Curr Heart Fail Rep
DOI 10.1007/s11897-011-0067-3

Does Contractility Modulation Have a Role in the Treatment of Heart Failure?

Daniel Burkhoff

Abstract Cardiac resynchronization therapy (CRT) is an established therapy for patients with systolic dysfunction, QRS duration greater than 120 ms, and New York Heart Association (NYHA) class III or IV symptoms. However, most patients with heart failure have QRS duration below 120 ms and 30% or more of CRT recipients are nonresponders. Cardiac contractility modulation (CCM) signals are nonexcitatory electrical impulses applied during the absolute refractory period that are intended to enhance contractile strength independent of QRS duration. Myocardial biopsy studies suggest that modulation of protein phosphorylation and gene expression underlie the mechanisms by which CCM exerts its effects. Two prospective randomized studies have investigated the impact of CCM on exercise tolerance and quality of life in patients with chronic heart failure. These studies have included predominantly patients with NYHA class III heart failure with QRS duration below 130 ms. This review summarizes results of these clinical studies and outlines additional studies underway to further clarify the role of CCM in the treatment of heart failure.

Keywords Heart failure · Cardiac contractility modulation · Cardiac resynchronization therapy · Myocardial infarction · Prevention · Ejection fraction · Refractory period · Peak VO2 · Anaerobic threshold · Quality of life

Introduction

Clinical studies have shown that cardiac resynchronization therapy (CRT) improves symptoms, quality of life, and exercise tolerance and reduces hospitalizations and mortality in patients with advanced heart failure (HF) and increased QRS duration [1, 2]. Although CRT studies are designed to include patients with QRS duration greater than 120 ms, it appears that best clinical results are achieved when QRS duration exceeds 150 ms [3]. The results of a recent study showed that patients with mechanical dyssynchrony by tissue Doppler imaging but a normal QRS duration did not benefit from CRT [4]. Considering the fact that about 70% of patients with HF have a normal QRS duration [5], development of a device-based treatment of such patients with persistent symptoms despite optimal medical therapy would have an important impact.

Cardiac contractility modulating (CCM) signals are relatively high-intensity electrical impulses applied during the absolute refractory period that are intended to enhance the strength of left ventricular contraction. In studies carried out in humans and animal models of HF, evidence shows that these signals impact fundamental aspects of myocardial cell biology without any impact on activation sequence. Therefore, CCM effects are independent of QRS duration and have even been shown to be additive to those of CRT in patients with prolonged QRS [6–8].

This review provides an overview of the mechanisms by which CCM signals impact on myocardial function and the clinical evidence that supports a role of CCM in the treatment of HF.

Cardiac Contractility Modulating: Concept and Underlying Mechanisms

Studies conducted almost 50 years ago showed that voltage clamping techniques could be used to modulate the amplitude and duration of electrical depolarization in isolated papillary muscles and that these effects were linked

D. Burkhoff (✉)
Division of Cardiology, Columbia University,
177 Fort Washington Avenue,
New York, NY 10032, USA
e-mail: db59@columbia.edu

Published online: 09 June 2011

to modulations of myocardial contractility [9–12]. Exploitation of the concepts generated from such studies to develop therapies for HF was not considered until it was demonstrated that significant contractile effects could be achieved by extracellular electrical currents delivered during the absolute refractory period [13, 14]; these signals came to be known as CCM signals. The pursuit of the therapeutic potential of CCM signals became appealing when their contractile effects were demonstrated in intact whole hearts, including in animal models and patients with HF [15–19••]. It was particularly interesting that global contractile effects could be achieved in whole hearts with chronic stimulation despite the fact that CCM signals were applied to only one region of the heart, typically from the left ventricular free wall or the right ventricular septal wall.

Several recent studies sought to define the mechanisms by which CCM signals impact on regional and global myocardial function. These studies showed that CCM signals have a rapid (within minutes) effect of intracellular protein phosphorylation (eg, phospholamban); that CCM signals shift myocardial gene expression from the fetal genotype typical of the HF state to the more normal adult genotype in the region where signals are delivered (an effect that is evident within several hours); and that, over longer periods of time, CCM signal application is able to induce reverse structural remodeling and improved left ventricular function [19••, 20••, 21••]. Importantly, these studies also showed that the contractile effects of CCM were not associated with increased myocardial oxygen consumption [22, 23].

Clinical Trials

The initial clinical study of CCM signals involved short-term (10–30 min) CCM signal application using a desktop signal generator and temporarily placed electrodes in patients with HF [6, 24]. The initial experiences with chronic CCM signal applications were obtained in two relatively small studies of patients with New York Heart Association (NYHA) class III symptoms and QRS duration of 120 ms or less [25, 26]. These studies provided initial basic safety data, specifically indicating that there were no adverse effects on ambient ventricular or atrial ectopy observed between baseline and 8 weeks of treatment; no other overt safety concerns were revealed. Additionally, improvements were reported in patient symptoms (assessed by NYHA class), quality of life (assessed by Minnesota Living with Heart Failure Questionnaire [MLWHFQ]) and ejection fraction (EF).

These feasibility studies were followed by a multicenter, randomized, double-blind, double-crossover study of CCM in patients with HF with NYHA class II or III symptoms despite optimal medical therapy, the FIX-CHF-4 study (Evaluation of the Safety and Effectiveness of the OPTIMIZER System in Subjects With Heart Failure; study conducted by, and the OPTIMIZER System manufactured by, IMPULSE Dynamics, Orangeburg, NY) [27••]. In this study, 164 patients with EF less than 35% and NYHA class II (24%) or III (76%) symptoms received a CCM pulse generator. Patients were randomly assigned to group 1 (CCM treatment 3 months, sham treatment second 3 months; n=80,) or group 2 (sham treatment 3 months, CCM treatment second 3 months; n=84). The coprimary endpoints were changes in peak oxygen consumption (VO_2) and MLWHFQ. Baseline EF (29.3%±6.69% vs 29.8%±7.8%), peak VO_2 (14.1±3.0 vs 13.6±2.7 mL/kg/min) and MLWHFQ score (38.9±27.4 vs 36.5±27.1) were similar between groups. Peak VO_2 increased similarly in both groups during the first 3 months (0.40±3.0 vs 0.37±3.3 mL/kg/min). This was interpreted as evidence of a prominent placebo effect. However, during the next 3 months, peak VO_2 decreased in the group switched to sham (−0.86±3.06 mL/kg/min) and increased in patients switched to active treatment (0.16±2.50 mL/kg/min). At the end of the second phase of the study, the difference in peak VO_2 between groups was about 1 mL/kg/min. MLWHFQ scoring behaved similarly, trending only slightly better with treatment (−12.06±15.33 vs −9.70±16.71) during the first 3 months, again consistent with a significant placebo effect. During the second 3 months, MLWHFQ scores increased in the group switched to sham (4.70±16.57) and decreased further in patients switched to active treatment (−0.70±15.13). Serious cardiovascular adverse events were tracked carefully in both groups. The most frequently reported events were episodes of decompensated HF, atrial fibrillation, bleeding at the OPTMIZER System implant site, and pneumonia. Importantly, there were no significant differences between "on" and "off" phases in the number or types of adverse events.

The largest study of CCM to date was a multicenter study involving 428 patients recruited from 50 sites in the United States (FIX-HF-5 study) [28••]. Patients were characterized by NYHA class III (89%) or IV (11%) symptoms, QRS duration 101 ms (cumulative average), and EF 26% (cumulative average). Patients were required to be receiving stable optimal medical therapy (OMT), defined as a β-blocker, angiotensin converting–enzyme inhibitor, or angiotensin-receptor blocker and a diuretic for at least 3 months (unless intolerant); the daily dose of each medication could not vary by more than a 50% reduction or 100% increase over the prior 3 months. Patients were randomly assigned (in a 1:1 ratio, stratified for ischemic or nonischemic underlying etiology) to OMT plus CCM (n=215) or OMT alone (n=213). Efficacy was assessed by changes in exercise tolerance and quality of life at 6 months compared to baseline. Exercise tolerance was indexed by

ventilaroty anaerobic threshold (VAT), which was the declared primary end point, and by peak VO_2. Quality of life was assessed by the MLWHFQ. The primary safety end point was a test of noninferiority between groups for the composite of all-cause mortality and all-cause hospitalizations (12.5% allowable Δ) at 12 months.

The study groups (control vs treatment) were comparable for age (58±13 y vs 59±12 y), chronic HF etiology (67% vs 65% ischemic etiology), QRS duration (101±0.5 ms vs 101±0.6 ms), EF (26%±7% vs 26%±7%), VAT (11.0±2.2 mL/kg/min vs 11.0±2.2 mL/kg/min), peak VO_2 (14.7±2.9 vs 14.8±3.2 mL/kg/min), and other important baseline characteristics. The safety end point of the study was met; by the end of 1-year follow-up, 52% of patients in the treatment group and 48% of patients in the control group met a study-specified safety end point, which was noninferior by both a Blackwelder's test of noninferiority and by a logrank test comparing Kaplan-Meier survival curves. Regarding efficacy, peak VO_2 was 0.7 mL/kg/min greater (P=0.024) and MLWHFQ score was 9.7 points better (P<0.0001) in the treatment group than in the control group. However, VAT, the primary end point, did not differ between the groups so the study was considered to be a negative study.

The study protocol indicated that efficacy effects would be explored in specific patient subsets. This analysis showed that particularly large effects on both VAT and peak VO_2 were observed in patients with a baseline EF of 25% or higher and NYHA class III symptoms. In this subgroup, VAT was 0.64 mL/kg/min greater (P=0.03), peak VO_2 was 1.31 mL/kg/min greater (P=0.001), and MLWHFQ was 10.8 points better (P=0.003) in the treatment group than in the control groups. Although prespecified in the protocol, the results of this analysis were considered retrospective and hypothesis generating. Accordingly, a new study has been initiated to prospectively confirm these findings.

This finding in the specified subgroup has interesting implications related to the purported mechanisms of action. As noted above, CCM signals are applied to one region of the heart and are believed to have direct and relatively rapid local effects. It is hypothesized that secondary remote effects are achieved over time when the local effect is large enough to have a sufficient effect on global function. Heart size at the initiation of CCM treatment increases as baseline EF decreases; therefore, it can be speculated that the larger the heart is, the less is the impact on global function and the less effective is the therapy. According to this outlook, the efficacy of CCM should improve as the heart size and EF increase.

To further test this hypothesis, an additional subgroup analysis was performed. There were 38 patients in the FIX-HF-5 study with an EF of 35% or higher. These patients were admitted to the study because the EF determined at the investigative site was less than 35%; however, all analyses were based on the core lab EF assessment. Of these 38 patients, 18 were in the treatment group and 20 were in the control group. In this subgroup, peak VO_2 was 2.96 mL/kg/min greater (P=0.03), VAT was 0.57 mL/kg/min greater (P = not significant), and MLWHFQ score was 18 points better (P=0.06) in the treatment group than the control group. Although not all of these differences were statistically significant in view of the small sample size, the trends showed even greater effects than in the group of patients with EF between 25 and 35%.

From a historical perspective, it is important to note that the US Food and Drug Administration (FDA) played a primary role in the design of this study. They required a 12-month follow-up period to ensure an adequate duration for assessment of safety. Given this relatively long follow-up duration, it was deemed unfeasible to perform a more preferable double-blind study, as in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study of CRT [1], because there would have been many opportunities in such a study for unblinding [29•]. Given that this would be an unblinded study, the FDA required use of VAT as the primary

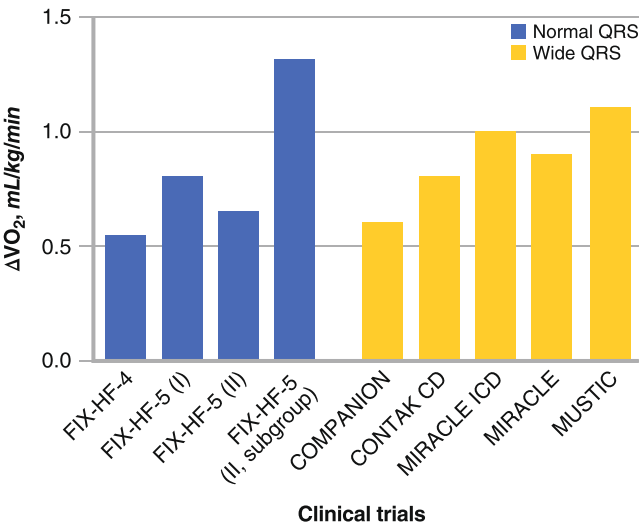

Fig. 1 Comparison of the effects of CCM [27••, 28••, 31] and CRT [1, 32–35] on peak VO_2 obtained from different clinical trials. Although studied in different populations, as detailed in the original papers (*yellow bars* studies in patients with wide QRS; *blue bars* studies in patients with narrow QRS), most of the other baseline features are very similar between the groups. With this as a caveat, the impact of CCM on peak VO_2 is comparable to the impact of CRT. Contak cardioverter-defibrillator manufactured by Boston Scientific, Natick, MA. (Δ)VO_2—(change in) oxygen consumption; CCM—cardiac contractility modulation; COMPANION—Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CONTAK CD—Contak cardioverter-defibrillator trial; CRT—cardiac resynchronization therapy; FIX-HF-4/FIX-HF-5—Evaluation(s) of the Safety and Effectiveness of the OPTIMIZER System in Subjects With Heart Failure; MIRACLE—Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD—Multicenter InSync Implantable Cardioverter-Defibrillator Randomized Clinical Evaluation; MUSTIC—Multisite Stimulation in Cardiomyopathy study

end point because, unlike the more traditional and well-studied end point of peak VO_2, it was considered to be unsusceptible to placebo effect. While theoretically appealing, this was the first study to use VAT as a primary end point, and many issues were encountered in reliably quantifying this parameter [30•]. Furthermore, there is no information from prior randomized studies confirming whether, or the degree to which VAT improves with any proven HF therapy.

To put the current results into clinical perspective, it is interesting to compare results obtained with CCM in patients with narrow QRS [27••, 28••, 31] to those obtained in several trials with CRT in patients with wide QRS duration (Fig. 1) [1, 32–35]. Although QRS durations of patients in these two groups of studies are different, examination of the other baseline features of patients enrolled in CRT trials revealed that they are remarkably similar to those of patients enrolled in CCM trials with regard to NYHA class [predominantly class III], chronic HF etiology (predominantly ischemic), EF (~25%), and peak VO_2 (~14.5 mL/kg/min), as well as other important baseline factors. With the caveat that patients with CRT have a longer QRS duration, the result of this comparison suggests that the impact of CCM on exercise tolerance as indexed by peak VO_2 is comparable to that of CRT. Early acceptance of CRT was based on demonstration of improved exercise tolerance and quality of life. However, CRT is now more widely accepted because of recent studies showing benefits on survival and HF exacerbations [3, 36]. Data on survival and HF exacerbation are not yet available for CCM, but are being investigated in a new study that has been initiated in Europe.

Conclusions

CCM signal delivery with a pacemaker-like device connected to the heart with standard pacing leads has been shown to be straightforward to implement clinically. Basic research suggests that CCM signals affect fundamental aspects of the biology of the failing cardiac myocyte, including effects of protein phosphorylation, myocardial gene expression, protein content, and function. Studies of proteins of particular interest in excitation and contraction suggest that CCM reverses the genotype and phenotype of the cells from the fetal program typical of HF to the more normal adult program.

To date, about 900 patients have received chronic CCM treatment. There is currently no other approved device-based therapy for patients with medically refractory symptoms and a narrow QRS duration. CCM is aimed largely at filling this gap. In addition, about 30% of patients with wide QRS duration who receive a CRT device do not improve clinically; initial studies suggest that there may be a role for CCM in this population as well.

Results of two randomized trials show that CCM improves exercise tolerance as indexed by peak VO_2. Other indices of exercise tolerance (eg, 6-minute hall walk) and quality of life (eg, NYHA class and MLWHFQ score) also have been shown to improve. The OPTIMIZER System, which delivers CCM signals, has received the CE (Conformité Européenne ["European Conformity"]) Mark and is available for clinicians to prescribe in countries that recognize the CE Mark. In the United States, the system is still being evaluated in clinical trials; the focus is to prospectively confirm the findings of significant effects of CCM on VAT in the subgroup of patients with EF of 25% or higher and NYHA class III symptoms. In addition, larger longer-term studies are being initiated to test the impact of CCM on mortality and hospitalizations. If positive, the results of these studies will add to the current body of evidence and further substantiate the role of CCM in the treatment of patients with medically refractory HF.

Disclosure Dr. Daniel Burkhoff is a consultant for, and owns stock interest in, IMPULSE Dynamics.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance,
- •• Of major importance

1. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346:1845–53.
2. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140–50.
3. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:1329–38.
4. Beshai JF, Grimm RA, Nagueh SF, et al.: Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes. N Engl J Med 2007.
5. Shenkman HJ, Pampati V, Khandelwal AK, et al. Congestive heart failure and QRS duration: establishing prognosis study. Chest. 2002;122:528–34.
6. Pappone C, Rosanio S, Burkhoff D, et al. Cardiac contractility modulation by electric currents applied during the refractory period in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol. 2002;90:1307–13.
7. Butter C, Meyhofer J, Seifert M, et al. First use of cardiac contractility modulation (CCM) in a patient failing CRT therapy: clinical and technical aspects of combined therapies. Eur J Heart Fail. 2007;9:955–8.

8. Nagele H, Behrens S, Eisermann C. Cardiac contractility modulation in non-responders to cardiac resynchronization therapy. Europace. 2008;10:1375–80.
9. Wood EH, Heppner RL, Weidmann S. Inotropic effects of electric currents: 1. Positive and negative effects of constant electric currents or current pulses applied during cardiac action potential. Circ Res. 1969;24:409–45.
10. Wood EH, Heppner RL, Weidmann S. Inotropic effects of electric currents: 2. Hypotheses: calcium movements, excitation-contraction coupling and inotropic effects. Circ Res. 1969;24:409–45.
11. Antoni H, Jacob R, Kaufmann R. Mechanical response of the frog and mammalian myocardium to changes in the action potential duration by constant current pulses. Pflugers Arch. 1969;306:33–57.
12. Kaufmann RL, Antoni H, Hennekes R, et al.: Mechanical response of the mammalian myocardium to modifications of the action potential. Cardiovasc Res 1971; 1:Suppl-70.
13. Blank M, Goodman R. Initial interactions in electromagnetic field-induced biosynthesis. J Cell Physiol. 2004;199:359–63.
14. Burkhoff D, Shemer I, Felzen B, et al. Electric currents applied during the refractory period can modulate cardiac contractility in vitro and in vivo. Heart Fail Revs. 2001;6:27–34.
15. Sabbah HN, Haddad W, Mika Y, et al. Cardiac contractilty modulation with the impulse dynamics signal: Studies in dogs with chronic heart failure. Heart Failure Reviews. 2001;6:45–53.
16. Mohri S, He KL, Dickstein M, et al. Cardiac contractility modulation by electric currents applied during the refractory period. Am J Physiol Heart Circ Physiol. 2002;282:H1642–7.
17. Morita H, Suzuki G, Haddad W, et al. Cardiac contractility modulation with nonexcitatory electric signals improves left ventricular function in dogs with chronic heart failure. J Card Fail. 2003;9:69–75.
18. Lawo T, Borggrefe M, Butter C, et al. Electrical signals applied during the absolute refractory period: an investigational treatment for advanced heart failure in patients with normal QRS duration. J Am Coll Cardiol. 2005;46:2229–36.
19. •• Imai M, Rastogi S, Gupta RC, et al.: Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. J Am Coll Cardiol 2007; 49:2120–8. *This paper describes the results of a detailed study of the biochemical and molecular effects of CCM in an established model of heart failure. The results demonstrate the relatively rapid primary effects on phosphorylation, gene expression, and protein content in the vicinity of the signal delivery and the presumed secondary effects on remote areas that are observed within a 3-month timeframe.*
20. •• Yu CM, Chan JY, Zhang Q, et al.: Impact of cardiac contractility modulation on left ventricular global and regional function and remodeling. JACC Cardiovasc Imaging 2009; 2:1341–9. *This study shows that CCM treatment for 3 months induces reverse ventricular remodeling, manifest as reduction in end-systolic and end-diastolic size and improved ejection fraction.*
21. •• Butter C, Rastogi S, Minden HH, et al.: Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. J Am Coll Cardiol 2008; 51:1784–9. *This myocardial biopsy study confirms that 3 months of CCM therapy in patients with heart failure induces reverse molecular remodeling and drives the genotype from the abnormal fetal program characteristic of heart failure to a more normal adult profile. Interestingly, the magnitude of changes in gene expression correlated with clinical effectiveness, as quantified by exercise tolerance and quality-of-life scores.*
22. Butter C, Wellnhofer E, Schlegl M, et al. Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption. J Card Fail. 2007;13:137–42.
23. Sabbah HN, Gupta RC, Rastogi S, et al. Treating heart failure with cardiac contractility modulation electrical signals. Curr Heart Fail Rep. 2006;3:21–4.
24. Pappone C, Vicedomini G, Salvati A, et al. Electrical modulation of cardiac contractility: clinical aspects in congestive heart failure. Heart Fail Rev. 2001;6:55–60.
25. Pappone C, Augello G, Rosanio S, et al. First human chronic experience with cardiac contractility modulation by nonexcitatory electrical currents for treating systolic heart failure: mid-term safety and efficacy results from a multicenter study. J Cardiovasc Electrophysiol. 2004;15:418–27.
26. Stix G, Borggrefe M, Wolpert C, et al. Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure. Eur Heart J. 2004;25:650–5.
27. •• Borggrefe MM, Lawo T, Butter C, et al.: Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. Eur Heart J 2008; 29:1019–28. *This was the first prospective, randomized, double-blind study showing that CCM improves exercise tolerance and quality of life in patients with heart failure and EF of 35% or less.*
28. •• Kadish A, Nademanee K, Volosin K, et al.: A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure. Am Heart J 2011; 161:329–37. *This article details the results of a prospective, randomized, unblinded study, conducted at 50 United States sites, involving 428 patients with NYHA class III or IV heart failure with QRS duration of 130 ms or less. Although the primary end point (improvement in anaerobic threshold) was not met, peak VO_2 was about 0.7 mL/kg/min greater in the treatment group compared to the control group. The primary safety end point of the study was met. The analysis revealed a subgroup of patients with particularly good response that now is being analyzed in a new study being conducted in the United States.*
29. • Abraham WT, Burkhoff D, Nademanee K, et al.: A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with systolic heart failure: rationale, design, and baseline patient characteristics. Am Heart J 2008; 156:641–8. *This article provides a detailed description of the methodology and rationale for the United States study design. Several anticipated difficulties of the study were discussed in detail.*
30. • Myers J, Goldsmith RL, Keteyian SJ, et al.: The ventilatory anaerobic threshold in heart failure: a multicenter evaluation of reliability. J Card Fail 2010; 16:76–83. *This article provides a detailed analysis of the United States study data highlighting the difficulties in using the anaerobic threshold as a primary study end point.*
31. Neelagaru SB, Sanchez JE, Lau SK, et al. Nonexcitatory, cardiac contractility modulation electrical impulses: Feasibility study for advanced heart failure in patients with normal QRS duration. Heart Rhythm. 2006;3:1140–7.
32. De Marco T, Wolfel E, Feldman AM, et al. Impact of cardiac resynchronization therapy on exercise performance, functional capacity, and quality of life in systolic heart failure with QRS prolongation: COMPANION trial sub-study. J Card Fail. 2008;14:9–18.
33. Thackray S, Coletta A, Jones P, et al. Clinical trials update: Highlights of the Scientific Sessions of Heart Failure 2001, a meeting of the Working Group on Heart Failure of the European Society of Cardiology. CONTAK-CD, CHRISTMAS, OPTIME-CHF. Eur J Heart Fail. 2001;3:491–4.

34. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289:2685–94.
35. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. J Am Coll Cardiol. 2002;40:111–8.
36. Cleland JG, Calvert MJ, Verboven Y, Freemantle N. Effects of cardiac resynchronization therapy on long-term quality of life: an analysis from the CArdiac Resynchronisation-Heart Failure (CARE-HF) study. Am Heart J. 2009;157:457–66.