Clin. Cardiol. 30, 498–502 (2007)

Cardiac Resynchronization Therapy and its Potential Proarrhythmic Effect

INDRANILL BASU RAY, M.D., D.N.B., LAHN FENDELANDER, M.S., JAGMEET P. SINGH, M.D., D. PHIL.
Harvard Thorndike Electrophysiology Institute, Department of Medicine, Beth Israel Deaconess Medical Center, Guidant Corporation, St. Paul, Minnesota; Cardiac Arrhythmia Service, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Summary

Cardiac resynchronization therapy (CRT) has become an established adjunctive treatment to optimal pharmacologic therapy in patients with advanced chronic heart failure (CHF), diminished left ventricular (LV) function and intraventricular conduction delay. Although CRT has been shown to improve ventricular hemodynamics, quality of life and exercise capacity, there is some evidence that it may rarely potentiate ventricular arrhythmias. As CRT is considered for an expanded population of CHF patients, and left-sided pacing is considered as an option for pacemaker-indicated patients (potentially without defibrillator backup), the effect of these pacing modalities on the incidence of ventricular tachyarrhythmia must be systematically studied and mechanistically understood. Strategies to prospectively predict the proarrhythmic potential of LV epicardial pacing need to be developed, and therapy accordingly individualized. This review attempts to summarize the current information on proarrhythmia in resynchronization therapy.

Key words: cardiac resynchronization, proarrhythmia, pacemakers, implantable devices, defibrillators, heart failure, sudden cardiac death

Address for reprints:
Jagmeet P. Singh, M.D., D. Phil.
Director, CRT Program
Cardiac Arrhythmia Service Heart Center
Massachusetts General Hospital
55 Fruit Street, Gray-Bigelow 109
Boston MA 02114, USA
e-mail: jsingh@partners.org

Received: June 13, 2006
Accepted: August 18, 2006

Published online in Wiley InterScience
(www.interscience.wiley.com).
DOI:10.1002/clc.17

Clin. Cardiol. 2007; 30: 498–502.

Introduction

Cardiac resynchronization therapy (CRT) has become an established adjunctive treatment to optimal pharmacologic therapy (OPT) in patients with advanced chronic heart failure (CHF), diminished LV function and intraventricular conduction delay. While CRT has been shown to improve ventricular hemodynamics, quality of life and exercise capacity,[1–3] the effect of this therapy on the incidence of ventricular arrhythmias is less clear. Several studies have suggested that CRT suppresses the incidence of ventricular tachyarrhythmic events,[4–6] citing reduced wall stress (as a result of reverse remodeling) and decreased repolarization dispersion (as a result of dual depolarization wavefronts) as potential mechanisms.[7,8] Other studies, however, have demonstrated the potential for proarrhythmia.[9–11] As CRT becomes more widely adopted and is considered for an expanded population of heart failure (HF) patients,[12,13] the effect of this pacing modality on the incidence of ventricular tachyarrhythmias must be thoroughly understood. This review attempts to summarize the current information on proarrhythmia in resynchronization therapy.

Clinical Benefit of CRT

To date, several controlled studies have demonstrated the efficacy of resynchronization therapy achieved through biventricular or left ventricular pacing. These studies have shown that CRT improves hemodynamics and symptoms in the acute setting as well as during chronic follow-up. The hemodynamic improvements begin almost immediately after pacing is initiated as evidenced by increases in aortic pulse pressure, left ventricular dP/dt_{max} and stroke volume.[14,15] Long-term results demonstrate evidence of reverse remodeling, increased

exercise capacity and functional class, improved quality of life and decreased hospitalization rates.[1–3,16,17] In addition, resynchronization therapy is associated with reduced sympathetic nervous activity[18] and increased heart rate variability,[19,20] suggesting potentially favorable neurohormonal effects. Several studies have suggested that CRT may also suppress premature ventricular contractions,[4,8] reduce ventricular tachyarrhythmic events[6,17] and decrease inducibility of sustained ventricular tachycardia (VT).[5]

Mortality Benefit of CRT

While the symptomatic relief afforded by cardiac resynchronization devices has been clearly demonstrated, the capability of the technology to reduce all-cause cardiac mortality is less well established. A decline in mortality due to pump failure has been clearly documented;[16] however, the impact on sudden cardiac death (SCD) and the development of malignant ventricular arrhythmias remains questionable.[21,22]

In a recent meta-analysis of nine randomized trials, cardiac resynchronization therapy was shown to significantly reduce all-cause mortality by 21%.[23] However, the authors indicated that there was no significant reduction in overall cardiac deaths, citing "a nonsignificant excess number of sudden cardiac deaths." Although there is the possibility that CRT may actually increase non-HF mortality due, in part, to an increased risk of sudden death, the overall favorable effect on HF mortality does not seem to be offset by an increase in the incidence of ventricular arrhythmias.[24] Of note, the meta-analyses cited above do not include mortality data from the COMPANION and CARE-HF trials, two of the larger CRT studies that had the statistical power to demonstrate mortality benefit.

COMPANION is the only trial to compare cardiac resynchronization therapy plus a defibrillator (CRT-D) with CRT alone.[3] The primary composite end point—death from any cause or hospitalization for any cause—was reduced by approximately 20% in both groups that received CRT or CRT-D plus optimal pharmacologic therapy, as compared with the group that received OPT alone. While the defibrillator did not appreciably affect the combined outcomes, which are heavily weighted by the hospitalization components, there was an incremental increase in the survival benefit of CRT-D, resulting in a substantial 36% mortality reduction ($p = 0.003$), as compared to OPT. Notably, recently published data on the mode of death in COMPANION indicate that sudden death was more common in the CRT vs. OPT group (7.8% vs. 5.8%) and, as seen in Fig. 1, accounted for a substantially greater fraction of all deaths in CRT vs. OPT (36.6% vs. 23.4%).[21] In terms of SCD, the point estimate appears "unfavorable" for CRT; however, this data must be interpreted with caution as the confidence intervals are fairly wide.

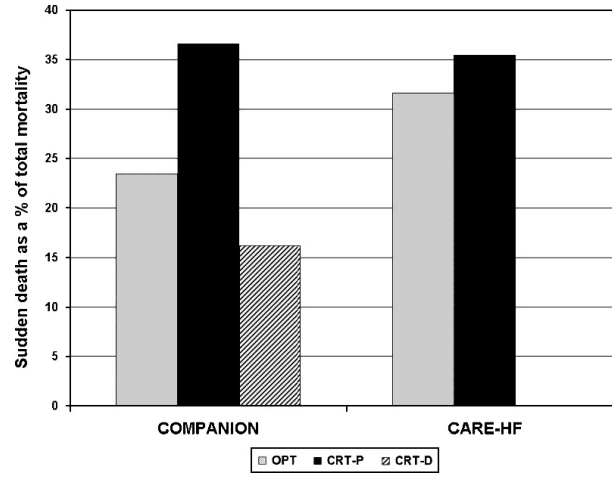

FIG. 1 Sudden death as a percentage of total mortality in COMPANION and CARE-HF. While both studies showed a decrease in all-cause mortality associated with CRT, the percentage of deaths classified as sudden was higher in the CRT group vs. OPT. (CRT = cardiac resynchronization therapy, OPT = optimal pharmacologic therapy).

A similar trend was observed in CARE-HF (Fig. 1). While results indicated a significant decrease in all-cause mortality in the CRT group vs. pharmacologic therapy (hazard ratio = 0.64, $p < 0.002$), the percentage of deaths classified as sudden was higher in the CRT group (35.4% vs. 31.7%).[16] It has been suggested that the use of a defibrillator might have further reduced the risk of sudden death.

While mortality trends from large trials may offer a suggestion that CRT may increase acute mortality in certain susceptible cohorts, this must ultimately be demonstrated in trials with prespecified short-term outcomes. More compelling data is presented in smaller studies that elucidate the electrophysiologic impact of epicardial pacing and the potentially proarrhythmic effects of cardiac resynchronization therapy.[9,10,25]

Proarrhythmic Mechanisms

Biventricular pacing in CRT is typically achieved with one pacing lead in the right ventricle and another in contact with the left ventricular epicardium via the coronary sinus. This configuration results in a reversal of the typical transmural activation sequence, thus delaying endocardial depolarization and subsequent repolarization. This reversal has been shown to create heterogeneous conduction patterns and increase transmural dispersion of repolarization (TDR) in experimental models.[9,25] Such nonuniformity is an established and important determinant of reentrant arrhythmias.

Using mathematical models and canine wedge preparations, Fish and colleagues showed a significant increase in TDR and QT interval when pacing was shifted from

the endocardium to the epicardium.[25] Similar results were reported by Medina-Ravell *et al*. along with an increased number of R-on-T extrasystoles and episodes of torsade de pointes (TdP) with epicardial pacing.[9]

The proarrhythmic potential of epicardial pacing is most likely determined by the characteristics of the altered activation sequence and the condition of the underlying substrate. The impact on potentiating triggers (e.g. local ischemia or PVC's) and modulation of autonomic tone may also play a role (Fig. 2). While aggregate data suggest that autonomic balance generally improves after CRT implantation, individual response has been shown to vary and can even worsen in nonresponders.[20] Such effects may be particularly detrimental in the compromised physiologic milieu of heart failure where the physiology may be considerably skewed to entertain prolonged repolarization. QT-prolonging pharmaceuticals and cardiomyopathy itself are conditions that may amplify the intrinsic spatial dispersion of repolarization, thus creating the substrate for the development of reentry.[26] These conditions also predispose M cells and Purkinje fibers to develop early afterdepolarization-induced extrasystoles, which are thought to trigger episodes of torsades de pointes.[27,28]

Clinical Evidence of Proarrhythmia

The most recent clinical evidence of this appears in a case series of ventricular tachyarrhythmias precipitated by biventricular pacing. Shukla *et al*. report 5 of 145 consecutive CRT patients who experienced VT or VF soon after implantation.[11] In all cases, the arrhythmia was resolved upon discontinuation of LV pacing. Medina-Ravell *et al*. describe 4 of 29 CRT patients who exhibited a marked increase in JTc and TDR with left or biventricular pacing, accompanied by frequent R-on-T ventricular extrasystoles that were completely inhibited by right ventricular endocardial pacing.[9] One of the four patients developed recurrent nonsustained polymorphic VT and another suffered incessant torsade requiring multiple shocks. In the same patient, torsade could be eliminated with RV pacing and reliably reproduced by turning biventricular pacing on, which was associated with significant QT prolongation (Fig. 3). Rivero-Ayerza *et al*. report a case study of left ventricular pacing-induced polymorphic VT identified at implant in a patient with no history of ventricular arrhythmias.[10] Lastly, it has been reported that the arrhythmia onset may range from several hours to days after the onset of pacing.[29]

Determining Arrhythmic Risk

Several studies have demonstrated an antiarrhythmic effect and have suggested that cardiac resynchronization diminishes the need for ICD therapy;[4,5,7,8] however, sudden death remains a significant contributor to HF mortality and more research is required to fully understand the electrophysiologic impact of this therapy. For this reason, all patients with a CRT indication and a concomitant defibrillator indication, including those based on the multicenter automatic defibrillator implantation trial (MADIT) and SCD-HeFT studies, should receive a resynchronization device with ICD backup.[30,31]

While one should exercise caution when a CRT device without a defibrillator is considered, it is not clear how to discern the cohort of patients likely to develop QT prolongation and subsequent arrhythmia with implantation. Patients with severe cardiac failure and prolonged QT, either disease or drug induced, may be considered at higher risk for proarrhythmia. Patients with nonischemic cardiomyopathy may be more susceptible due to existing electrical heterogeneity and the tendency to develop polymorphic VT.[26,28] In patients with ischemic cardiomyopathy, CRT has been shown to decrease the inducibility of ventricular tachycardia.[5,32] In such cases, however, it may be important to note the final position of the left ventricular pacing lead in relation to the scar. It could be speculated that inappropriately positioned LV leads, through the effect on the cardiac substrate, ventricular activation pattern or cardiac autonomic tone,[20] could be proarrhythmic.

LV epicardial pacing prolongs the QT interval more than RV or biventricular pacing.[9] In subjects with

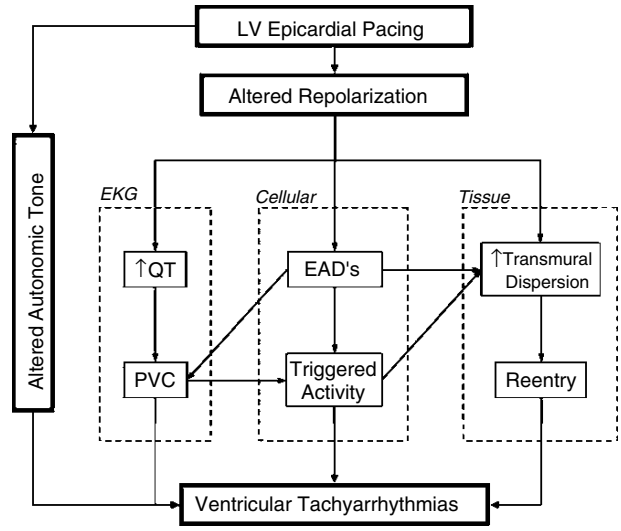

FIG. 2 Epicardial pacing results in a reversal of the typical transmural activation sequence, which can create heterogeneous conduction patterns, increase transmural dispersion of repolarization, prolong the QT interval, potentiate early afterdepolarizations and alter the autonomic tone. One of these mechanisms or a combination thereof may lead to proarrhythmia in a susceptible cohort of patients. (EAD = early afterdepolarization, PVC = premature ventricular contraction).

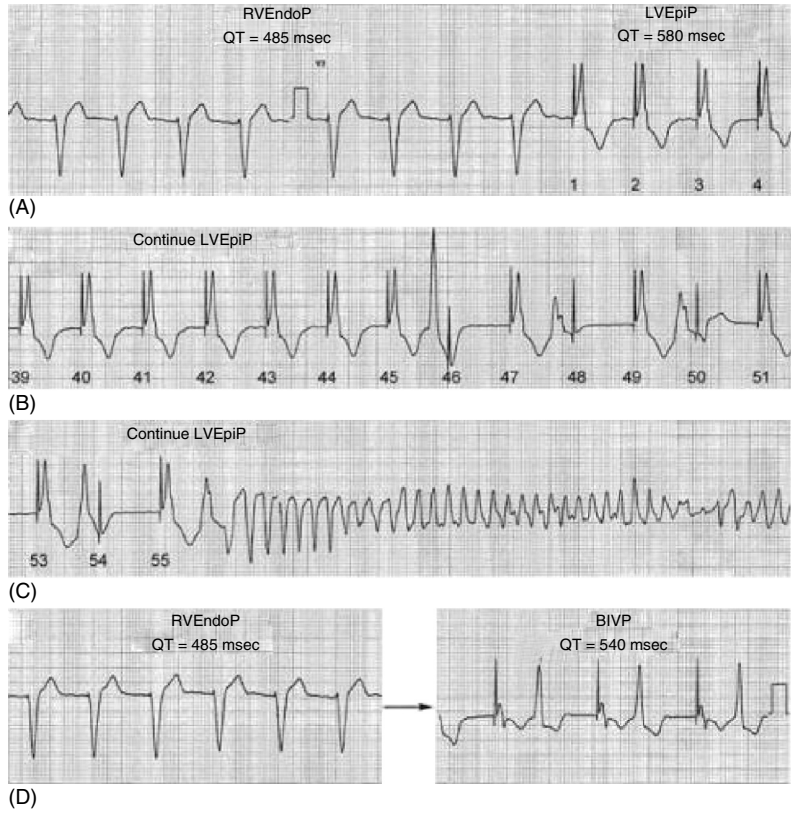

FIG. 3 Pacing site–dependent changes in QT interval, R-on-T ventricular extrasystoles, and the onset of TdP in a patient with CRT-D when changed from right ventricular (RVEndoP) to left ventricular (LVEpiP) pacing. RV endocardial pacing yielded a QT interval of 485 ms. Immediately after switching to LVEpiP (mode VOO), the QT interval increased to 580 ms (A). Ventricular extrasystoles started at the 46th beat of LVEpiP (B) and initiated one episode of TdP at the 55th beat (C) that was terminated by an implantable cardioverter-defibrillator (ICD) shock. Modified and reprinted, with permission from Medina-Ravell *et al.*[9].

ischemic heart disease and areas of slow conduction around the LV pacing site, CRT devices can be programmed to preactivate the left ventricle before the RV stimulus. One could speculate that programmed preactivation of the LV may contribute to QT prolongation and an increased propensity for proarrhythmia in a select group of patients.

It has been suggested that programmed stimulation using an epicardial approach may be used to assess transmural heterogeneity of repolarization and thus could conceivably be used at implant to stratify postimplant risk.[33] Other noninvasive measures of repolarization abnormalities such as QT dispersion, QT dynamicity and T-wave alternans could also be used to assess overall vulnerability to arrhythmias.[34,35]

Conclusion

Large-scale studies on the safety and efficacy of cardiac resynchronization suggest that this therapy may have a neutral or antiarrhythmic effect. However, a potentially proarrhythmic effect has been described, and while relatively infrequent, clinicians should be aware of this phenomena. The ultimate impact on arrhythmic vulnerability is likely dependent on propagation patterns and the underlying cardiac substrate. As indicated by several studies noted here, reversal of transmural activation and repolarization may set the stage for reentry and proarrhythmia. Conversely, certain biventricular pacing configurations could cause favorable wavefront interactions resulting in an overall protective effect.

As cardiac resynchronization therapy is considered for an expanded population of CHF patients[12,13] and left-sided pacing is considered as an option for pacemaker-indicated patients (potentially without ICD backup),[36] the effect of these pacing modalities on the incidence of ventricular tachyarrhythmias must be systematically studied and mechanistically understood. Strategies to prospectively predict the proarrhythmic potential of LV epicardial pacing need to be developed, and therapy accordingly individualized. Finally, it should be noted that while endocardial LV pacing presents significant challenges, it is a more physiologic alternative and may be a viable pacing strategy in the future.[37]

References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, et al.: Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346(24):1845–1853
2. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, et al.: Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003;42(12):2109–2116
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, et al.: Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350(21):2140–2150
4. Walker S, Levy TM, Rex S, Brant S, Allen J, et al.: Usefulness of suppression of ventricular arrhythmia by biventricular pacing in severe congestive cardiac failure. *Am J Cardiol* 2000;86(2):231–233
5. Zagrodzky JD, Ramaswamy K, Page RL, Joglar JA, Sheehan CJ, et al.: Biventricular pacing decreases the inducibility of ventricular tachycardia in patients with ischemic cardiomyopathy. *Am J Cardiol* 2001;87(10):1208–1210; A7
6. Ermis C, Seutter R, Zhu AX, Benditt LC, VanHeel L, et al.: Impact of upgrade to cardiac resynchronization therapy on ventricular arrhythmia frequency in patients with implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2005;46(12):2258–2263
7. Kies P, Bax JJ, Molhoek SG, Bleeker GB, Zeppenfeld K, et al.: Effect of left ventricular remodeling after cardiac resynchronization therapy on frequency of ventricular arrhythmias. *Am J Cardiol* 2004;94(1):130–132
8. Martinelli Filho M, Pedrosa AA, Costa R, Nishioka SA, Siqueira SF, et al.: Biventricular pacing improves clinical behavior and reduces prevalence of ventricular arrhythmia in patients with heart failure. *Arq Bras Cardiol* 2002;78(1):110–113
9. Medina-Ravell VA, Lankipalli RS, Yan GX, Antzelevitch C, Medina-Malpica NA, et al.: Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization: does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes? *Circulation* 2003;107(5):740–746
10. Rivero-Ayerza M, Vanderheyden M, Verstreken S, de Zutter M, Geelen P, et al.: Images in cardiovascular medicine. Polymorphic ventricular tachycardia induced by left ventricular pacing. *Circulation* 2004;109(23):2924–2925
11. Shukla G, Chaudhry GM, Orlov M, Hoffmeister P, Haffajee C: Potential proarrhythmic effect of biventricular pacing: fact or myth? *Heart Rhythm* 2005;2(9):951–956
12. Moss AJ, Brown MW, Cannom DS, Daubert JP, Estes M, et al.: Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT): design and clinical protocol. *Ann Noninvasive Electrocardiol* 2005;10(suppl 4):34–43
13. Achilli A, Sassara M, Ficili S, Pontillo D, Achilli P, et al.: Long-term effectiveness of cardiac resynchronization therapy in patients with refractory heart failure and "narrow" QRS. *J Am Coll Cardiol* 2003;42(12):2117–2124
14. Nelson GS, Berger RD, Fetics BJ, Talbot M, Spinelli JC, et al.: Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 2000;102(25):3053–3059
15. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, et al.: Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. The Pacing Therapies for Congestive Heart Failure Study Group. The Guidant Congestive Heart Failure Research Group. *Circulation* 1999;99(23):2993–3001
16. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, et al.: The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352(15):1539–1549
17. Yu C-M, Bleeker GB, Fung JW-H, Schalij MJ, Zhang Q, et al.: Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;112(11):1580–1586
18. Hamdan MH, Zagrodzky JD, Joglar JA, Sheehan CJ, Ramaswamy K, et al.: Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. *Circulation* 2000;102(9):1027–1032
19. Adamson PB, Kleckner KJ, VanHout WL, Srinivasan S, Abraham WT: Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation* 2003;108(3):266–269
20. Fantoni C, Raffa S, Regoli F, Giraldi F, La Rovere MT, et al.: Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure. *J Am Coll Cardiol* 2005;46(10):1875–1882
21. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, et al.: Mode of death in advanced heart failure the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) Trial. *J Am Coll Cardiol* 2005;46(12):2329–2334
22. Daubert JC, Leclercq C, Mabo P: There is plenty of room for cardiac resynchronization therapy devices without back-up defibrillators in the electrical treatment of heart failure. *J Am Coll Cardiol* 2005;46(12):2204–2207
23. McAlister FA, Ezekowitz JA, Wiebe N, Rowe B, Spooner C, et al.: Systematic review: cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med* 2004;141(5):381–390
24. Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, et al.: Cardiac resynchronization and death from progressive heart failure: A meta-analysis of randomized controlled trials. *JAMA* 2003;289(6):730–740
25. Fish JM, Di Diego JM, Nesterenko V, Antzelevitch C: Epicardial activation of left ventricular wall prolongs QT interval and transmural dispersion of repolarization: Implications for biventricular pacing. *Circulation* 2004;109(17):2136–2142
26. Akar FG, Rosenbaum DS: Transmural electrophysiological heterogeneities underlying arrhythmogenesis in heart failure. *Circ Res* 2003;93(7):638–645
27. Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, et al.: Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. *Circ Res* 1991;69(6):1427–1449
28. Yan G-X, Rials SJ, Wu Y, Liu T, Xu X, et al.: Ventricular hypertrophy amplifies transmural repolarization dispersion and induces early afterdepolarization. *Am J Physiol Heart Circ Physiol* 2001;281(5):H1968–H1975
29. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, et al.: The Multisite Stimulation in Cardiomyopathies Study I. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344(12):873–880
30. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, et al.: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346(12):877–883
31. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, et al.: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352(3):225–237
32. Garrigue S, Barold SS, Hocini M, Jais P, Haissaguerre M, et al.: Treatment of drug refractory ventricular tachycardia by biventricular pacing. *Pacing Clin Electrophysiol* 2000;23(11):1700–1702
33. Roden DM: A surprising new arrhythmia mechanism in heart failure. *Circ Res* 2003;93(7):589–591
34. Bloomfield DM, Steinman RC, Namerow PB, Parides M, Davidenko J, et al.: Microvolt t-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: A solution to the multicenter automatic defibrillator implantation trial (MADIT) II conundrum. *Circulation* 2004;110(14):1885–1889
35. Zabel M, Portnoy S, Franz MR: Electrocardiographic indexes of dispersion of ventricular repolarization: An isolated heart validation study. *J Am Coll Cardiol* 1995;25(3):746–752
36. Puggioni E, Brignole M, Gammage M, Soldati E, Bongiorni MG, et al.: Acute comparative effect of right and left ventricular pacing in patients with permanent atrial fibrillation. *J Am Coll Cardiol* 2004;43(2):234–238
37. Fish JM, Brugada J, Antzelevitch C: Potential proarrhythmic effects of biventricular pacing. *J Am Coll Cardiol* 2005;46(12):2340–2347