Cardiac resynchronization therapy: which device to implant?

Resynchronisation cardiaque : quelle prothèse implanter ?

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Summary

Cardiac resynchronization therapy is now a validated treatment for patients with moderate to severe heart failure despite optimal drug treatment with left ventricular systolic dysfunction and cardiac dyssynchrony defined by wide QRS greater than 120 ms. Once an indication for cardiac resynchronization therapy has been confirmed the choice of the most appropriate device (pacemaker or intracardiac cardioverter defibrillator (ICD)) needs to be made. In heart failure patients the risk of sudden death, mainly but not always related to arrhythmic cause is high. Previous studies of primary prevention of sudden cardiac death in patients with a poor left ventricular function have shown that ICD therapy significantly reduces overall mortality and arrhythmic mortality. However patients candidates to cardiac resynchronization therapy are different from those included in the ICDs trials because they are older and have more comorbidities. The choice of the devices has to consider the potential benefit of the therapy, the comorbidities, the life expectancy but also the cost-effectiveness and the potential complications related to the device. Now, new devices provide information about the hemodynamic status of this heart failure population and thus provide an early detection of heart failure decompensation. The development of home monitoring should alert very early the physicians of the occurrence of a heart failure decompensation and thus to avoid recurrent hospitalisations for heart failure decompensation.

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Résumé

la resynchronisation cardiaque est une technique aujourd’hui validée chez les patients en insuffisance cardiaque sévère malgré un traitement médical optimal avec dysfonction ventriculaire gauche systolique et un asynchronisme cardiaque défini par une durée des QRS supérieure à 120 ms. Une fois l’indication de resynchronisation cardiaque retenue, le choix de la prothèse la plus approprié (stimulateur ou défibrillateur) se pose. Les données de la littérature ont montré que ces patients sont exposés à la mort subite qui est le plus souvent, mais pas toujours, d’origine rythmique. Les études de prévention primaire ont montré le bénéfice significatif du défibrillateur implantable sur la mortalité globale et sur la
Introduction

When implemented in patients with advanced, drug-refractory congestive heart failure (CHF) due to left ventricular (LV) systolic dysfunction and ventricular dysynchrony (defined by a ≥120 ms QRS duration) (1,2), cardiac resynchronization therapy (CRT) alleviates symptoms, increases exercise capacity and improves quality of life (3-7). CRT also exerts salutary effects on LV remodeling within 3 months, with significant decreases in LV end-systolic and end-diastolic volumes, and a considerable increase in LV ejection fraction (EF) (3-7). More importantly, recent trials specifically designed to evaluate the effects of CRT on morbidity and mortality have demonstrated a significant decrease in hospitalization rates, particularly for decompensated CHF, and a significant decrease in the risk of death from all-causes and sudden cardiac death, including cases where CRT was not associated with cardioversion and defibrillation (6-8).

Finally, various analyses have shown that CRT is cost-effective despite the high cost of the devices (9,10). Recently issued European and North American guidelines for the treatment of chronic CHF recommend CRT in patients presenting in New York Heart Association (NYHA) CHF functional class III or IV despite optimal drug treatment, with a depressed LV function and dilated LV, and >120 ms QRS on surface electrocardiogram (ECG). The level of recommendation is particularly high with respect to alleviation of symptoms and lowering of hospitalization rates, as well as reducing mortality (1,2). It is, therefore, predictable that CRT will markedly increase over the next few years.

Technological progress in the field of CRT has been particularly prominent over the past 10 years. New, specifically designed and dedicated tools, such as guiding sheaths to catheterize the coronary sinus or over-the-wire LV stimulation leads, have considerably increased the LV lead implant success rate, which, in large trials, reaches 90% (6,7). Likewise, pulse generators have markedly evolved over the past 15 years with the development of atrio-biventricular defibrillators (CRT-D), the availability of completely independent LV and right ventricular (RV) channels, as well as CHF diagnostic and prognostic tools. Therefore, once an indication for CRT has been confirmed, the choice of the most appropriate device needs to be made.

Choice of cardiac resynchronization therapy system: atrio-biventricular pace-maker versus atrio-biventricular cardioverter defibrillator

The choice of a CRT-D hinges on the prevalence of sudden cardiac death among patients suffering from CHF, which, in various clinical studies conducted in the past 20 years, has ranged between 35 and 45% (10-15). It is noteworthy that this prevalence has decreased in the last few decades, as a result of the beneficial effects conferred by pharmacologic intervention, including beta-adrenergic blockade, spironolactone and, more recently, eplerenone (11-15).

The MERIT-HF trial has shown that, among all fatal events, the proportion of sudden death was inversely correlated with severity of CHF. Thus, 64% of patients in NYHA functional class II suffered sudden death compared to 59% in class III and 33% in class IV, in contrast to 56% of deaths due to end stage CHF. Conversely, only 12% and 26% of deaths were heart failure deaths among patients in functional classes II and III, respectively (12). The MUSTIC trial showed that, in candidates for CRT, sudden death accounted for 50% of fatal cardiovascular events (16), while in CARE-HF, 35% of deaths were sudden at the end of a mean follow-up of 29 months (8). These observations raise the issue of the systematic implantation of a CRT-D in all candidates for CRT. However, despite the prominent representation of ventricular tachyarrhythmias among the various causes of sudden death, ventricular defibrillation cannot prevent all events, since other mechanisms, such as asystole or electro-mechanical dissociation might be implicated.

The choice of device hinges, first of all, on whether the implant is indicated for primary or secondary prevention. Secondary prevention indications pertain to survivors of out-of-hospital cardiac arrest or to patients who suffer from hemodynamically unstable ventricular tachyarrhythmias. The secondary prevention AVID, CASH and CIDS trials demonstrated a 20-30% lowering of overall mortality and 33-59% decrease in arrhythmic deaths by implantable cardioverter defibrillators (ICD) (17-19). Therefore, CRT candidates who have a secondary prevention indication for an ICD should undergo implantation of a CRT-D. The clinical appropriateness of this choice was confirmed by the MIRACLE-ICD trial (20).
The issue of primary prevention in patients presenting with CHF is more complicated. One important variable that needs to be considered is the ischemic versus non-ischemic etiology of the underlying cardiomyopathy. The MADIT I, MUSTT and MADIT II trials have all confirmed the benefit conferred by ICD in survivors of myocardial infarction (MI) who have developed an ischemic cardiomyopathy (21-23). MADIT I and MUSTT included patients with LVEF <35% or <40%, who presented with non-sustained ventricular tachyarrhythmias and inducible ventricular tachycardia (21,22). The decrease in overall mortality by ICD was 55% and nearly 75% for arrhythmic mortality. The more recent results of MADIT II have confirmed the effectiveness of ICD in patients who, instead of being selected on the basis of rhythm criteria, were enrolled if they had a LVEF <30% after >1-month-old MI (23). In MADIT II, where the majority of patients remained in NYHA functional class I or II despite treatment with angiotensin-converting enzyme (ACE) inhibitors in 75% and beta-adrenergic blockers in 70%, the prophylactic implantation of ICD lowered overall mortality by 31% and arrhythmic mortality by 61% at 2 years. The benefit conferred by the ICD was even greater among patients whose QRS complex on surface ECG was >120 ms, with a lowering of overall mortality reaching 63%. The results of MADIT II also showed a highly significant lowering of the rate of sudden cardiac death in the ICD-treated group compared to the control group, and a slightly higher rate of death from non-sudden cardiac causes in the ICD-treated group, although the difference was not statistically significant (p=0.32). It is also noteworthy that, in survivors of MI, the benefit conferred by the ICD was distinctly greater in the subgroup with very severe LV dysfunction (LVEF <25%), whether in primary or secondary prevention trials (17-19, 21-23). Finally, in the DYNAMIT trial, the implantation of an ICD within 40 days after onset of acute MI had no effect on long-term, all-cause mortality (24).

In patients suffering from non-ischemic cardiomyopathies, the debate pertaining to the primary prevention of sudden death has been rekindled by the recently published results of the SCD-HeFT trial (25). The CAT and AMIOVIRT trials had previously shown no benefit conferred by ICD on all-cause mortality in patients suffering from non-ischemic cardiomyopathies (26,27). The results of the DEFINITE study showed a slightly lower overall mortality in the ICD-treated than in the control group, although the difference was not statistically significant (p=0.08). In contrast, the rate of sudden death due to ventricular tachyarrhythmias was significantly lower in the ICD-treated group. Furthermore, a subgroup analysis showed a significantly lower overall mortality in patients treated with an ICD who were in NYHA functional class III, though this type of post hoc analysis needs to be interpreted with caution (28).

The SCD-HeFT trial included over 2500 patients suffering from ischemic or non-ischemic cardiomyopathies, in NYHA CHF functional classes II or III, and with a LVEF <35% (25). The mean age of the population was 60 years, and mean LVEF was 25%. Ischemic and non-ischemic cardiomyopathies were evenly distributed. ACE inhibitors or angiotensin receptor blockers (ARB) were administered to 96%, beta-adrenergic blockers to 70%, spironolactone to 20%, and loop diuretics to 80% of patients. The study population was divided into a placebo-treated group, a group treated with amiodarone in doses adjusted for body-weight, and an ICD-treated group. The yearly mortality was 7% (i.e. 35% at 5 years in the placebo-treated group), and survival in the group of patients treated with amiodarone was the same. In contrast, in the ICD-treated group, the 5-year overall mortality was 23% lower, corresponding to a 7% lower absolute risk of death. Analyses of pre-specified subgroups revealed a greater survival benefit conferred by the ICD to patients in NYHA functional class II than class III, and a similar benefit in patients suffering from ischemic and non-ischemic cardiomyopathy.

Finally, the results of the COMPANION trial confirmed the effectiveness of ICD therapy in patients with ischemic or non-ischemic cardiomyopathies (6). The 1520 patients included in this trial were CRT candidates, defined as severe CHF (NYHA functional class III or IV), a LVEF <35%, a >120 ms QRS duration, and a >150 ms PR interval. All patients were treated with an optimal drug regimen and had been hospitalized for management of CHF within the prior 12 months. No patient had an indication for implantation of an ICD. The mean age of the population was 67 years, 87% were in NYHA functional class III, mean LVEF was 20% and mean QRS duration was 160 ms. Ischemic cardiomyopathy was the underlying disease in 55% and left bundle branch block was present in 70% of patients. Treatment with an ACE inhibitor or ARB was administered to 90%, beta-adrenergic blockers to 70% and spironolactone to 55% of patients. The study population was divided into three groups in a 1:2:2 ratio to receive optimal medical regimen only, optimal medical regimen + CRT, or optimal medical regimen + CRT + ICD. This trial showed that CRT, with or without ICD, lowered the primary endpoint of death from all causes and hospitalizations by 20%, a statistically significant treatment effect. Deaths or rehospitalizations for management of cardiovascular events were decreased by 30% in both groups treated with CRT compared with the group assigned to optimal medical regimen only, and the combined endpoint of deaths and hospitalizations for management of CHF was decreased by 35% in both groups assigned to CRT. However, the secondary study endpoint of all-cause mortality was significantly lowered (by 36%) in the CRT + ICD group only, compared with the group assigned to the optimal medical regimen. CRT + optimal medical therapy decreased overall mortality by 24% compared with an optimal medical regimen only, a difference that approached significance (p=0.06). It should be emphasized, however, that the COMPANION trial was not designed to compare CRT with ICD therapy.

The recently published results of CARE-HF further complicate the debate. At the end of a mean follow-up of 29 months, CRT associated with optimal medical therapy had lowered the combined endpoint of all-cause mortality and rehospitalizations for cardiac causes by 37% (p<0.001), as well as overall mortality by 36% (p<0.002) (7). The approximate 35% rate of sudden death was similar in both groups. However, the CARE-HF trial extended to a mean of 37 months confirmed the persistence of an overall survival benefit conferred by CRT (-40%; p=0.0001), along with a lower rate of CHF-related deaths (-45%; p=0.003), and a highly significant reduction in the rate of sudden deaths (-46%; p=0.005). A study from the Netherlands revealed that, at the end of a mean follow-up of 18 months, appropriate ICD therapy had been delivered to 35% of recipients of CRT-D systems implanted for secondary, and 21% of recipients of CRT-D systems implanted for primary prevention.
It is noteworthy that, in this study, no predictor of appropriate ICD therapy was identified.

While CHF is a syndrome that predominantly affects populations approaching 75 years of age, these various clinical studies enrolled patients between the ages of 60 and 65 years. Furthermore, patients suffering from CHF often present with major comorbidity. A clear-cut strategy with regard to the implantation of CRT-P versus CRT-D devices cannot be proposed. A crude solution would consist of implanting a CRT-D system in all CRT candidates. This seems inappropriate however, because of the widely different costs of devices (CRT-D are 3-5 times more expensive than CRT-P), and the old age and major comorbidity of some of the candidates. In some patients, the indication might be strictly functional, which does not justify the implantation of a CRT-D (30). The MADIT II trial, for example, showed no benefit conferred by ICD in patients whose glomerular filtration rate was <35 ml/min/1.73 m² (31). Therefore, in CRT candidates with a secondary prevention indication for an ICD, CRT-D should be implanted systematically, provided that, physiologically, they are in an “acceptable” state of health. In CRT candidates who have a primary indication for ICD implant, the physiological state must be scrutinized even more rigorously when choosing a device. Young patients, who are, by definition, potential cardiac transplantation candidates, should undergo implantation of a CRT-D, regardless of whether they present with an ischemic or non-ischemic cardiomyopathy. Conversely, for elderly patients with major concomitant illnesses and a limited life-expectancy, the choice of CRT-P appears more reasonable. The “gray zone” in-between these two types of populations represents the main challenge. Patient and relatives must be thoroughly informed of the benefit and disadvantages offered by each type of device, particularly of the risk of inappropriate shocks and lead fractures associated with CRT-D therapy.

**Importance of independent right and left ventricular channels**

New developments in the design of atrio-biventricular devices provide independent left and right ventricular channels. This important technologic progress has lowered the rate of re-operation for dysfunctional external connectors that were used in the early applications of CRT. The advantages offered by these independent ventricular channels include the selective sensing of right and left ventricular activity, and the separate programming of left and right ventricular stimulation output. The latter might be particularly important in cases of high capture thresholds, particularly at the LV lead, in cases of phrenic nerve stimulation, or when LV versus RV lead impedance is markedly different. Finally, new CRT-D devices allow the programming of interventricular delay and sequential activation of the ventricles. Single-center studies performed in small numbers of patients have shown an increase in LVEF and cardiac output, better left intraventricular resynchronization, and mitigation of mitral regurgitation by sequential RV and LV, compared with simultaneous ventricular stimulation (32,33). These noteworthy observations need to be verified in larger prospective studies. The RHYTHM ICD II study, which compared an optimized VV delay based on echocardiographic measurement of stroke volume versus simultaneous biventricular stimulation (VV delay = 0 ms) found no clinical benefit conferred by an optimized VV delay (34).

**Diagnostic and prognostic tools for heart failure**

Recipients of atrio-biventricular systems are primarily patients who suffer from CHF. The latest generation of devices include tools that allow the evaluation of important variables such as patient activity and respiratory indices, which improve the quality of follow-up. The recent results of the MID-HEFT study, based on measurements of intrathoracic impedance, have opened noteworthy perspectives (35). In the presence of pulmonary fluid overload, impedance between the RV lead and pulse generator decreased. Conversely, after treatment and alleviation of pulmonary fluid overload, intrathoracic impedance increased. This study, which included 33 patients hospitalized for cardiac decompensation, showed that intrathoracic impedance fell by an average of 12% within 2 weeks before hospitalization. This study also showed an inverse correlation between increase in intrathoracic impedance on the one hand and fall in pulmonary capillary pressure and vascular overload on the other (r = -0.90; p<0.001). An algorithm based on the magnitude of fall in intrathoracic impedance might allow the delivery of a warning to the patient and physician of impending pulmonary vascular fluid overload, thereby prompting a reduction in number of hospitalizations or, at least, a shortening of their duration. Other hemodynamic variables are under examination or in the process of being validated, including peak endocardial acceleration, left atrial pressure, RV pressure, or pulmonary arterial pressure. Currently available devices are also capable of analyzing variations in sinus rate, the prognostic importance of which has been highlighted in several studies (36,37).

**Conclusions**

The number of CRT-D implants is expected to increase, even when taking into consideration important factors such as patient age and comorbidity. The CRT-P versus CRT-D debate is unlikely to be settled by evidence-based medicine, since 1600 patients would be needed per study group, followed for 3 years, to show a 3.8% absolute decrease in all-cause mortality by CRT-D compared with CRT-P, with 90% power (8). Devices equipped with separate RV and LV channels allow more precise programming of several parameters and, if confirmed by ongoing studies, the programming of an optimized individual interventricular delay. New devices allow the evaluation of CHF and optimization of its management. Cardiac resynchronization is usually delivered by biventricular stimulation, although experimental and uncontrolled clinical studies suggest that isolated LV stimulation might be a viable alternative. Finally, in patients suffering from CHF, in whom the prevalence of atrial fibrillation is high, the inclusion of an atrial fibrillation prevention algorithm by atrial stimulation might be valuable.
Finally, the development of home monitoring should be very helpful in the next future to detect very early the heart failure decompensation.

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