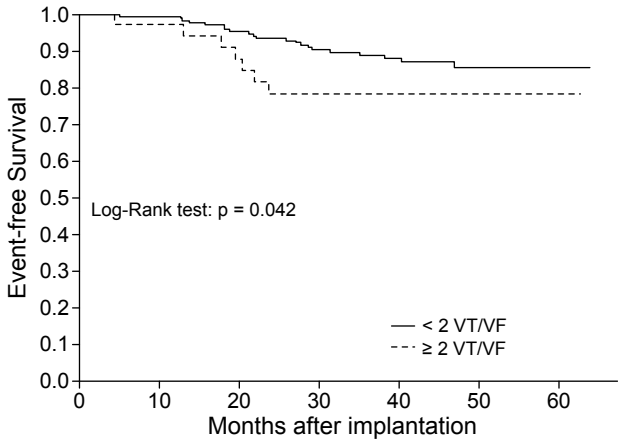

Figure 3. Kaplan–Meier estimates of time to death for patients with <2 or ≥2 treated arrhythmic episodes during follow up.

In our series, a history of coronary artery bypass grafting turned out to be an independent predictor of frequent arrhythmic episodes during follow up. Moreover, as expected,[13,14] the prevalence of ischemic heart disease was higher among inducible patients.

The inducibility of VT in ischemic patients has been found to be associated with a higher incidence of subsequent ventricular arrhythmias and SCD,[6] whereas the predictive value of programmed stimulation in patients with dilated cardiomyopathy remains less clear.[8,9] These differences have been attributed to the different electrophysiological substrates of these two disease entities.[16]

The induction of polymorphic VT or VF has been regarded as a non-specific response in most studies, both in patients with ischemic and in those with non-ischemic heart disease.[17,18] However, we did not attempt to investigate the predictivity of induced VT or VF separately. Indeed, the classification of events relies on ICD detection criteria and programming, or on subjective electrogram data interpretation. Moreover, such an analysis would have required a larger study sample size. The same approach was adopted in a substudy of DEFINITE,[14] in which investigators found that the inducibility of VT or VF in patients with non-ischemic cardiomyopathy predicted a greater than twofold risk of the subsequent occurrence of appropriate ICD intervention.

ICD population survival

Our findings confirm that patients receiving ICD therapies are at higher risk of death. Indeed, several authors[19-22] have noted an association between shocks for ventricular tachyarrhythmias and worsened outcome, in particular death from pump failure. Whether shock therapy in itself worsens clinical outcome is still debated, and conflicting results have recently been published regarding the impact of inappropriate ICD shocks on total mortality.[23,24] Nonetheless, regardless of the role of shocks, it is clear that the severity of the underlying myocardial disease process provides the electrophysiological substrate for tachyarrhythmias and influences both the rate of ICD interventions and the subsequent outcome. Indeed, in the present study we found an association between increased mortality and frequent appropriate ICD therapies, including both shocks and anti-tachycardia pacing.

Defibrillator therapies should not be considered a surrogate for SCD. Indeed, it has been demonstrated that appropriate shocks occur more frequently than SCD, and many episodes of VT that are treated by the ICD could terminate spontaneously.[25] Nonetheless, it has been shown that, in patients with heart failure who receive an ICD for primary prevention, the occurrence of appropriate ICD therapy is an independent predictor of a poor outcome.[20] Therefore, this patient group would require more thoughtful consideration, in order to reassess the therapeutic options that might modify the prognosis.

In our population, 31% of patients received appropriate defibrillation therapy during the 24-month follow up, in agreement with previous results by Daubert et al.[14] However, the rate of spontaneous arrhythmic events depends largely on the characteristics of the population, which, in the "real world" setting, may differ from those of patients enrolled in trials.

The same applies to the inducibility rate observed, which may depend on the characteristics of the population undergoing analysis and on the induction protocol adopted. Indeed, in the MADIT II study, an aggressive protocol was adopted for arrhythmia induction in ischemic patients, resulting in an inducibility rate of 36%.[13] By contrast, we observed a 14% inducibility rate, in agreement with the results obtained in non-ischemic patients of the DEFINITE substudy,[14] in which a similar protocol of programmed stimulation through the ICD was applied.

Limitations

As the study sample size was small, the numbers of

patients inducible on EP testing or receiving appropriate therapies during follow up were also small. However, previous studies investigating the predictive role of programmed ventricular stimulation have involved samples of comparable size.[14] EP testing was conducted through the ICD, with stimulation at only one ventricular site. However, this method has been shown to produce results comparable to the standard invasive approach.[26] Moreover, this method is easy and straightforward and can be applied in clinical practice during implantation at the time of defibrillation threshold testing. In our EP study, a sustained arrhythmia was defined as one satisfying the detection criteria of the ICD. Presumably, some of these episodes could spontaneously terminate before becoming clinically relevant. However, the aim of the analysis was to predict ICD intervention during follow up, when the device is programmed to deliver therapies under the same conditions.

Conclusions

In summary, we found that patients with inducibility of VT or VF were more likely to experience frequent appropriate ICD therapies during follow up. These patients have higher mortality during a 24-month follow-up period and might constitute a subgroup of patients, among the large cohort of patients who undergo ICD implantation,[27] who require more careful treatment and follow up.

References

1. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med. 1996; 335: 1933-1940.
2. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 1999; 341: 1882-1890.
3. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med. 2002; 346: 877-883.
4. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med. 2004; 350: 2151-2158.
5. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005; 352: 225-237.
6. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med. 2000; 342: 1937-1945.
7. Arsenos P, Gatzoulis K, Dilaveris P, et al. Arrhythmic sudden cardiac death: substrate, mechanisms and current risk stratification strategies for the post-myocardial infarction patient. Hellenic J Cardiol. 2013; 54: 301-315.
8. Poll DS, Marchlinski FE, Buxton AE, Josephson ME. Usefulness of programmed stimulation in idiopathic dilated cardiomyopathy. Am J Cardiol. 1986; 58: 992-997.
9. Grimm W, Hoffmann J, Menz V, Luck K, Maisch B. Programmed ventricular stimulation for arrhythmia risk prediction in patients with idiopathic dilated cardiomyopathy and nonsustained ventricular tachycardia. J Am Coll Cardiol. 1998; 32: 739-745.
10. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006; 48: e247-346.
11. Schaumann A, von zur Mühlen F, Herse B, Gonska BD, Kreuzer H. Empirical versus tested antitachycardia pacing in implantable cardioverter defibrillators: a prospective study including 200 patients. Circulation. 1998; 97: 66-74.
12. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004; 350: 2140-2150.
13. Daubert JP, Zareba W, Hall WJ, et al. Predictive value of ventricular arrhythmia inducibility for subsequent ventricular tachycardia or ventricular fibrillation in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol. 2006; 47: 98-107.
14. Daubert JP, Winters SL, Subacius H, et al. Ventricular arrhythmia inducibility predicts subsequent ICD activation in nonischemic cardiomyopathy patients: a DEFINITE substudy. Pacing Clin Electrophysiol. 2009; 32: 755-761.
15. Kossaify A, Refaat M. Programmed ventricular stimulation—indications and limitations: a comprehensive update and review. Hellenic J Cardiol. 2013; 54: 39-46.
16. Hsia HH, Marchlinski FE. Electrophysiology studies in patients with dilated cardiomyopathies. Card Electrophysiol Rev. 2002; 6: 472-481.
17. Brembilla-Perrot B, Donetti J, de la Chaise AT, Sadoul N, Aliot E, Juillière Y. Diagnostic value of ventricular stimulation in patients with idiopathic dilated cardiomyopathy. Am Heart J. 1991; 121: 1124-1131.
18. Bourke JP, Richards DA, Ross DL, McGuire MA, Uther JB. Does the induction of ventricular flutter or fibrillation at electrophysiologic testing after myocardial infarction have any prognostic significance? Am J Cardiol. 1995; 75: 431-435.
19. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. J Am Coll Cardiol. 2008; 52: 1111-1121.
20. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure.

N Engl J Med. 2008; 359: 1009-1017.
21. Moss AJ, Greenberg H, Case RB, et al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation. 2004; 110: 3760-3765.
22. Stabile G, D'Agostino C, Gallo P, et al. Appropriate therapies predict long-term mortality in primary and secondary prevention of sudden cardiac death. J Cardiovasc Med (Hagerstown). 2013; 14: 110-113.
23. Dichtl W, Wolber T, Paoli U, et al. Appropriate therapy but not inappropriate shocks predict survival in implantable cardioverter defibrillator patients. Clin Cardiol. 2011; 34: 433-436.
24. van Rees JB, Borleffs CJ, de Bie MK, et al. Inappropriate implantable cardioverter-defibrillator shocks: incidence, predictors, and impact on mortality. J Am Coll Cardiol. 2011; 57: 556-562.
25. Ellenbogen KA, Levine JH, Berger RD, et al. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? Circulation. 2006; 113: 776-782.
26. Kleiman RB, Callans DJ, Hook BG, Marchlinski FE. Effectiveness of noninvasive programmed stimulation for initiating ventricular tachyarrhythmias in patients with third-generation implantable cardioverter defibrillators. Pacing Clin Electrophysiol. 1994; 17: 1462-1468.
27. Inama G, Pedrinazzi C, Landolina M, et al. Use of implantable cardioverter defibrillator and cardiac resynchronization therapy: an Italian survey study on 220 cardiology departments. J Cardiovasc Med (Hagerstown). 2012; 13: 675-683.