Chapter 20

Electrical Devices (Resynchronization and Defibrillators) in the Treatment of Cardiomyopathies: Indications, Present and Future of these Therapies

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Abstract

Cardiomyopathies are heart diseases involving high risk of heart failure and sudden cardiac death. In this chapter, we review the use of electrical devices (cardiac resynchronization therapy and implantable cardioverter defibrillator) to reduce the progression of heart failure and prevent arrhythmogenic sudden death in patients affected with these pathologies. The future of these therapies is a more appropriate indication for primary prevention of sudden death (defibrillator) and treatment of heart failure in a broader spectrum of patients (resynchronization).

Keywords: cardiac resynchronization therapy, implantable cardioverter defibrillator, cardiomyopathy, heart failure, sudden death

1. Introduction

Cardiomyopathies (CMP) are a group of diseases that affect the cardiac muscle associated with myocardial dysfunction and can be caused by known disorders such as hypertension, ischemic heart disease, valvular disease, and so on. Other causes, such as genetic illnesses, inflammatory processes, metabolic, or toxic diseases, may also be responsible for this pathology. Its origin could also be primary, i.e., not known cause. One simple and initial classification of the CMP divides them into ischemic and nonischemic ones. In 1995, the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) Task Force on the Definition

and Classification of the Cardiomyopathies classified them into dilated, hypertrophic, restrictive, arrhythmogenic right ventricular dysplasia, and other [1]. Since these diseases can have mechanical and/or electrical dysfunction, in this chapter, we review the usefulness of electrical therapies (cardiac resynchronization therapy or/and implantable cardioverter defibrillator) to treat heart failure and arrhythmogenic sudden cardiac death associated with these diseases.

The etiology of heart failure may be predictive of long-term outcome: survival of peripartum CMP was better; medium in hypertension, myocarditis, sarcoidosis, and substance abuse; and worse in infiltrative myocardial disease –amyloidosis and hemochromatosis-, HIV disease, chemotherapy with doxorubicin, ischemic heart disease, or connective tissue disease. And in all of them, the added presence of diabetes involves an increased risk of mortality.

Heart failure is a complex clinical syndrome that causes inadequate systemic perfusion to meet the body's metabolic demands with usually increased left ventricular filling pressures. The two leading causes of death in patients with heart failure are arrhythmic or sudden cardiac death and progressive pump failure [2]. Life-threatening ventricular arrhythmias are common in patients with heart failure and CMP, and unexpected sudden cardiac death and sudden cardiac death during episodes of clinical worsening of heart failure each account for approximately one-third of deaths. Management of patients with heart failure includes several strategies: controlling contributing factors, lifestyle modification, pharmacological therapy, rehabilitation, preventive care, and electrical devices if indicated. The mode of death in patients with heart failure is more likely to be "sudden" in patients with New York Heart Association (NYHA) II-III classes and related to pump failure in patients with NYHA IV class [3].

Ventricular arrhythmias are common in heart failure and CMP. The prognosis of these arrhythmias depends on the cause of the CMP [4]. There is no preventive drug therapy to treat ventricular arrhythmias (i.e., amiodarone). However, those patients with nonsustained ventricular tachycardia may be candidates (with preliminary electrophysiological study) to an implantable cardioverter defibrillator. Patients with spontaneous sustained ventricular tachycardia are at high risk for sudden cardiac death; patients with heart failure or CMP who are survivors of sudden cardiac death due to ventricular tachycardia or ventricular fibrillation must be treated with implantable cardioverter defibrillator for secondary prevention [4, 5] (**Figure 1**).

A pacemaker placed in right ventricle can exacerbate heart failure by several mechanisms: firstly, contraction of the right ventricle before the left ventricle (interventricular dyssynchrony), and secondly the "left bundle branch block effect" causing that septum contracts before the lateral wall (intraventricular dyssynchrony); the final outcome of both phenomena results in a reduced efficiency of cardiac pump. It is likely that a pacemaker placed in right atrium and right ventricle provides benefit in heart failure, but DAVID trial, which included patients with left ventricular ejection fraction ≤40% and without indication for bradycardia showed that pacing with DDD function (dual, atrial and ventricular, pacing and sensing, and also dual, triggered and inihibited, response to sensing, according to accepted international code accepted in 2002) [6] can worsen heart failure. The same concept could be generalized to patients with CMP [7].

Therapy known as cardiac resynchronization can optimize cardiac function, symptoms, and survival in patients with heart failure with left ventricular dysfunction (with left ventricular

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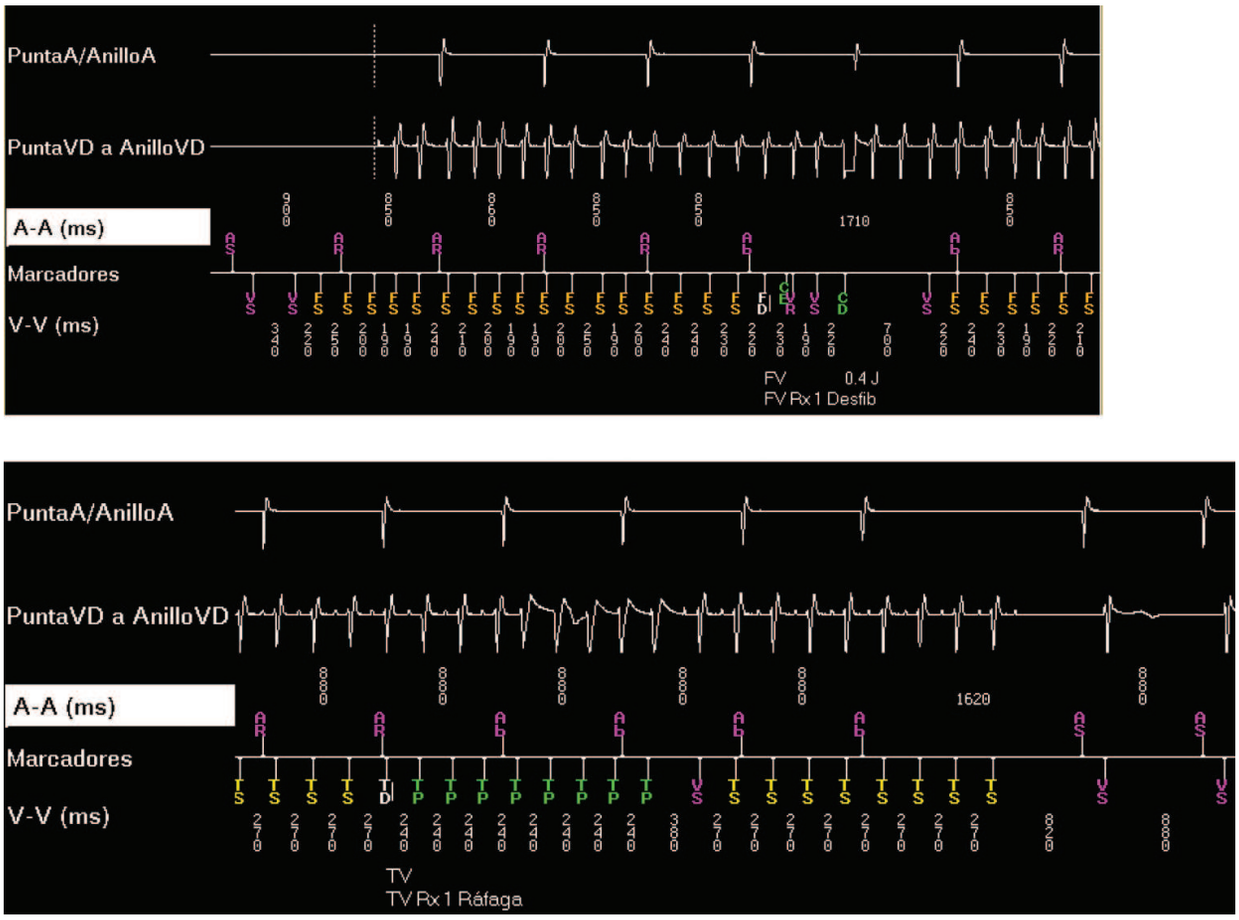

Figure 1. Endocavitary registry of two ventricular arrhythmias: ventricular tachycardia, treated with anti-tachycardia pacing (ATP), and ventricular fibrillation, treated with defibrillation (0.4 J).

ejection fraction ≤35% and wide QRS with left bundle branch block), added to optimal medical treatment. On the other hand, implantable cardioverter defibrillator can abort sudden arrhythmic deaths, thus prolonging survival in patients with cardiac disease and that patients may progress in later stages to more advanced heart failure.

2. Ischemic CMP

Risk stratification of a patient who has an acute myocardial infarction and ischemic CMP should include: identification of risk for recurrent ischemic events and identification of high risk of death (arrhythmic or non-arrhythmic of origin). Postinfarction mortality has decreased by optimizing the initial therapy (reperfusion) and secondary prevention measures [4].

2.1. Role of implantable cardioverter defibrillator

Several works (VALIANT [8]) described an increased risk of sudden cardiac death in patients with postinfarction left ventricular failure; the rate of sudden cardiac death or resuscitated cardiac arrest was 1.4 % in the first month, with a rate of 2.3% if left ventricular ejection fraction <30%), but the frequency of use of reperfusion therapy and beta-blockers was low. Two studies

(DINAMIT [9] and IRIS [10]) showed no improvement in survival after implantable cardioverter defibrillator placement between 31 and 40 days post infarction. Several risk factors are associated with threatening arrhythmia: low ejection fraction of left ventricle or history of heart failure, ventricular tachycardia induced in the electrophysiologic study, spontaneous ventricular premature beats and nonsustained ventricular tachycardia seen in the 24-hour Holter, and other. On the other hand, reperfusion therapy has decreased the predictive value of these variables. Finally, implantable cardioverter defibrillator should be recommended in patients with a left ventricular ejection fraction ≤30% (MADIT II criteria) or with ischemic CMP, left ventricular ejection fraction ≤35%, and NYHA II or III heart failure (SCD-HEFT criteria) [11] (**Figure 2**). In recent guidelines [12, 13], implantable cardioverter defibrillator is an effective therapy to reduce sudden cardiac death in patients with previous myocardial infarction and left ventricular dysfunction, which have hemodynamically unstable sustained ventricular tachycardia, and in patients with recurrent ventricular tachycardia and normal/near normal left ventricular function.

2.2. Role of cardiac resynchronization therapy

The usefulness of resynchronization is demonstrated in patients with ischemic CMP. In several pivotal studies, which demonstrated the utility of resynchronization (CARE-HF, COMPANION, etc), there was a significant percentage of patients with ischemic CMP. In other old studies [14], patients with ischemic CMP may respond less favorably to resynchronization compared with patients with idiopathic dilated CMP. In recent years, studies comparing the effectiveness of this therapy in ischemic vs dilated CMP have been developed [15]; estimated survival at 4 years were 55% for ischemic and 77% for dilated CMP, and no significant difference was found in the incidence of inappropriate implantable cardioverter defibrillator shocks between both groups. Patients with implantable cardioverter defibrillator functionality remained at higher risk for death after controlling for pre-implant variables (hazard ratio (HR), 1.6). So, patients with dilated CMP experienced greater improvement in left ventricular systolic function and reverse remodeling than those with ischemic CMP, which means sustaining a greater survival benefit.

Another study [16] showed that after atrioventricular node ablation along with biventricular pacemaker placement, in patients with heart failure and refractory atrial fibrillation, echocardiographic reverse remodeling was lower in patients with ischemic compared with dilated CMP [16], with a greater number of hospitalizations due to heart failure in this first group and less improvement of left ventricular ejection fraction.

Finally, a combination of resynchronization + surgery in dilated ischemic CMP could be useful: optimization of ventricular function by myocardial revascularization with synchronized contraction of papillary muscle by biventricular pacing could improve the abnormal conformation/shape of the left ventricle, responsible for the functional mitral regurgitation. Therefore, preoperative assessment of myocardial viability and synchronism of the papillary muscles is the key to the success of this intervention.

Recent clinical guidelines [17] show greater benefit of CRT in several subgroups: women, QRS ≥150 ms, and nonischemic CMP. Despite the lower efficacy against nonischemic patients, the implant in these patients is recommended.

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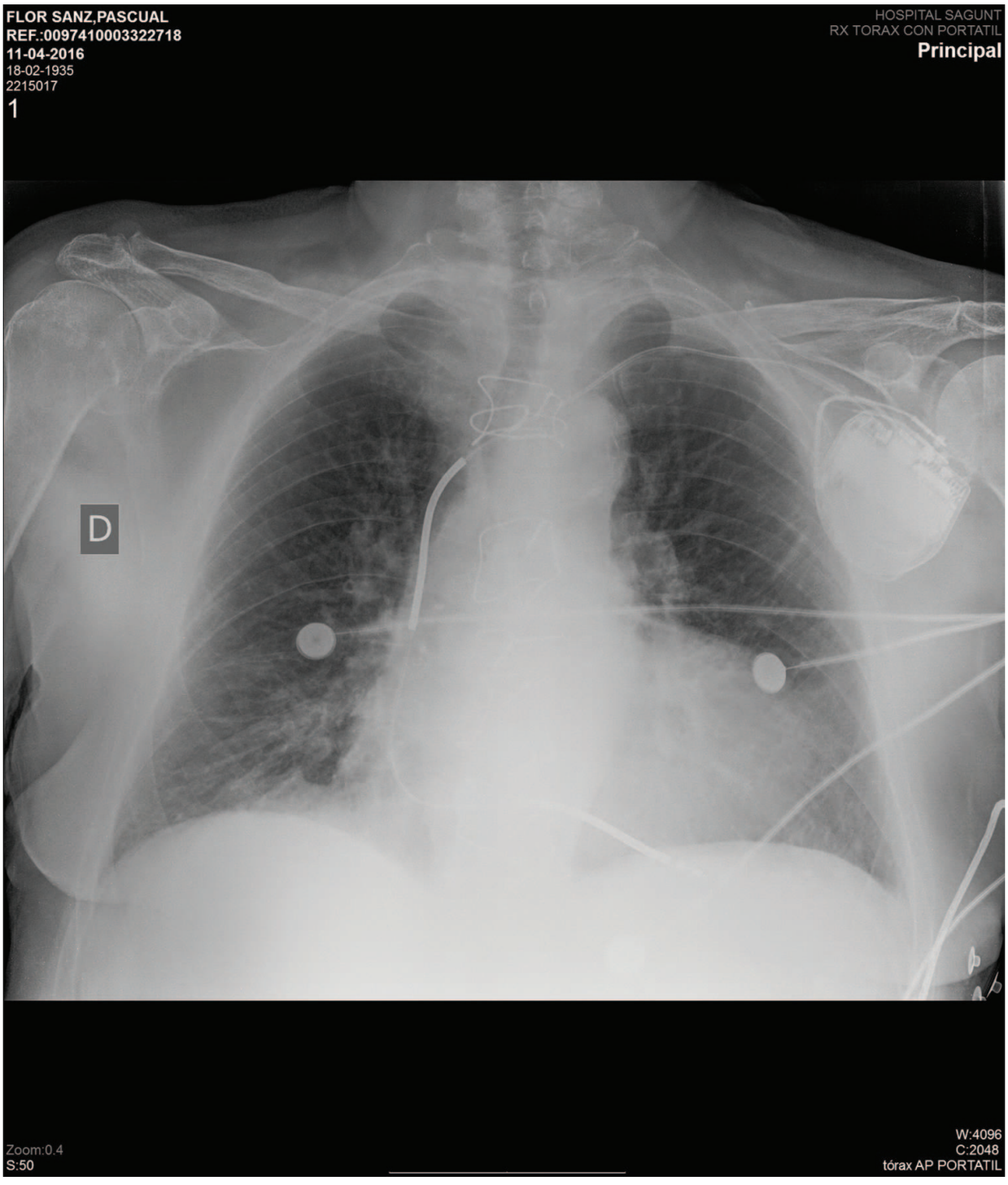

Figure 2. Monocameral implantable cardioverter defibrillator in a patient with ischemic dilated cardiomyopathy.

3. Myocarditis

It is an inflammatory disease of the myocardium, characterized from a histopathologic point of view by inflammatory infiltrates within the myocardium associated with degeneration and necrosis, with a nonischemic origin. The most common etiology is infectious, followed by immune (drugs, autoimmune diseases, etc) and toxic (drugs, metals, radiation, etc). Acute

myocarditis can lead to chronic myocarditis or dilated CMP up to 10% of cases [18, 19]. In patients with sudden cardiac death, sustained ventricular tachycardia, ventricular fibrillation, and/or dilated CMP with ventricular dysfunction, the decision to implant and implantable cardioverter defibrillator should be based on the same indications as in other CMP, according to clinical practice guidelines [13]. It seems reasonable to delay the placement of an implantable cardioverter defibrillator until the resolution of the acute episode, meanwhile can be raised using a vest defibrillator as a bridge in high-risk patients [20]. Once dilated CMP has been developed, implantation of a cardiac resynchronization therapy device is recommended in patients with severe depression of left ventricular systolic function (<35%) and left bundle block in functional class II–IV [21].

In clinical guidelines [12, 13], implantable cardioverter defibrillator is indicated if inflammatory infiltrates persist in biopsies and if there is abnormal fibrosis in magnetic resonance; these elements are risk factors for sudden cardiac death.

4. Hypertrophic CMP

Patients with hypertrophic CMP can develop left ventricle outflow tract gradient/obstruction, diastolic dysfunction, myocardial ischemia, mitral regurgitation, and systolic dysfunction (in advanced stages) [22]. Therapeutic options to decrease the pressure gradient are as follows: drugs (beta-blockers or calcium antagonists), septal resection surgery, septal percutaneous reduction with ablation with alcohol, and atrial ventricular permanent pacing.

4.1. Role of cardiac resynchronization therapy

The aim consists of reducing the left ventricular outflow tract gradient, probably related with heart failure, classically using DDD pacemaker, and more recently with cardiac resynchronization therapy. In several works (1970s and 1980s), right atrial and right ventricular pacing, with short auricular-ventricular interval is performed, with positive effects: pre-excitation from right ventricular apex—with paradoxical septal movement and ejection speed reduction, delayed septal contraction—with systolic anterior motion of mitral valve improvement, and reduction of mitral regurgitation and subaortic gradient; a critical issue is to maintain constant ventricular and auricular capture. However, the success of the therapy lies in optimized individual programming of stimulation parameters to maintain atrial ventricular synchrony. The maintained benefit in functional status of sequential atrial ventricular pacing has been demonstrated in long series of cases (median follow-up of 8.5 years) [23]. Lenarczyk et al. [24] shows in his preliminary study a decrease in outflow tract gradient and improvement of the functional status. In several series, we can see a symptomatic benefit and an improvement of exercise capacity, although evolution is erratic. In recent guidelines for the treatment of hypertrophic CMP [25], cardiac resynchronization therapy is recommended in the following situations: sequential conventional pacing for reducing gradient or facilitating medical treatment if gradient ≥50 mmHg, sinus rhythm and refractory symptoms to medical treatment with contraindication to myectomy or septal ablation, with high risk to develop atrial ventricular block

after it; resynchronization is also indicated in patients who meet indications of bicameral implantable cardioverter defibrillator to make sequential pacing.

We are waiting for the results of the study TRICHAMPION (clinicaltrials.gov NCT01614717): triple chamber pacing in hypertrophic obstructive cardiomyopathy patients. This is a prospective, randomized, single blind trial including N = 80 patients with atrial pacing only in back-up versus atrial biventricular pacing for 1 year. Expected preliminary results will be in 2016.

Recent clinical guidelines [17] show, in the absence of current clinical trials, the option of considering cardiac resynchronization therapy in individual patients with left ventricular failure data and asynchrony. And for patients with left ventricular outflow tract obstruction and treated with dual chamber pacemaker or implantable cardioverter defibrillator, you must schedule a short atrial ventricular interval for maximum apical right ventricle pre-excitation without altering left ventricle diastolic filling.

4.2. Role of implantable cardioverter defibrillator

Hypertrophic CMP is the most frequent cause of sudden cardiac death in adults under 35 years; annual mortality is 1% and half of it is sudden cardiac death [26, 27]. In the Spanish Implantable Cardioverter Defibrillator registry [28], 6% of carriers of this device had a previous diagnosis of hypertrophic CMP. Unfortunately, sudden cardiac death could be the first manifestation of this entity, so it is necessary a risk stratification. However, although implantable cardioverter defibrillator is recommended for high-risk patients with hypertrophic CMP, there is no agreement on its general use. In European centers, a conservative approach has been adopted: in primary prevention, there is indication to implant an implantable cardioverter defibrillator if at least two risk factors are present [27]; but that does not mean it is accompanied by theoretical high risk. It can be seen at an annual rate of 11.1% adequate treatment in secondary prevention and 1.6% in primary prevention.

In several series [29], differences are observed in the placement criteria (**Table 1**) between hospitals and even populations of each center. It is remarkable that patients with an episode of resuscitated sudden cardiac death or sustained ventricular tachycardia had fewer risk factors than those with implantable cardioverter defibrillator for primary prevention (1.94 vs 2.96). The main factors associated with appropriate therapies were history of resuscitated sudden death and sustained ventricular tachycardia. These data reflect the difficulty in identifying patients at risk and make adequate primary prevention. The history of sustained ventricular tachycardia or ventricular fibrillation makes unnecessary to look for other risk factors. On the other hand, the presence of ventricular aneurysm, myocardial infarction, or systolic dysfunction may indicate the need for this therapy.

The current selection criteria do not predict in a reliable manner the occurrence of sudden cardiac death or ventricular arrhythmias. On the other hand, the quantification of fibrosis or genetic study may help proper selection of candidates for implantable cardioverter defibrillator for primary prevention. This becomes more important if we consider the associated complications in the primary prevention group (unnecessary electric shocks, battery replacements, etc). A new algorithm [30] can give greater discriminatory power than previous ones.

• Resuscitated SD
• Sustained VT
• Family history of SD
• Causeless recurrent syncope (without apparent cause)
• Ventricular hypertrophy (≥30 mm)
• Subaortic gradient (left ventricular outflow tract, LVOT >30 mmHg at rest)
• Abnormal response to exertion in less than 45 years (inability to increase 25 mmHg systolic arterial pressure)
• NSVT in Holter ECG (three or more ventricular beats, followed by more than 120 beats/min and less than 30 s in length)

Table 1. Checked risk factors of sudden death. SD, sudden death. VT, ventricular tachycardia. NSVT, non sustained VT.

Recent clinical guidelines [12, 13] recommend, in the absence of clinical trials, the use of implantable cardioverter defibrillator for secondary prevention in patients with aborted cardiac arrest or sustained ventricular tachycardia associated with a high risk of subsequent lethal arrhythmia. Also, recommendations for implantable cardioverter defibrillator therapy for primary prophylaxis are based on the 5-year SCD risk calculated using the HCM Risk-SCD model and taking into account the age and general health of the patient.

5. Dilated MCP

The etiology of this CMP is varied: idiopathic 50% (**Figure 3**), myocarditis 9%, ischemic CMP 7%, infiltrative disease 5%, and other (peripartum, arterial hypertension, treatment with doxorubicin, etc.

Chagas disease: It is a protozoal infection due to *Tripanosoma cruzi*. It is the leading cause of dilated CMP in Central/South America and is the leading cause of cardiovascular death in patients between 30 and 50 years old. Cardiac involvement is manifested as arrhythmias, heart failure, and thromboembolic phenomena. In these countries it is a major cause of sudden cardiac death. Nonsustained ventricular tachycardia, NYHA functional class, and left ventricular ejection fraction are predictors of mortality, with a 16% survival at 36 months in patients with NYHA class IV and left ventricular ejection fraction <35% despite optimal medical treatment [31]. With similar indications to previous trials (severe heart failure despite optimal medical treatment, QRS > 120 ms, left ventricular ejection fraction <35%, and left ventricular end-diastolic diameter >55 mm assessed by Doppler echocardiography), improved NYHA functional status is obtained, with increase in left ventricular ejection fraction and reduction in left ventricular end diastolic diameter; 33% of patients do not respond to cardiac resynchronization therapy, probably by the advanced NYHA class.

Pharmacological treatment has little benefit, and recurrence rates of severe arrhythmia are close to 100%. Mortality is high—40% at 1 year, with frequent need for implantable cardioverter defibrillator implantation when evolves to dilated CMP [32]. Recent guidelines

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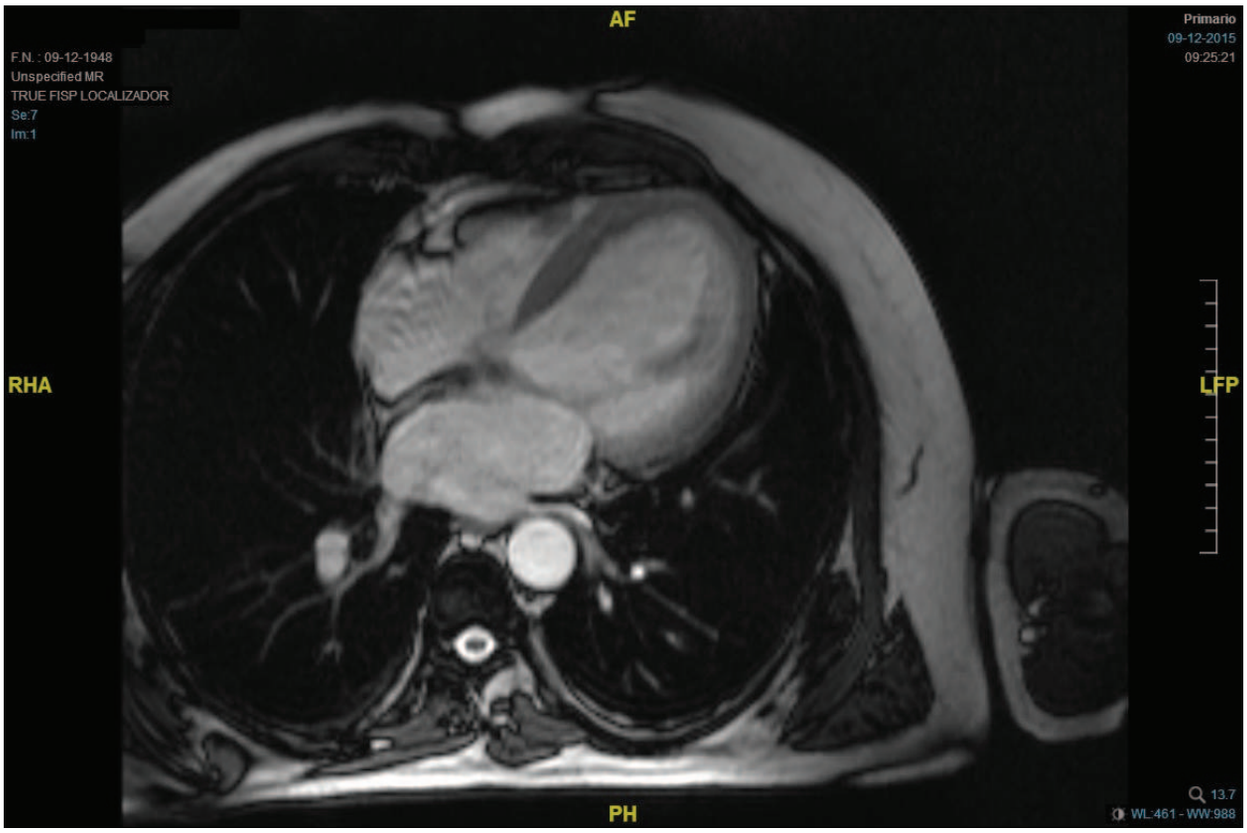

Figure 3. MR image of a patient with idiopathic dilated cardiomyopathy, with increased ventricular dimensions with a homogeneous myocardial uptake signal.

[11, 12] say that implanted cardioverter defibrillator should be considered in patients with left ventricular ejection fraction <40% when they are expected to survive >1 year with good functional status

Stress CMP (*takotsubo*) does not seem to be an indication for treatment with cardiac resynchronization therapy even in cases with refractory heart failure (usual indication of these devices in ambulatory patients).

Cardiac involvement in *Becker muscular dystrophy* varies from myocardial hypertrophy with preserved systolic function to severe left ventricular dilatation with anomalies in contractility by anomalies in contractility and severe depression of systolic function. Cardiac resynchronization therapy implantation depends on the baseline condition and comorbidities of patients. Few cases have been described [33].

Peripartum: It is a rare form of nonischemic CMP defined as heart failure secondary to left ventricular systolic dysfunction with a left ventricular ejection fraction <45% toward the end of pregnancy or in the months following delivery, where no other cause of heart failure can be found. The treatment of peripartum CMP is similar to that employed for other types of heart failure with left ventricular dysfunction; however, modifications to standard therapy are often necessary to ensure the safety of the mother and the unborn or breastfeeding child. The time to potential recovery from severe remodeling of ventricular function is difficult to predict [34]. In

general, severely reduced left ventricular ejection fraction is linked to a higher risk of life-threatening ventricular tachyarrhythmic events, and implantation of a defibrillator is often recommended. An alternative for these patients can be the wearable cardioverter/defibrillator, with temporary protection during a phase of high arrhythmic risk [35]. An elevated incidence of ventricular fibrillation episodes during an early phase of peripartum CMP in patients with severely reduced left ventricular ejection fraction and heart failure symptoms and uninterrupted vest defibrillator wearing for up to 6 months can protect these young mothers from dying suddenly and yield important information about a potential permanent risk that will indicate implantable cardioverter defibrillator implantation. Recent guidelines [12, 13] point that implantation of an implantable cardioverter defibrillator in patients with ventricular arrhythmia or low left ventricular ejection fraction should follow standard guidelines; the high rate of spontaneous recovery of dilated CMP after delivery must be considered when decisions are made.

Amyloid CMP: The efficacy and safety of implantable cardioverter defibrillator are uncertain. Sudden cardiac death is common in patients with cardiac amyloidosis, but electromechanical dissociation seems to be a significant cause of sudden death [36]. In recent guidelines [12, 13], implantable cardioverter defibrillator should be considered in patients with ventricular arrhythmia causing hemodynamic instability who are expected to survive >1 year with good functional status.

Idiopathic dilated CMP: Several observational registries [37] show that early diagnosis and tailored medical therapy are independent protectors against pump-failure death/heart transplant, and lower left ventricular ejection fraction is a predictor of sudden death, while implantable cardioverter defibrillator has a protective role.

Any observational study [38] shows the usefulness of cardiac resynchronization therapy in patients with *dilated CMP of valvular origin after corrective valve surgery* (an underrepresented population in randomized controlled trials). In patients with left bundle branch block, wide QRS (161 ms), and advanced functional class (III 82% - IV), there is a functional improvement in class and better data in left ventricular remodelation and asynchrony.

5.1. Role of cardiac resynchronization therapy

The usefulness of resynchronization has been recorded in clinical trials that included patients with severe depression of left ventricular systolic function, complete left bundle brain block, and heart failure syndrome. One important issue has been described recently: the relationship between QRS duration and left ventricular remodelation. Several factors that help to predict response to cardiac resynchronization replacement have been identified: systolic pulmonary artery pressure, renal function, left ventricular dyssynchrony, inappropriate left ventricular electrode position, ischemia, and 6-minute walking distance; but it remains unclear if QRS duration, measured before cardiac resynchronization therapy, can predict its effectiveness (conflicting results, with data pointing to one direction and to the opposite [39]). And patients with nonischemic CMP are more likely to benefit from cardiac resynchronization therapy compared to patients with ischemic CMP. According to the reduction of left ventricular end-diastolic diameter 6 months after cardiac resynchronization therapy, patients were divided into responder and nonresponder; measured parameters were not statistically different before

resynchronization. After 6 months, responders exhibited significant reversal of their left ventricular remodeling, with improved left ventricular ejection fraction and exercise tolerance, and a shorter QRS compared to nonresponders; the preoperative parameters were not predictive of the ultimate response of patients to resynchronization. Zhang [39] also shows that QRS duration change correlated with reduction in left ventricular end-diastolic diameter; QRS duration that can easily measured before and after resynchronization may be a predictive factor of response to cardiac resynchronization therapy in patients with heart failure due to dilated CMP. In a Spanish work, it is exposed that early normalization of ejection fraction after resynchronization is long-term maintained and identify better clinical and arrhythmic prognosis [40].

Cardiac resynchronization therapy is not strongly recommended for patients with narrow QRS. There are some described cases of CRT implant in patients with dilated CMP and narrow QRS in which it was obtained a dramatic response optimizing the atrioventricular delay, remembering the importance of atrioventricular optimization for successful resynchronization.

In addition, early normalization of left ventricular function in idiopathic dilated CMP is held long term after resynchronization device implant and indicates an improvement in prognosis from clinical and arrhythmic points of view. A decrease in cardiovascular mortality is observed, and also there is a decrease of arrhythmic events; this finding is consistent as described by García Lunar et al. [41]. The question is whether resynchronization device must be associated with implantable cardioverter defibrillator over time or even this mixed device (resynchronization + defibrillator) must be replaced by a resynchronization device only, especially if patient has inappropriate therapies.

It is stated in clinical guidelines [17] that the benefit is greater in patients with wider QRS and left bundle branch block and in women and non-ischemic cardiomyopathy, intermediate in men with ischemic cardiomyopathy; and lesser, or even non-responsive, in patients with narrow QRS and without left bundle block.

5.2. Role of implantable cardioverter defibrillator

Life-threatening ventricular arrhythmias are common in patients with heart failure and CMP, and their presence may lead to sudden death. These devices may have a primary and secondary indication. Secondary prevention with implantable cardioverter defibrillator is planned in patients with heart failure and CMP, also dilated CMP, who survive to an episode of sudden cardiac death. This indication is based on the results of several studies, AVID (entry criteria: left ventricular ejection fraction <40%), CASH, and CIDS. Some studies show a greater benefit of defibrillators in younger patients [42], whereas other studies did not found such differences [43, 44]. Also, there are studies focused on primary prevention in nonischemic dilated CMP; the trials CAT [45] and AMIOVIRT [46] showed a nonsignificant trend to decreased mortality, due to its methodological limitations. Other trials (DEFINITE, SCD-HeFT y COMPANION) did show reduction in mortality. At the view of these results and the results of a recent meta-analysis, primary prevention with implantable cardioverter defibrillator in patients with dilated CMP, left ventricular ejection fraction ≤35%, and NYHA II-III is recommended. The ability to induce ventricular arrhythmias is not predictive of sudden cardiac death in patients

with nonischemic CMP; thus, electrophysiology testing does not have a role in risk stratification of these patients [5] (**Figure 4**).

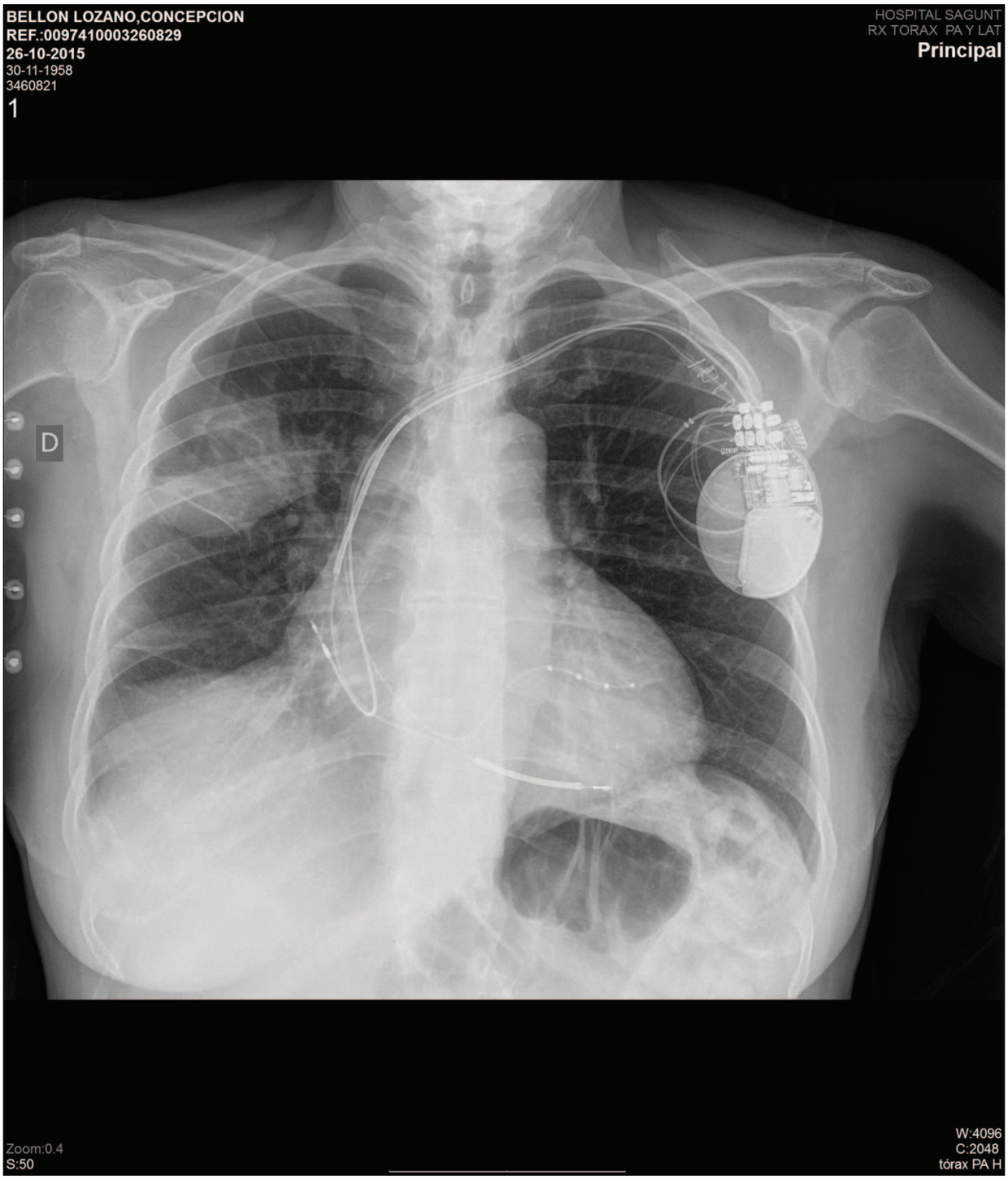

Figure 4. Cardiac resynchronization therapy in the same patient with idiopathic dilated cardiomyopathy. An alveolar condensation in the medium lobe compatible with nosocomial pneumonia (coincident with device implantation) can be seen.

As we have said before, in recent guidelines [12, 13], implantable cardioverter defibrillator is recommended, as secondary prophylaxis, in patients with hemodynamically nontolerated ventricular tachycardia/ventricular fibrillation, who are expected to survive for >1 year with good functional status. And for primary prophylaxis, defibrillator is recommended in patients with symptomatic heart failure (NYHA class II–III) and left ventricular ejection fraction ≤35% despite ≥3 months of treatment with optimal medical treatment who are expected to survive for >1 year with good functional status.

6. Restrictive CMP

This is the least frequent in the group of CMP and the only one for which the WHO/ISFC Task Force 81 does not offer specific diagnostic criteria. The diagnosis is based on clinical signs of heart failure due to a restriction on the diastolic filling of the heart with preserved systolic function and in the absence of hypertrophy or ventricular dilation. Amyloidosis, mucopolisacaridosis, and Löeffler's endocarditis are the more frequent causes. Treatment does not follow standard treatment guidelines as in other cases of cardiomyopathies and is based on a careful management of diuretics and vasodilators. The management of restrictive CMP is difficult because the underlying processes usually do not respond to intervention and is mostly palliative. In several cases, there has been an indication of implantable cardioverter defibrillator to prevent sudden cardiac death in high-risk patients; recent guidelines [12, 13] make a similar recommendation to other diseases with poor prognosis and state that defibrillators are recommended in patients with sustained ventricular arrhythmia causing hemodynamic instability who are expected to survive >1 year with good functional status to reduce the risk of sudden cardiac death. In relation to its pathophysiology, there is no indication to resynchronization. In most cases of restrictive CMP, caused by amyloidosis or other infiltrative diseases, there is a very poor prognosis, except in the case that the patient will receive a heart transplant. In patients with sarcoidosis, defibrillator implantation is recommended if left ventricular ejection fraction is <35%, maintained after a period of immunosuppression, and considered in patients with induced ventricular tachycardia in electrophysiology test and with late gadolinium enhancement in cardiac gammagraphy, although the left ventricular function is normal [47].

7. Arrhythmogenic right ventricular cardiomyopathy (ARVC)

It is a CMP, a hereditary disease of the desmosomal proteins, and is associated with sudden cardiac death; there is a fibrofatty replacement of the right ventricle myocardium that initially produces typical regional wall motion abnormalities that later become global and finally leads to right ventricular dilatation [48]. Its mechanism is re-entrant arrhythmias.

7.1. Role of implantable cardioverter defibrillator

Selection of patients for defibrillator is controversial. Natural history of the disease suggests several risk factors for sudden cardiac death: marked right ventricle dilatation, left ventricular

involvement with left ventricular reduced function, occurrence of prior hemodynamically unstable rapid sustained monomorphic ventricular tachycardia or ventricular fibrillation, and history of syncope; T-wave inversions could be a predictor of any ventricular arrhythmia in follow-up and a younger age; probably, the major risk for death was reduced left ventricular function [49]. Inducible sustained monomorphic ventricular tachycardia did not predict the presence of the same arrhythmia in the follow-up (although Bhonsale et al. found a relationship in their work [50]). When defibrillator is placed, anti-tachycardia pacing is highly successful in terminating sustained monomorphic ventricular tachycardia and should be programmed for all sustained monomorphic ventricular tachycardia, regardless of heart rate. Some authors comment that defibrillator implant with primary prevention has an excessively low rate of appropriate therapies, and the criteria for risk stratification have little predictive power; for these reasons, there should be revised. New genetic techniques help us to classify left ventricular hypertrophy in some patients as Fabry disease or other metabolopathies, with different prognosis and risk of sudden death than primary hypertrophic CMP. In addition, some registries have short (3.3 years) follow-up, and there have been appropriate therapies 9–10 years after the implant; given the youth of these patients and the long at-risk period, it is

Predictor variable	Definition	Coding
Age	Age at evaluation [30]	Continuous, years
Family history of SCD	History of sudden cardiac death in one or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post-or ante-mortem diagnosis) [13, 22, 28, 29]	Binary (yes = 1/no = 0)
Maximal wall thickness	The greatest thickness in the anterior septum, posterior septum, lateral wall, and posterior wall of the LV, measured at the level of the mitral value, papillary muscles, and apex using parasternal short-axis plane using 2D echocardiography at the time of evaluation [15, 17, 20, 23, 24, 26]	Continuous, mm
Fractional shortening	(LV end-diastolic dimension-LV end-systolic dimension)/LV end-diastolic dimension measured by M-Mode or 2D echocardiography at time of evaluation [23]	Continuous, %
Left atrial diameter	Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long-axis plane at the time of evaluation [30]	Continuous, mm
Maximal left ventricular outflow tract gradients	The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three- and five-chamber views. Peak outflow tract gradients were determined using the modified Bernoulli equation: Gradient = 4V [2], where V is the peak aortic outflow velocity [13, 18, 22, 27, 28]	Continuous, mmHg
Nonsustained ventricular tachycardia	≥3 consecutive ventricular beats at a rate of ≥120 bpm and <30 s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation [13, 17, 28, 29]	Binary (yes = 1/no = 0)
Unexplained syncope	History of unexplained syncope at or prior to evaluation [13, 20, 25, 28, 30]	Binary (yes = 1/no = 0)

Table 2. HCM Risk-SCD tool. HCM, hypertrophic CMP. SCD, sudden cardiac death. LV, left ventricle.

very important to perform long follow-up periods. The number of inappropriate therapies can decrease with better diagnostic algorithms. Recent guidelines for management of this disease [51] highlight several elements; the most important, little usefulness of algorithms based on binary variables that do not take into account the magnitude of each risk factor, with poor discriminatory power between high and low risk. Therefore, it is recommended to use the HCM Risk-SCD tool (**Table 2**) [30]. Recent guidelines [12, 13] state that defibrillator implantation is recommended in patients with a history of aborted sudden cardiac death and hemodynamically poorly tolerated ventricular tachycardia (secondary prevention) and should be considered in patients who have hemodynamically well-tolerated sustained Ventricular tachycardia or have one or more recognized risk factors for ventricular arrhythmia with a life expectancy >1 year.

7.2. Role of cardiac resynchronization therapy

It has been described as any case of mixed defibrillator-resynchronization device in special circumstances. In advanced cases of this disease, with low voltages in electrical signal from right ventricle, there can be difficult to detect ventricular tachyarrhythmias. The advanced degree of atrioventricular block indicates permanent cardiac pacing. There must be a catheter in coronary sinus for sensing and pacing, and another catheter in right ventricle as backup if left ventricle catheter capture fails, taking into account the high degree of atrioventricular block.

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