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Cardiac Resynchronization in Mildly Symptomatic Heart Failure Patients

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1. Introduction

Despite advances in detection and therapy heart failure remains a major and growing social problem.
The Framingham Heart Study (Lloyd-Jones et al., 2002) demonstrated that one out of five 40 year-old adults will develop heart failure symptoms at some point in their lifetime.
In the United States (Lloyd-Jones et al., 2010), there are 5 million heart failure patients in a total population of 294 million and in Europe; there are 10 million heart failure patients in a total population of 666 million (Mosterd A et al.,1999). Health-care expenditure for heart failure typically accounts for 1% to 2% of total health costs, of which hospitalizations constitute 60% to 70% (Berry C et al., 2001; Rydén-Bergsten & Andersson, 1999).

2. Clinical profiles and prognosis in heart failure

Heart failure is a syndrome rather than a primary diagnosis and has many potential etiologies, various clinical features, and numerous clinical subsets; some patients never develop cardiac dysfunction, and others with cardiac dysfunction may or not develop clinical heart failure.
Heart failure is a progressive disorder that is frequently preceded by asymptomatic left ventricular (LV) systolic dysfunction. In the early stages of LV systolic dysfunction individuals are typically asymptomatic, partly because of compensatory mechanisms involving the autonomic nervous system, neurohormones, and changes in the cardiac structure and function.
Whether the dysfunction is primarily systolic, diastolic or combined, it leads to neurohormonal and circulatory abnormalities, usually resulting in characteristic symptoms such as fluid retention, shortness of breath, and fatigue, especially on exertion. The severity of clinical symptoms may vary substantially during the course of the disease and may not correlate with changes in underlying cardiac function. Although the mechanisms responsible of heart failure progression to a symptomatic state are not clear, many modifiable factors have been identified that predispose or aggravate the remodelling process and the development of cardiac dysfunction. Treatment of systemic hypertension, with or without LV hypertrophy, reduces the development of heart failure.
In patients with atherosclerotic cardiovascular disease the prevention of myocardial infarction is of crucial importance, since its occurrence confers an 8-to 10-fold increase in the risk of subsequent heart failure (Lindenfeld et al., 2010).

Others modifiable risk factors include anemia, diabetes, hyperlipidemia, obesity, valvular abnormalities, alcohol, certain illicit drugs, some cardiotoxic medications, and diet.

Cardiac resynchronization therapy by means of cardiac biventricular stimulation has proved to be an essential therapy for heart failure, especially in highly symptomatic patients with LV systolic dysfunction.

In fact, current guidelines recommend cardiac resynchronization therapy in patients with left ventricular ejection fraction (LVEF) <35%, QRS prolongation (> = 120ms), and New York Heart Association (NYHA) class III or IV heart failure.

These recommendations are consequent to multiple prospective, randomized trials demonstrating the benefits of cardiac resynchronization therapy in advanced heart failure: symptoms can be reduced and exercise capacity improved, overall mortality decreased and LV function increased. In particular cardiac resynchronization therapy was able to slow heart failure progression.

Therefore, it appeared reasonable to test cardiac resynchronization therapy in patients who have structural heart disease but have not yet developed severe heart failure symptoms, especially considering the relatively high percentage of mortality and hospitalizations in mild symptomatic heart failure patients (Zannad et al., 2011). The possibility of using cardiac resynchronization therapy in this population justifies an attempt to define and identify mild symptomatic patients.

The current American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for heart failure (Hunt et al., 2009) divide cardiovascular disorders into four stages, the first two of which (A and B) do not include symptomatic patients.

Stage A denotes a high risk for heart failure but without evidence of structural heart disease and includes individuals with hypertension, diabetes or known atherosclerotic disease. Stage B includes individuals with cardiac abnormalities "structural heart disease but without symptoms". Stage C includes individuals with symptomatic heart failure with underlying structural heart disease. Stage D includes individual with advanced structural heart disease and refractory symptoms of heart failure requiring specialized interventions.

In a study of a community cohort, Ammar et al. (Ammar et al., 2007) provided information regarding the prevalence and the mortality associated with each heart failure stage, giving prognostic validation to heart failure staging.

Participants were classified according to their medical history, symptoms questionnaire, physical examination, and echocardiogram. In the cohort, 32% were normal, 22% were stage A, 34% were stage B, 12% were stage C, and 0.2% were stage D. Mean B-type natriuretic peptide concentrations (pg/ml) increased by stages: stage 0= 26, stage A=32, stage B= 53, stage C= 137 and stage D=353.

Survival at 5 years was 99% in normal subjects, 97% in stage A, 96% in stage B, 75% in stage C, and 20% in stage D.

Before ACC/AHA decided to adopt heart failure stages, classification focused solely on the patients' clinical symptoms, using the NYHA functional classification (class I-IV). In NYHA classification all patients had structural heart disease and class I included asymptomatic patients, while class II included mildly symptomatic patients.

Baldassseroni et al. (Baldasseroni et al., 2002) analyzed data from the Italian Network on Cardiac HF Registry including 5517 unselected patients with cardiac heart failure due to various causes and found that NHHA class I-II was present in 71% of all patients and in 67,2% of left bundle branch block (LBBB) patients.

Moreover the authors indicated that the presence of LBBB is an unfavorable prognostic marker in patients with cardiac heart failure and the negative effect does not depend on age, cardiac heart failure severity, or drug prescriptions.
When combining ACC/AHA and NYHA classifications, NYHA class I can be included in Stage B and NYHA class II-III in Stage C (see table 1). It should be considered however that these stages included both patients with systolic and diastolic LV dysfunction. Instead, studies which evaluated the role of cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure enrolled only patients with systolic LV dysfunction. Some previous studies can be analyzed in order to define percentage prevalence and characteristics of patients with systolic LV dysfunction in NYHA functional class I and II.
A recent metanalysis (T.J. Wang et al., 2003) reported a prevalence of asymptomatic LV systolic dysfunction varying from 0.9% to 12.9%.
The prevalence of asymptomatic LV systolic dysfunction was twofold to eightfold higher in men than in women and higher in the elderly. Moreover the prevalence was highest among individuals with known coronary heart disease, ranging from 4.8% to 8.5%.
In SOLVD study (Studies of LV Dysfunction prevention), the development of heart failure was analyzed in patients with asymptomatic LV systolic dysfunction defined by an LVEF < 35%. Among the total population 30% in the placebo group compared with 21% in the enalapril group developed heart failure over a period of 8.3 years. In the Framingham study, a mortality rate of 40% in asymptomatic patients with a marginally reduced LVEF (<50%) was found over a period of 5 years.
Iuliano et al. (Iuliano et al., 2002) performed a retrospective analysis to examine the association between QRS prolongation (>120 ms) and mortality in patients with a LVEF <40% and reported that NYHA I and II classes were present respectively in 1,2 % and 54 % of all patients and in 1,4% and 48 % of patients with QRS > 120 ms. Moreover they concluded that QRS prolongation is an independent predictor of both increased total mortality and sudden death in patients with heart failure.
Edelmann et al. (Edelmann et al., 2011) evaluated data of 4259 patients with preserved or reduced LVEF. NYHA I and II classes were present respectively in about 7-8% and 50% of population with reduced LVEF. Moreover the authors underlined how comorbidities can condition symptoms appearance.
De Marco et al. (De Marco et al., 2004) analyzed data of 11804 patients with left ventricular dysfunction (LVEF < 40%). Percentages of NYHA I and II classes proved to be respectively 19, 5 % and 50, 8 %.
On the basis of these data it can be noted that the number of mildly symptomatic heart failure patients with systolic dysfunction is comparable to the number of highly symptomatic patients who at present have the widest indication for cardiac resynchronization therapy. This is very important considering the influence of heart failure therapy on health-care costs in terms of devices and hospitalization.

3. Therapy of heart failure

Obviously the first approach in asymptomatic or mildly symptomatic patients is medical therapy. In fact angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and B- blockers have been proven to provide cardiovascular benefit to patients at any stage of heart failure.

ACC/AHA Stage		NYHA Functional Class	
Stage	Description	Class	Description
A	Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.	No comparable functional class	
B	Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.	I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
C	Patients who have current or prior symptoms of HF associated with underlying structural heart disease.	II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
		III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.	IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

ACC/AHA - American College of Cardiology/American Heart Association; HF - heart failure; NYHA - New York Heart Association

Table 1. ACC/AHA vs NYHA Classification of Heart Failure

Even if medical treatment of heart failure improves prognosis and reduces symptoms by impeding molecular disease mechanisms, reversing self-propelling neurohormonal reactions and reducing afterload burden, drugs cannot abolish electrical dyssynchrony or resynchronize mechanical delay.
Therefore any intervention despite optimal heart failure medication capable of slowing or even reversing disease progression, thereby reducing hospitalizations may help to reduce healthcare costs in these patients. Cardiac resynchronization therapy can be considered an intervention of this type. Some studies have indicated the utility of cardiac resynchronization therapy in these patients determining an enlargement of cardiac resynchronization therapy indications. A synthesis of these studies is reported in table 2 and 3 and a more detailed description of them in the following paragraphs.

4. Cardiac resynchronization therapy

4.1 Contak CD

Contak CD was the first study which investigates in NYHA I/II the effect of cardiac resynchronization therapy with defibrillator (CRT-D) compared with defibrillator (ICD) only to stratify NYHA I/II and NYHA III/IV heart failure patients with or without cardiac resynchronization therapy. Enrollment criteria were an LVEF ≤35% and a QRS width ≥ 120ms. The total population consisted of 490 patients, 32% of whom were in NYHA class II at the time of study enrollment, LBBB was present in 55%, and the mean QRS width was 160ms. During follow-up in patients in NYHA class II at baseline no significant symptomatic improvement was achieved in the cardiac resynchronization therapy group compared with the control group. Nonetheless in NYHA class II patients, cardiac resynchronization therapy was linked to significant improvement in LV dimension but not in LVEF over either 3 or 6 months.
This study was limited by the presence of the patients' clinical instability (passing from a NYHA functional class to another), by the presence of suboptimal medical therapy at enrollment, and by a major change in trial design midway through the investigation resulting in a combination of the 3- and 6-month control period from two different phases of study in the data analysis, and by difficulties inherent in subgroup analysis.

4.2 Miracle ICD-II

Miracle ICD-II examines the effect of CRT-D compared with ICD only exclusively in NYHA II patients with an indication for ICD therapy. LVEF was ≤35 and QRS ≤ 130 ms. Primary end points in this trial were cardiac function tests, NYHA classification and quality of life. There was only a 6 months follow up. Results of function tests were not significantly different in CRT-D patients compared with those receiving ICD alone. However, cardiac resynchronization therapy produced significant improvement in LV systolic and diastolic volumes and left ventricular ejection fraction indicating that cardiac resynchronization therapy promotes reverse remodelling even in patients with less symptomatic heart failure. The fact that these effects did not improve exercise capacity is not completely unexpected because patients with mildly symptomatic heart failure usually have better-preserved exercise tolerance than those with advanced heart failure. Nevertheless, the beneficial impact of cardiac resynchronization therapy on parameters that characterize adverse cardiac remodelling is interesting and important and should be put into perspective.

TRIAL	CONTAK CD (Higgins 2003)	MIRACLE ICD II (Abraham, 2004)	REVERSE (Linde, 2008)
Number of patients	581	186	610
Follow-up (months)	6	6	12
Ejection Fraction (%)	≤ 35	≤ 35	≤ 40
QRS (ms)	≥ 120	≥ 130	≥ 120
Cardiac rhythm (for inclusion)	sinus	sinus	sinus
NYHA class (%) I	-	-	18
II	32	100	82
III	60	-	-
IV	8	-	-
Mean QRS (ms)	160	166	153
LBBB (%)	54	88,2	NR
Primary End-point	HF clinical composite response	Change in peak VO2	HF clinical composite response
Secondary End-point	VO2, NYHA class, quality of life, 6 min WT, LV volumes, LVEF	VE/VCO2, NYHA class, quality of life, 6 min WT, LV volumes, LVEF	LVESVi, LVEF
Results	CRT improves functional status	No change primary end-point, improvements in secondary end-points	No change primary end-point, improvements in secondary end-points

AF – atrial fibrillation; AFl – atrial flutter; CRT – cardiac resynchronization therapy; HF – heart failure; LV – left ventricle; LVEF – left ventricular ejection fraction; LVESVi – left ventricular endsystolic volume indexed; VO2 - peak oxygen consumption; NR – not reported.

Table 2. Characteristics of clinical trials evaluating effects of cardiac resynchronization therapy in asymptomatic or mild symptomatic heart failure patients with left ventricular dysfunction

TRIAL	REVERSE European (Daubert, 2009)	MADIT-CRT (Moss, 2009)	RAFT (Tang, 2010)
Number of patients	262	1820	1798
Follow-up (months)	24	28	40
Ejection Fraction (%)	≤ 40	≤ 30	≤ 30
QRS (ms)	≥ 120	≥ 130	≥ 120 / ≥ 200 paced
Cardiac rhythm (for inclusion)	sinus	sinus	sinus, paced / persistent AF, Afl
NYHA class (%) I	17	15	-
II	83	85	80
III	-	-	20
IV	-	-	-
Mean QRS (ms)	153	158	158
LBBB (%)	NR	70	72
Primary End-point	HF clinical composite response events	Death from any cause, non fatal heart failure events	Death from any cause, HF hospitalization
Secondary End-point	LVESVi, LVEF	Recurring HF events, echocardiographic changes at 1 year	Death from any cause, death from any cardiovascular cause, HF hospitalization
Results	CRT better in terms of primary and secondary end-points	CRT better in terms of primary and secondary end-points	CRT improves HF and mortality

AF – atrial fibrillation; AFl – atrial flutter; CRT – cardiac resynchronization therapy; HF – heart failure; LV – left ventricle; LVEF – left ventricular ejection fraction; LVESVi – left ventricular endsystolic volume indexed; VO2 - peak oxygen consumption; NR – not reported.

Table 3. Characteristics of clinical trials evaluating effects of cardiac resynchronization therapy in asymptomatic or mild symptomatic heart failure patients with left ventricular dysfunction

These findings motivated three studies: the Resynchronization Reverse Remodeling in Systolic LV dysfunction (REVERSE), the Multicenter Automatic Defibrillator Implantation With cardiac resynchronization therapy (MADIT-CRT), and the Resynchronization /defibrillation for Ambulatory heart failure Trial (RAFT) trials which all aimed at assessing whether cardiac resynchronization therapy improves the clinical condition and prevents disease progression in such heart failure patients.

4.3 REVERSE

REVERSE was a multicenter, randomized, double-blind controlled study enrolling 610 patients during the scheduled follow-up period of 12 months; 419 with cardiac resynchronization therapy (or CRT-D) switched on and 191 with cardiac resynchronization therapy switched off. Patients were required to be in sinus rhythm, in NYHA class I (17%) or class II (83%) for at least 3 months before enrollment; LVEF had to be ≤ 40%, LV end-diastolic dimension ≥ 55mm, and QRS duration ≥120ms. European patients (n=261) enrolled in 35 centers had to be followed up for 24 months within their randomized group.

All patients had been receiving optimal medical therapy for heart failure, including stable doses of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker and a beta-blocker for at least 3 months. Patients were excluded if they had been classified as NYHA functional class III or IV or had been hospitalized for heart failure in the 3 months before enrollment.

The primary end point of this study was defined as a heart failure composite response, with response groups classified as “worsened” (death, hospitalization for heart failure, crossover because of worsening heart failure, worsening NYHA class, or worsened heart failure determined by patient global assessment score), “improved” or unchanged.

Secondary end points were LV volumes, LVEF, and heart failure hospitalization. Other endpoints took into consideration 6-minute walk test, quality-of-life scores, and episodes of ventricular tachycardia or ventricular fibrillation. A CRT-D device was implanted in 82% of the CRT-ON and 85% of the CRT-OFF group. About 20% were women, 56% had ischemic cardiomyopathy, mean QRS duration was 153ms, and mean LVEF was 26%.

The REVERSE trial showed for the first time that cardiac resynchronization therapy improves ventricular structure and function (a significant decrease in LV end-diastolic and end-systolic volume indexes, as well as an increase in LVEF) in patients with asymptomatic and mildly symptomatic heart failure. In contrast, there was no significant difference between the percentage of patients who worsened in the composite primary end point compared with the percentage of patients who remained unchanged or improved. In addition, REVERSE demonstrates a significant reduction in heart failure morbidity defined as the need for hospitalization in patients with worsening heart failure in as much as in patients with active cardiac resynchronization therapy there was a statistically significant 53% relative risk reduction in time to first heart failure hospitalization. Finally, REVERSE found no significant improvement in quality of life or exercise capacity with cardiac resynchronization therapy which is not surprising in a group of patients with little functional impairment at baseline.

Out of the 262 European patients, who remained in their double-blind assignment for 24 months, 180 were assigned to CRT-ON and 82 to CRT-OFF. In contrast to the main study 19% patients worsened with CRT-ON compared with 34% with CRT-OFF (p=0.01).

However, no difference in 6-minute walk distance, quality of life, or NYHA classification was observed between the two groups. LV end-systolic volume index decrease by a mean of 27.5 ± 31.8 mL/m² in the CRT-ON group compared with 2.7 ± 25.8 mL/m² in the CRT –OFF group ($p<0.0001$). Reverse remodelling by cardiac resynchronization therapy was thus progressive, with the greatest effect during the first 6 months and further improvement developing over the following 12 months. This progressive reverse remodelling was accompanied by a significant delay in time to first heart failure hospitalization or death (HR 0.38; $p= 0.003$) with cardiac resynchronization therapy, suggesting that cardiac resynchronization therapy prevents the progression of disease in patients with asymptomatic or mildly symptomatic LV dysfunction when it is utilized for a period of 1 to 2 years.
We have to consider that the baseline characteristics in the European cohort of REVERSE had some key differences with respect to the North American subgroup. The European group had a lower proportion of ischemic cardiomyopathy, a lower incidence of prior myocardial infarction, a lower body mass index and longer average QRS duration.

4.4 MADIT–CRT

MADIT–CRT was designed to determine whether CRT-D in high-risk, relatively asymptomatic patients with ischemic and nonischemic cardiomyopathy would significantly reduce the combined end point of all-cause mortality or heart failure events, whichever of the two occurred first, as compared with ICD therapy alone. The secondary objectives were measures of reverse remodelling after 12 months and all-cause mortality was one of the tertiary end points.
In order to satisfy inclusion criteria, patients with ischemic causes had to be classified as in NYHA class I or II, and those with nonischemic causes had to be classified as in NYHA class II. All patients had to have LVEF <30% and sinus rhythm with QRS > 130 ms. MADIT-CRT had a group sequential design as in other MADIT trials. Randomization to arms was done on a 3:2 basis, and patients were stratified by ischemic or nonischemic cardiomyopathy in each study center.
Secondary endpoint was recurrent heart failure events; tertiary end point was focused particularly on LV volume and LVEF changes assessed by echocardiography 1 year after enrollment.
The study population consisted of 1820 patients (1089 in the CRT-D arm and 731 in the ICD-only arm); 25% were female, 45% had nonischemic cardiomyopathy, the mean LVEF was 24%, the mean QRS duration was 158 ms, and 70% of the patients had an LBBB configuration. The average follow-up for all patients was 2.4 year.
During follow-up the primary end point occurred in 187 out of 1089 patients in the CRT-D group (17.2%) and 185 out of 731 patients in the ICD-only group (25.3%). There was not a significant difference in benefit between patients with ischemic cardiomyopathy and those with nonischemic cardiomyopathy. The superiority of cardiac resynchronization therapy was driven by a 41% reduction in the risk of heart failure events, a finding that was evident primarily in a prespecified subgroup of patients with a QRS duration of 150 ms or more. An analysis of the Kaplan-Meier estimate of heart failure survival probability shows that there was already an early diverging of curves in favour of CRT-D after 2 months.
The annual mortality rate (3%) was equally low in both arms of randomization.
Moreover a significant reverse LV remodelling was found at 1 year with a mean increase in LVEF of 11%, and a drop in both mean LV end-diastolic volume (52 ml), and in LV end-

systolic volume (57 ml). These analyses prove that CRT-D can induce a significant reversal of the structural remodelling process, even in patients without or with only mild symptoms of heart failure (NYHA I/II). A slight but still significant reduction in mitral regurgitation was noticed in the CRT-D arm.

Exercise capacity, measured by a 6-minute walk test, did not improve with CRT-D; both quality-of- life scores showed a trend toward improved scores, but the difference before and after cardiac resynchronization therapy was not significant. The biomarker brain natriuretic peptide was significantly reduced in CRT-D patients (-35 pg/dl) but not in the ICD-only arm.

Therefore MADIT-CRT clearly demonstrated that heart failure progression can be prevented within 2.5 years of follow-up in patients with structural heart disease without or with only mild symptoms of heart failure at the time of CRT-D.

Prevention of heart failure progression is combined with reverse ventricular remodelling. Since patients in NYHA I/II or stage B heart failure have almost no limitations on their exercise capacity and have a relatively low overall mortality rate, it is difficult to demonstrate a significant increase in exercise capacity or decrease in overall mortality within a relatively short time.

4.5 RAFT

In conclusion **RAFT** study enrolled 1798 patients in NYHA class II or III heart failure, with a LVEF of 30% or less, and an intrinsic QRS duration of 120 ms or more, or a paced QRS duration of 200 ms or more, in order to receive either an ICD alone or a CRT-D. The primary outcome was death from any cause or hospitalization for heart failure.

The primary outcome, death or hospitalization for heart failure occurred in 364 out of 904 patients (40.3%) in the ICD group, as compared with 297 out of 894 patients (33.2 %) in the CRT-D group ($p<0.001$). The time to the occurrence of the primary out-come was significantly prolonged in the CRT-D group ($p<0.001$).

During the course of the trial the mortality rate in the two groups was 23.5 %(422 out of the 1798 patients).

In the CRT-D group, the 5-year actuarial rate of death was 28.6%, as compared with 34.6% in the ICD group. The time until death was significantly prolonged (relative risk reduction, 25%) in the CRT-D group ($p=0.003$).

The number of patients who were hospitalized for heart failure was lower in the CRT-D group, with 174 patients hospitalized (19.5%), as compared with 236 (26.1%) in the ICD group ($p<0.001$).

However, the number of device-related hospitalizations was higher in the CRT-D group, with 179 hospitalizations (20%) as compared with 110 (12.25) in the ICD group ($p<0.001$).

Among patients with NYHA class II heart failure and among those with class III heart failure, the two study interventions were associated with similar reductions in the risk of death or hospitalization for heart failure, death from any cause, and hospitalization for heart failure.

5. Concluding remarks

Taking these studies into consideration, cardiac resynchronization therapy in mild systolic heart failure results in reverse remodelling and clinical improvements comparable to those we see in advanced heart failure stages. In particular cardiac resynchronization therapy proved to be advantageous especially in patients with a prolonged QRS (> 150 ms) which probably indicates the existence of ventricular dyssynchrony. This should be considered even in the light of a recent study (Bleeker et al., 2006) which demonstrated that the severity of baseline LV dyssynchrony, assessed with color-coded tissue Doppler imaging, was comparable between patients in NYHA class II and those in NYHA classes III to IV. In their study NYHA II class patients showed a significant improvement in LVEF and reduction in LV end-systolic volume after cardiac resynchronization therapy, similar to the one in patients in NYHA classes III to IV. Cardiac resynchronization therapy should therefore be considered in patients with a reduced LVEF, wide QRS (and/or dyssynchrony), and minimal or asymptomatic heart failure in addition to optimal medical therapy. All these data confirm the pertinence of the recent update on cardiac resynchronization therapy guidelines which included indications for mildly symptomatic heart failure patients. Further reinforcement of this consideration derives from the fact that cardiac resynchronization therapy has been considered a cost-effective intervention for patients with mildly symptomatic heart failure and for asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms.

Another aspect that should be analyzed is the rationale for the combined use of cardiac resynchronization therapy and ICD in these heart failure patients. This is particularly important in as much as sudden death is the leading cause of mortality in mild systolic heart failure (MERIT HF, 1999). Therefore, the potentially greatest benefit of ICDs is likely to be conferred on patients with mild-to- moderate heart failure.

The Sudden Cardiac Death in Hearth Failure (SCD-HeFT) trial showed a lowering of all-cause mortality by ICD therapy in patients with mild-to-moderate heart failure and LVEF <35%. The risk reduction was limited to functional class II patients. No treatment benefit was observed among the 30% of patients who were in NYHA functional class III.

EVADEF study demonstrated that ICD implantation effectively reduces sudden cardiac death so that mildly symptomatic patients tend to die of progressive heart failure.

Finally, Gold et al. (Gold et al., 2011.) studied a patient population receiving CRT-D devices (83 % out of the entire REVERSE cohort) and concluded that cardiac resynchronization therapy did not affect the overall frequency of ventricular tachyarrhythmias even if this arrythmia increased in CRT-ON patients without reverse remodelling, whereas it decreased in those with reverse remodelling. In their opinion these data could rise the issue of whether or not ICD backup is chronically needed in those patients with normalization of LV structure and function with cardiac resynchronization therapy. However the incidence of ventricular arrhythmias was similar in NYHA I and II patients, and in those with ischemic or nonischemic cardiomyopathy as well. Accordingly, neither the etiology nor the severity of heart failure was able to predict which patients were more likely to experience appropriate ICD therapy thereby benefiting from ICD backup with cardiac resynchronization therapy. Thus the authors concluded that further confirmation of their results are needed before a strategy of excluding ICD backup in certain mild symptomatic cardiac resynchronization therapy patients can be recommended.

Thus on the basis of these remarks it is difficult to affirm at present, that the use of cardiac resynchronization therapy in mildly symptomatic heart failure patients should not be combined with ICD.

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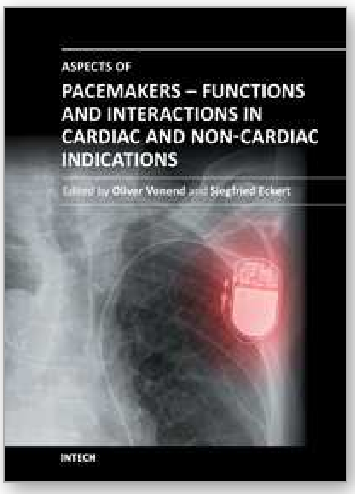

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Outstanding steps forward were made in the last decades in terms of identification of endogenous pacemakers and the exploration of their controllability. New â€œartificalâ€ devices were developed and are now able to do much more than solely pacemaking of the heart. In this book different aspects of pacemaker â€“ functions and interactions, in various organ systems were examined. In addition, various areas of application and the potential side effects and complications of the devices were discussed.

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