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Review

Cardiac resynchronization therapy in ischemic and non-ischemic cardiomyopathy

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ABSTRACT

Cardiac resynchronization therapy (CRT) using a biventricular pacing system has been an effective therapeutic strategy in patients with symptomatic heart failure with a reduced left ventricular ejection fraction (LVEF) of 35% or less and a QRS duration of 130 ms or more. The etiology of heart failure can be classified as either ischemic or non-ischemic cardiomyopathy. Ischemic etiology of patients receiving CRT is prevalent predominantly in North America, moderately in Europe, and less so in Japan. CRT reduces mortality similarly in both ischemic and non-ischemic cardiomyopathy, whereas reverse structural left ventricular remodeling occurs more favorably in non-ischemic cardiomyopathy. Because the substrate for ventricular arrhythmias appears to be more severe in cases of ischemic as compared with non-ischemic cardiomyopathy, the use of an implantable cardioverter-defibrillator (ICD) backup method could prolong the long-term survival, especially of patients with ischemic cardiomyopathy, even in the presence of CRT. The aim of this review article is to summarize the effects of CRT on outcomes and the role of ICD backup in ischemic and non-ischemic cardiomyopathy.

Contents

1. Introduction

Cumulative survival from all-cause mortality decreases proportionally with QRS duration in patients with advanced heart failure [1]. Prolongation of QRS duration with left bundle-branch block (LBBB) morphology imposes left ventricle (LV) activation delay via a transmural functional line of block located between the LV septum and the lateral wall [2], resulting in ventricular dyssynchrony. Optimization of cardiac performance had been proposed by use of biventricular pacing in patients with drug-refractory congestive heart failure and an intraventricular conduction delay using the epicardial [3,4] and subsequently, a transvenous route with electrodes selectively inserted in the cardiac veins through coronary

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sinus over the LV free wall [5]. The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study proved the clinical benefits of atrial-synchronized biventricular pacing in patients with moderate-to-severe heart failure (New York Heart Association (NYHA) class III or IV) who had a left ventricular ejection fraction (LVEF) of 35% or less and a QRS interval of 130 ms or more [6]. This biventricular pacing system has been called cardiac resynchronization therapy (CRT), and become an established therapeutic approach for symptomatic heart failure with prolonged QRS duration.

With regards to mortality, the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) study demonstrated for the first time a better prognosis of patients with CRT plus a defibrillator (CRT-D) than those using optimal pharmacologic therapy alone [7]. In the subgroup analyses, hazard ratios for death from any cause of CRT-D as compared with pharmacologic therapy were 0.73 (95% confidence interval [CI], 0.52 to 1.04, $P = 0.082$) and 0.50 (95% CI, 0.29 to 0.88, $P = 0.015$) in ischemic and non-ischemic cardiomyopathy, respectively. A test for the interaction between the treatment effects and the etiology of cardiomyopathy was not significant [7]. In the Cardiac Resynchronization – Heart Failure (CARE-HF) study, CRT reduced all-cause mortality similarly in both ischemic and non-ischemic cardiomyopathy [8,9]. In agreement, the survival benefit with CRT-D over an implantable cardioverter-defibrillator (ICD) was consistent in a subgroup analysis of patients with ischemic cardiomyopathy and in those with non-ischemic cardiomyopathy [10,11]. This review article aims to summarize the effects of CRT on outcomes and the importance of ICD backup in ischemic and non-ischemic cardiomyopathy.

2. Current guidelines and appropriate use criteria for CRT

According to current guidelines in the United State (US) and Europe, CRT is indicated as class I (i.e., a procedure or treatment that should be performed where the benefits outweigh the risks) for patients who have LVEF of 35% or less: LBBB with a QRS duration of 150 ms [12] (130 ms [13]) or greater; and NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy. In addition, CRT may be considered to be appropriate for patients who have LVEF of 30% or less, LBBB with a QRS duration of 150 ms or greater, and NYHA class I, if the etiology of heart failure is ischemic [14]. The latter recommendation is based on the limited data from the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) study, in which patients with ischemic cardiomyopathy and NYHA class I were enrolled in about 15% of total subjects [11]. In MADIT-CRT, patients with ischemic or non-ischemic cardiomyopathy, LVEF of 30% or less, and a QRS duration of 130 ms or more, were randomly assigned to receive CRT plus a defibrillator (CRT-D), or an ICD alone. CRT-D (compared with ICD) was found to reduce the primary endpoint, death from any cause or a nonfatal heart-failure event (hazard ratio in the CRT–D group, 0.66; 95% CI, 0.52 to 0.84; $P = 0.001$). In this regard, the MADIT-CRT study demonstrated the effectiveness of CRT in combination with a defibrillator; that is, (a) the treatment of heart failure with reverse remodeling by using CRT, and (b) the primary prevention of sudden cardiac death by using a defibrillator.

3. Proportion of ischemic and non-ischemic etiology in CRT recipients in North America, Europe, and Japan

The rate of ischemic heart failure patients was over 50% in most of the randomized studies of CRT conducted in North America and Europe [6,7,10,11,15–17], except for 36% in CARE-HF (Cardiac Resynchronization – Heart Failure) [8] (Table 1). This trend is consistent with that in a cohort study using the National Impatient Sample (NIS), which is the publicly-available healthcare database in the United States (US) [18]. It is interesting to know that the CARE-HF study enrolled patients at only European centers, and that the CeRtiTude cohort study [19], which enrolled ischemic cardiomyopathy less than 50%, was also conducted in Europe. In contrast, patients with non-ischemic cardiomyopathy were most common at a rate of about 70% in Japan, on the basis of the Japan Cardiac Device Treatment Registry (JCDTR) database [20] (Table 1, Fig. 1).

With regard to medication, patients in the cohort studies were less likely to receive angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin receptor blockers (ARB) and/or beta-blockers compared with those in the contemporary randomized studies.

4. Reverse remodeling with CRT in ischemic and non-ischemic cardiomyopathy

The rate of responders assessed by the improvement of NYHA class status in the MIRACLE study was 67% in the CRT group, and was significantly higher than that (38%) in the control group [6]. More objectively, patients with echocardiographic changes of 25% (or 15% [21]) reduction in left ventricular end-systolic volume (LVESV), 15% reduction in left ventricular end-diastolic volume (LVEDV), 20% reduction in left atrial volume (LAV) and/or 8% increase in LVEF, a year following CRT, have been considered to show favorable responses and significant reverse remodeling [22].

Gasparini et al. reported for the first time that patients with non-ischemic etiology had a greater increase in LVEF and a decrease in NYHA functional class after CRT than did patients with ischemic heart disease [23]. Sub-analysis of the prospective randomized studies including MIRACLE (Multicenter InSync Randomized Clinical Evaluation) [24], CARE-HF [9], REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) [25] and MADIT-CRT [22] confirmed the occurrence of more favorable reverse remodeling in non-ischemic than in ischemic cardiomyopathy (Table 2).

Goldenberg et al. identified factors associated with reverse remodeling following CRT using data from MADIT-CRT, and created a response score [26] (Table 3). They proposed a combined assessment of these factors for improved selection of patients for CRT. A similar analysis was performed for predicting patients with LVEF normalization ($> 50\%$), which found a total of six relevant factors: female gender, non-ischemic etiology, LBBB, baseline LVEF $> 30\%$, LVESV ≤ 170 mL and LAV index ≤ 45 mL/m^2 [27]. Therefore, it is an undoubted fact that non-ischemic cardiomyopathy shows a better response with regard to reverse LV structural remodeling than ischemic cardiomyopathy (Fig. 2).

5. The effects of CRT on morbidity and mortality in ischemic and non-ischemic cardiomyopathy

On the basis of sub-analysis of the CARE-HF study, CRT decreased the primary composite endpoint (i.e., all-cause mortality or hospitalization for a major cardiovascular event) and principal secondary endpoint (i.e., all-cause mortality) in both ischemic and non-ischemic cardiomyopathy [9]. Patients with ischemic etiology were older, with a higher prevalence of male gender, and were more likely to be NYHA class IV, indicating the presence of more advanced heart failure. The authors concluded (a) the benefits of CRT in patients with or without ischemic heart disease were similar in relative terms, (b) but as patients with

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