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Ventricular Arrhythmias Due to a Transient of Correctable Cause in MADIT-II Patients: Prevalence and Clinical Relevance

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1. Introduction

Post-infarction patients with severe left ventricular dysfunction are at high risk of sudden cardiac death. Antiarrhythmic therapy does not improve survival in such patients and, therefore, implantable cardioverter defibrillators (ICD) emerged as treatment of choice for both primary and secondary prevention of mortality after myocardial infarction (MI). The MADIT (Multicenter Automatic Defibrillator Implantation Trial) (1), and MUSTT (Multicenter Unsustained Tachycardia Trial) trials (2) were the first primary prevention ICD trials documenting a substantial reduction in mortality with an ICD in postinfarction patients with depressed ejection fraction, nonsustained ventricular tachycardia, and inducible sustained ventricular tachycardia. The MADIT II trial broadened the indications for prophylactic ICD use in post-infarction patients with ejection fraction of 30% or less without a requirement for additional risk stratification (3). The benefit from ICD therapy in patients with low ejection fraction was recently confirmed by results from the SCD-HeFT (Sudden Cardiac Death in Heart Failure) (4) and COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trials (5).

2. Triggers of ventricular arrhythmias

Most investigations failed to reveal a transient cause for the development of ventricular arrhythmias in the majority of patients with severe left ventricular dysfunction. Singh et al. showed that among a comprehensive list of baseline clinical, echocardiographic, and electrophysiological variables in the MADIT-II study, more symptomatic patients (NYHA functional class >II) with blood urea nitrogen (BUN)>25 mg/dl, and no beta-blocker use are

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at a higher risk for first appropriate ICD therapy and death (6). Several data suggest that transient triggers (ischemia, heart failure, hypokalemia) may cause such events in a substantial proportion of patients. Ventricular premature Beats (VPB) have been found to trigger ventricular tachycardia (VT) especially in the setting of structural heart disease (7). Psychological stress may also be an important trigger. The impact of sympathetic activity on electrical instability is corroborated by the finding of a decreased baroreflex sensitivity in patients with clinical VT (8,9). In this chapter, we report the prevalence and clinical relevance of ventricular arrhythmias due to a transient arrhythmia triggers in patients with ischemic dilated cardiomyopathy undergoing primary prevention ICD implantation.

3. Methods

We collected data of 31 patients with ischemic cardiomyopathy (age 73±8 years, 25 males) who experienced the first arrhythmic event, defined as appropriate ICD intervention on sustained VT or fibrillation (VF), after the implantation of an ICD according to MADIT-II criteria (i.e. LVEF ≤ 30%). Patients were enrolled in our Institution between 2006 and 2008. All ICDs were uniformly programmed. Stored electrograms and ICD data disks from the included patients were reviewed by two expert electrophysiologists. Episodes of spontaneous sustained VT that were terminated by anti-tachycardia pacing or direct-current cardioversion were identified. VF was defined as a rapid, disorganized rhythm with variable cycle length, morphology, and amplitude of the electrogram with difficulty in precisely identifying all activation complexes. Polymorphic VT was diagnosed when electrograms displayed a ventricular tachycardia with almost constant amplitude but with variability in the cycle length and/or morphology of the electrograms. Monomorphic VT was defined as a ventricular tachycardia with a uniform beat-to-beat cycle length and electrogram morphology.

Transient arrhythmia triggers were assessed at the time of the arrhythmic event by means of a complete clinical and laboratory evaluation, including serum electrolyte assessment, echocardiography and coronary angiography in all patients. Patients whose VT/VF was associated with a transient or correctable cause were classified by two independent and blinded investigators into: acute myocardial ischemic event (including myocardial infarction or unstable angina), proarrhythmic drug reaction, worsening of heart failure, electrolyte imbalance (hypokalemia or hypomagnesemia) or other causes.

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as number and percentages. Comparisons between groups were performed with the two-tailed t test for continuous variables and chi-square test for discrete variables. A probability (p) value <0.05 was considered statistically significant. Analyses were performed with the PASW 18.1 statistical software (SPSS Inc.).

4. Results

Baseline characteristics of the patients included in the study are summarized in Table 1. All patients had ischemic cardiomyopathy and the mean left ventricular ejection fraction was 28% ± 5%. Overall, 19 (61%) patients had ICD shock, either on VT (10/19, 53%) or on VF (9/19, 47%). The remaining 12 (39%) patients experienced effective ATP on VT. The mean time from ICD implantation to the ICD intervention was 23 ± 16 months.

Characteristics	
Total number	31
Age, years	73 ± 8
Sex, males	25 (81)
Age at implant, years	70 ± 8
Type of ICD, n (%)	
Dual-chamber	25 (81)
Single-chamber	6 (19)
Sinus Rhythm, n (%)	23 (74)
Atrial Fibrillation, n (%)	8 (26)
Risk factors, n (%)	
Smoke	6 (19)
Hypertension	8 (26)
Diabetes	10 (32)
Hypercholesterolemia	12 (39)
Drug Therapy, n (%)	
Beta blockers	30 (97)
ACE-Inhibitors	31 (100)
Diuretics	17 (55)
Statins	28 (90)
Left ventricular EF, %	28 ± 5
NYHA functional class	2.4 ± 0.7
Creatinine, mg/dL	1.4 ± 0.4

Table 1. Baseline clinical characteristics of the study patients.

The mean time from ICD implantation to the first arrhythmic event was 24±16 months. The first arrhythmic event consisted of VF in 9 (29%) and sustained VT in 22 (71%) patients, of which 10 treated with an ICD shock and 12 with effective anti-tachycardia pacing. No significant differences in baseline characteristics were found between patients with different types of ICD intervention. A transient or correctable trigger for the arrhythmic event was identifiable in 9 (29%) patients and consisted of worsening heart failure in 5 (16%), clinical and angiographic evidence of acute ischemia in 3 (10%) and electrolyte abnormalities (i.e. hypokalemia) in 1 (3%). Ventricular fibrillation was more often associated with a transient trigger compared with sustained VT (67% vs. 14%, respectively, p=0.007). Interestingly, all three patients with acute ischemia as a trigger had VF as arrhythmic event.

5. Discussion

A number of well-known precipitating factors significantly increase the electrical instability of the heart. Among them, exacerbation of heart failure is one of the most important trigger factor suggesting that arrhythmia may simply be a marker of already-worsening HF. In our study worsening heart failure constituted 16% of cases. Previous analysis of the SCD-HeFT data (10) showed findings similar to those of the MADIT-II study. In the SCD-HeFT study, 33% of HF patients received an ICD shock, and among those patients, the most common cause of death was progressive HF (10,11). Myocardial ischemia is important factor. In this study, there were three patients in whom myocardial ischemia was proven to be the trigger for electrical instability and presented with VF as arrhythmic event. VF and myocardial ischemia are inseparable. Presence of one precipitates and perpetuates the other. Transmural heterogeneities in myocardial action potential and ionic currents produce transmural asymmetry in conduction during acute ischemia. Acute transmural ischemia depresses the excitability and velocity of conduction more rapidly in the epicardium than in the endocardium leading to increased dispersion. The occurrence of potentially lethal arrhythmia is the end result of a cascade of pathophysiological abnormalities (12-14). Other triggering factors include the development of electrolyte disturbances such as profound hypokalemia, which was demonstrated in one of our patients. Electrical instability is enhanced upon patients in whom drug treatment for congestive heart failure often acts to further increase electrolyte disturbances.

6. Clinical implication

The ICD has become the therapy of first choice to prevent sudden cardiac death in high-risk patients. Our study also supports the well-understood clinical notion that continued clinical vigilance toward preventing heart failure exacerbations and coronary events might decrease the risk of sudden cardiac death and ICD therapy in these patients. Interestingly importance of heart failure deterioration (i.e.,worsening of clinical status) suggests that this subset of patients have a wider margin to deteriorate and have additional predictive value as a determinant of ICD therapy. This also supports the evidence that in sicker heart failure subjects, the cause of death is more likely owing to pump failure. These results are corroborated by recent studies that show that preventing progression of heart failure with cardiac resynchronization therapy reduces the incidence of arrhythmic events (15,16).

Acute myocardial ischemia in high risk patients is arrhythmogenic, often leading to fatal outcome in the clinical setting. The arrhythmic outcome of an event between trigger and substrate differs. Genetic predisposition and governing responses of ion channels to myocardial ischemia might have a greater role than what is known at present. Efforts to understand these arrhythmias better can do early identification of patients with myocardial ischemia prone to arrhythmias. One of the most important aspects of the current study relates to potential prognostic implications of triggers. At present, there is a paucity of information on this clinically important issue.

Finally, in interpreting our results, it must be recognized that not all triggers causing arrhythmias appropriate ICD shocks for VT/VF would have been detected, and further identification of clinical triggers may help us to higher surveillance and vigilance of possible triggers to avoid primary shock that further deteriorate mortality and heart failure progression, increase in sympathetic tone that may give rise to proarrhythmic side effects of

antiarrhythmic drugs may also constitute a precipitating factor for recurrent ventricular tachycardia or fibrillation.

7. Conclusion

Due to the increasing number of patients with severe left ventricular dysfunction, further studies are needed to optimize priority of such patients for ICD therapy. Optimal pharmacologic and anti-ischemic (CABG, percutaneous transluminal coronary angioplasty) therapy, accurate and rapid correction of electrolytes disturbances are essential for proper prevention of shock and mortality in addition to ICD therapy.

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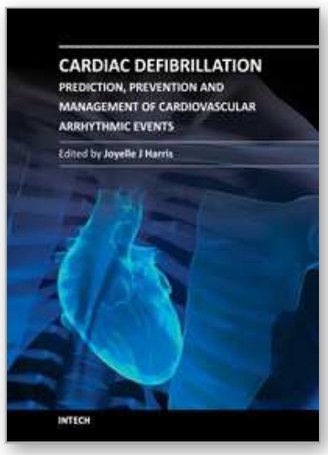

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Millions of people throughout the world currently depend on appropriate, timely shocks from implantable cardioverter defibrillators (ICDs) to avoid sudden death due to cardiovascular malfunctions. Therefore, information regarding the use, applications, and clinical relevance of ICDs is imperative for expanding the body of knowledge used to prevent and manage fatal cardiovascular behavior. As such, the apt and timely research contained in this book will prove both relevant to current ICD usage and valuable in helping advance ICD technology. This book is divided into three comprehensive sections in order to cover several areas of ICD research. The first section introduces defibrillator technology, discusses determinants for successful defibrillation, and explores assessments of patients who receive defibrillation. The next section talks about predicting, preventing, and managing near catastrophic cardiovascular events, and research presented in the final section examine special cases in ICD patients and explore information that can be learned through clinical trial examinations of patients with defibrillators. Each chapter of this book will help answer critical questions about ICDs.

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