

Editorial

Restratification at Time of Implantable Cardioverter Defibrillator Replacement



Reestratificación en el momento del recambio del desfibrilador automático implantable

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Based on the results of several large, randomized, clinical trials, implantable cardioverter defibrillators (ICDs) have become a “gold standard” therapy in prevention of sudden cardiac death. Under current guidelines, ICDs are implanted in patients who survived cardiac arrest or hemodynamically unstable ventricular tachycardia, as well as in primary prevention, mainly for those with ischemic or nonischemic cardiomyopathy with left ventricular ejection fraction (LVEF) $\leq 35\%$, New York Heart Association functional class II/III, optimal pharmacotherapy, good life expectancy, and no identifiable reversible causes of low LVEF.¹ Current guidelines do not distinguish between patients implanted *de novo* and those undergoing elective battery replacement. No doubts exist about the need to replace ICD in secondary prevention patients; however, a debate continues on how to approach subjects implanted in primary prevention referred for elective replacement due to battery depletion. Despite decades of clinical experience, no consensus exists on how to stratify the risk of sudden cardiac death. The current approach, in which low LVEF is considered the only risk stratifier, is far from optimal. A substantial number of ICD recipients who are eligible for a device replacement have never developed arrhythmia requiring ICD therapy. As evidenced by randomized trials and ICD registries, only 20% to 30% of patients implanted for primary prevention receive appropriate ICD shocks. Therefore, at the time of generator replacement physicians have to face 2 problematic groups of patients: *a*) those who have never had appropriate therapy but still present low LVEF qualifying them for an ICD, and *b*) those who have never had ICD shocks and at the time of replacement present with improved LVEF falling beyond ICD indications criteria.

Patients who have not received any antiarrhythmic therapy most probably constitute a group of subjects who were “too healthy” or “too sick” for ICD implantation. There is an ongoing debate on how to stratify the risk of sudden cardiac death and better identify patients with low LVEF who develop ICD-treatable arrhythmia. Even though a plethora of noninvasive risk markers such as electrocardiogram and imaging techniques, laboratory tests, and simple bedside tests has been investigated, no

consensus has been achieved so far. The rate of death without appropriate ICD therapy is substantial. Patients with multiple comorbidities and those with advanced heart failure are prone to die from noncardiac or nonarrhythmic causes that could not be prevented by ICD therapy. The study by Goldenberg et al² showed that a bedside clinical risk score composed of 5 variables (New York Heart Association functional class $> II$, age > 70 years, blood urea nitrogen > 26 mg/dL, QRS duration > 120 ms, and atrial fibrillation) was able to identify patients who did not benefit from ICD implantation. A group from Leiden³ proposed the FADES (Functional class, Age, Diabetes, Ejection fraction, Smoking) score to identify patients who would die without appropriate therapy. In patients with a FADES score of 3.0–5.5 points, the cumulative incidence of death without appropriate ICD therapy was 41%.

In patients who at the time of generator replacement present with LVEF above ICD indications limits, 3 potential clinical situations should be considered: *a*) there was an unrecognized reversible cause of left ventricular dysfunction at the time of implantation; *b*) spontaneous positive remodeling occurred, and *c*) a patient might have had inappropriately assessed LVEF at the time of implantation and in fact has never fulfilled the implantation criteria. Recent data from the MADIT-CRT⁴ trial showed that 38% of patients enrolled in a trial based on the criterion of LVEF $< 30\%$ had significantly higher ejection fraction values (in the range of 30.1%–45.3%) when echocardiographic data was analyzed centrally by echo experts. The subjective nature of LVEF estimation and poor reproducibility of the results have always been criticized in the context of using LVEF as a sole risk marker for sudden cardiac death.

To avoid the risk of inappropriate qualification for ICD therapy related to spontaneous positive remodeling, a limit of at least 40 days after myocardial infarction and 9 months after a new onset of nonischemic cardiomyopathy is required. However, it seems there is a substantial proportion of patients who will recover left ventricular function over a longer period of time, especially among those with nonischemic cardiomyopathy. Attempts are always being made to exclude reversible causes such as tachycardiomyopathy, myocarditis, excessive alcohol consumption, nonadherence to drug therapy, or suboptimal treatment. In patients with atrial fibrillation, it should also be emphasized that a restoration of a sinus rhythm by cardioversion or ablation may significantly improve left ventricular function.

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Heart failure is a progressive disease; however, it shows visible shifts from one New York Heart Association functional class to another and fluctuations in LVEF over time. Clinical characteristics of a patient with left ventricular dysfunction change over time not only in terms of left ventricular function or heart failure advancement but also in terms of heart rate (sinus rhythm vs atrial fibrillation), coexisting comorbidities, or even as simple a marker as age. Recent years brought an increasing interest in spontaneous positive remodeling, described as heart failure with recovered ejection fraction. The etiopathogenesis and natural history of this clinical entity has not yet been fully elucidated. The reason for spontaneous positive remodeling in the absence of reversible cause is unclear even though it is suggested that transient unrecognized injury or inflammation may play a role. A recent study by Basuray et al⁵ demonstrated that patients with recovered LVEF have better survival than those with reduced or preserved ejection fraction. Nevertheless, these patients remained at high risk of rehospitalization due to cardiac causes. Whether positive structural remodeling can be extrapolated to a lower risk of future arrhythmic events remains unclear. Furthermore, it is more likely that the presence of scar and fibrosis is more arrhythmogenic than low LVEF itself, as documented by several magnetic resonance imaging studies. It also should be noted that autonomic nervous system changes may play a role in arrhythmogenesis. Data from REFINE and CARISMA studies⁶ demonstrated that a favorable recovery of parameters reflecting autonomic tone expressed as improved heart rate variability and turbulence paralleled an increase in LVEF in postinfarction patients. Notably, a lack of recovery in heart rate turbulence was associated with nearly 10-fold higher risk of life-threatening arrhythmias in the CARISMA study and a 7-fold higher risk of reaching the primary end point in the REFINE study. More importantly, these changes were related to arrhythmic mode of death.⁶

A limited number of studies have aimed to investigate the rate of positive remodeling in ICD recipients and its impact on ICD therapy. Most of them focused on nonischemic cardiomyopathy and showed an improvement in LVEF above guidelines criteria in 12% to 45% of cases.^{7,8} Naskuk et al⁹ observed no significant difference in ICD shocks between patients who improved and did not improve in LVEF at the time of replacement. Similarly, DEFINITE trial¹⁰ participants whose left ventricular function improved during follow-up were characterized by lower mortality rate but similar rate of appropriate ICD shocks compared to a group whose LVEF decreased. The MADIT-CRT trial showed that a positive remodeling, defined as $\geq 15\%$ reduction in left ventricular end systolic volume at 1-year follow-up, was observed in 25% of patients randomized to an ICD arm and was related to lower risk of heart failure or death, compared to the ICD group with no remodeling. Predictors of such a favorable LVEF increase included systolic blood pressure ≥ 140 mmHg, serum creatinine < 1 mg/dL, QRS from 130 ms to 160 ms, and nonischemic cardiomyopathy.¹¹

Little is known about long-term benefit from ICD therapy in patients free from arrhythmic events at the time of device replacement and the risk of sudden cardiac death in patients with recovered LVEF. The multicenter, prospective INSURE trial¹² showed that among patients without former ICD intervention at the time of replacement, the rate of appropriate therapy at 1, 2, and 3 years of follow-up was estimated at 10.6%, 17.6%, and 21.4%, respectively. However, it was 2 times lower than in patients who had already experienced ICD intervention. Van Welses et al¹³ reported 14% cumulative incidence of appropriate ICD therapy for ventricular tachycardia/fibrillation at 3-year follow-up. A recent study by Kini et al,¹⁴ based on a retrospective review of medical charts of primary prevention patients undergoing elective ICD replacement in years 2006-2013, showed that 26% of these patients no longer met indications for ICD implantation according

to current guidelines. This group did not experience appropriate therapy prior to replacement and demonstrated an improvement in LVEF to $\geq 40\%$. More interestingly, an additional 34% of patients had not received ICD therapy but their LVEF was not reassessed at the time of replacement. Patients who had not met ICD criteria still received appropriate ICD therapy during longer follow-up, even though the rate was substantially lower than in a subgroup of patients who remained in the LVEF-driven high-risk group (2.8% vs 10.7% annually). Further follow-up over a mean of 3 years in a group of 59 patients who no longer met ICD implantation criteria showed that 4 of 5 had received ICD shocks for ventricular tachycardia/fibrillation.

The problem of reevaluation is getting even more complicated in cardiac resynchronization therapy (CRT) patients in whom positive remodeling and increase in LVEF is observed as an expected effect of a therapy itself. The benefit from CRT with defibrillation (CRT-D) lies not only in reduction of arrhythmic risk but predominantly in reduced risk of heart failure deterioration and subsequent prolongation of life with better quality. A retrospective analysis of CRT-D patients with improved LVEF who experienced no appropriate ICD therapy during the first year after implantation was reported by Manfredi et al.¹⁵ In patients with primary prevention indications for CRT-D therapy the estimated 2-year risk of appropriate therapy was 3.3%, 2.5%, and 1.9% for those in whom post-CRT LVEF increased to 45%, 50%, and 55%, respectively. Therefore, the authors concluded that CRT super-responders who show near-normalization of LVEF have a low risk of ventricular arrhythmia and subsequent need for ICD therapy. Such a normalization of LVEF could be predicted by nonischemic origin of cardiomyopathy and higher baseline LVEF.

Following the line of research to identify patients who benefit from ICD therapy, Fontenla et al,¹⁶ in their article published in *Revista Española de Cardiología*, reported on clinical factors associated with appropriate ICD therapy before and 2 years after generator replacement. The authors report that ventricular arrhythmias were observed in 62% of patients at the time of replacement and in 20% of patients during the first 2 years after implantation. The authors found that male sex, presence of structural heart disease or heart failure, and absence of resynchronization function were independently associated with arrhythmia occurrence and need for therapy. This study provides another interesting puzzle in a problem of ICD/CRT-D replacement, but is not free of limitations. The studied population derived from a multicenter national registry was very heterogeneous, including patients with ICD or CRT-D implanted for primary (58%) or secondary prevention (42%) with a variety of underlying diseases, from cardiomyopathies with depressed LV function to patients with chanelopathies. Clearly, in clinical practice, the risk for developing arrhythmia and the pathogenesis of this final event will be different according to the underlying disease, even though a relationship between arrhythmia and LVEF was not observed by the authors. It is also difficult to compare patients with ICD and CRT-D, especially in terms of heart failure as a covariate related to arrhythmia, as this covariate is modified by CRT itself. Programming of the ICD, which might influence the results, was left at the discretion of physicians.

In summary, Fontenla et al¹⁶ brought up an important clinical issue of reassessing ICD patients at the time of device replacement. However, the question of whether a patient who improved in left ventricular function over time continues to be at high risk of arrhythmic events preventable by an ICD remains open. Even though most physicians would opt to replace an ICD regardless of whether or not a patient meets the criteria for implantation, it seems that it is high time to strengthen our efforts to restratify patients with improved LVEF who had not experienced ICD therapy by the time of battery replacement. It also should be noted that,

apart from a clinical problem, we face an ethical dilemma by suggesting that the ICD is no longer required and neglecting replacement in patients in whom we previously recommended ICD as a life-saving therapy. It is obvious that, similar to primary implantation, replacement of a generator should involve conscious participation by the patient and should be preceded by a clear presentation of all benefits and risks related to a procedure.^{1,17}

CONFLICTS OF INTEREST

None declared.

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