View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

© 2004 by the American College of Cardiology Foundation
Published by Elsevier Inc.

ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.08.044

**EXPRESS PUBLICATION**

# Cardiac Resynchronization Therapy: A Novel Adjunct to the Treatment and Prevention of Systemic Right Ventricular Failure

Jan Janoušek, MD,* Viktor Tomek, MD,* Václav Chaloupecký, MD, PHD,* Oleg Reich, MD, PHD,* Roman A. Gebauer, MD,* Josef Kautzner, MD, PHD,† Bohumil Hučín, MD, PHD*

*Prague, Czech Republic*

**OBJECTIVES** This study aimed to evaluate the technical feasibility and hemodynamic benefit of cardiac resynchronization therapy (CRT) in patients with systemic right ventricle (RV).

**BACKGROUND** Patients with a systemic RV are at high risk of developing heart failure. Cardiac resynchronization therapy may improve RV function in those with electromechanical dyssynchrony.

**METHODS** Eight patients (age 6.9 to 29.2 years) with a systemic RV and right bundle-branch block (n = 2) or pacing from the left ventricle (LV) (n = 6) with a QRS interval of 161 ± 21 ms underwent CRT (associated with cardiac surgery aimed at decrease in tricuspid regurgitation in 3 of 8 patients) and were followed-up for a median of 17.4 months.

**RESULTS** Change from baseline rhythm to CRT was accompanied by a decrease in QRS interval (−28.0%, p = 0.002) and interventricular mechanical delay (−16.7%, p = 0.047) and immediate improvement in the RV filling time (+10.9%, p = 0.002), Tei index (−7.7%, p = 0.008), estimated RV maximum +dP/dt (+45.9%, p = 0.007), aortic velocity-time integral (+7.0%, p = 0.028), and RV ejection fraction by radionuclide ventriculography (+9.6%, p = 0.04). The RV fractional area of change increased from a median of 18.1% before resynchronization to 29.5% at last follow-up (p = 0.008) without a significant change in the end-diastolic area (+4.0%, p = NS).

**CONCLUSIONS** The CRT yielded improvement in systemic RV function in patients with spontaneous or LV pacing-induced electromechanical dyssynchrony and seems to be a promising adjunct to the treatment and prevention of systemic RV failure. (J Am Coll Cardiol 2004;44:1927–31)
© 2004 by the American College of Cardiology Foundation

Approximately one million patients with congenital heart disease live in Europe and the same number live in the U.S. (1,2); this population is linearly increasing in developed countries thanks to successful surgical and catheter interventions carrying low immediate risk. In the long term, morbidity due to a suboptimal functional result, however, is significant (3). Heart failure is the second most frequent cause of late mortality (4) in this population. According to a recent study (5), patients with a systemic right ventricle (RV) or single ventricle are especially prone to develop heart failure. Its incidence may reach up to 29%. Heart transplant carries only a 50% survival at 12 years in the pediatric and adolescent age groups (6), and should be delayed or avoided whenever possible. Beneficial acute hemodynamic effects of temporary resynchronization of the subpulmonary RV in patients after surgery for congenital heart disease have been recently reported (7–9). This study aimed to assess the acute and mid-term effects of cardiac resynchronization therapy (CRT) in young patients with a systemic RV and electromechanical dyssynchrony.

From the *Kardiocentrum, University Hospital Motol and the †Institute for Clinical and Experimental Medicine, Prague, Czech Republic. Supported by grant NA/7620-3 of the Internal Grant Agency of the Ministry of Health of the Czech Republic.

Manuscript received July 6, 2004; revised manuscript received August 8, 2004, accepted August 17, 2004.

## METHODS

**Patient group.** Eight patients with a systemic RV and either spontaneous (right bundle-branch block, n = 2) or dual-chamber left ventricular (LV) pacing-induced RV desynchronization (n = 6, mean pacing duration 73 ± 45 months) (Table 1) underwent CRT either for significant RV dysfunction despite standard congestive heart failure therapy (n = 6, mean shortening fraction 9.7 ± 6.1%, mean fractional area of change 16.5 ± 4.6%, Patients #1 to #6) (Table 1, Fig. 1) or as a preventive measure associated with thoracotomy for other indication (n = 2, Patients #7 and #8) (Table 1). In three of eight patients, CRT was combined with surgery aimed at a decrease in tricuspid regurgitation (Patients #2, #4, and #7) (Table 1). Concurrent pulmonary artery debanding was performed in one Senning patient (Patient #1) (Table 1) after retraining of the LV for late arterial switch operation had failed. All patients gave informed consent. The study was approved by the institutional review committee and is in accordance with the Declaration of Helsinki.

**The CRT system.** Three thoracotomy, four mixed (Fig. 2), and one transvenous lead systems were used. The RV leads were placed at the border between basal and mid-ventricular free wall segments (Table 1). Areas of late ventricular activation were targeted by measuring the local

**Abbreviations and Acronyms**

AV = atrioventricular
CRT = cardiac resynchronization therapy
RV = right ventricle/ventricular
LV = left ventricle/ventricular

activation times during the implantation procedure. In case of two RV leads (four of eight patients), two unipolar epicardial electrodes (Model 4965, Medtronic Inc., Minneapolis, Minnesota) were connected as cathode and anode using a Y adapter (A1-CS-SB, Biotronik GmbH & Co., Berlin, Germany) to the LV port of the Insync III Model 8042 pulse generator (Medtronic Inc.) programmed to bipolar configuration. The CRT was achieved by atrial synchronous simultaneous biventricular pacing with an echocardiographically optimized atrioventricular (AV) delay (10) in seven of eight patients. In one patient (Patient #1) (Table 1), RV bifocal pacing was used with the AV delay set to deliver the pacing pulse at the beginning of a spontaneous QRS complex to achieve complete fusion with intrinsic ventricular activation at different heart rates according to both resting and exercise electrocardiogram.

**Follow-up.** Patients were followed for a median of 17.4 months (range 7.7 to 19.7 months) on CRT. Testing of the acute hemodynamic response to CRT was performed by echocardiography at a median of 4.5 days (range 2 to 10 days) after CRT implantation. Measurements were obtained within 10 to 15 cardiac cycles during voluntary end-expiratory apnea while switching from baseline rhythm to CRT. Both measurements were done in three consecutive cardiac cycles, and data were averaged. In case of conventional dual-chamber pacing at baseline (n = 6), AV delay optimization was performed for each pacing mode separately (10). A System Five ultrasound machine along with Echopac software (Vingmed, GE, Horton, Norway) was used for evaluation, applying the following methods:

*Interventricular mechanical delay* = RV − LV pre-ejection period (11)

*Modified dyssynchrony index* = time difference between the longest and shortest QRS to peak myocardial strain (by tissue Doppler imaging) interval in four mid-ventricular RV segments (septal and lateral segment evaluated from the apical four-chamber view, anterior and posterior segment from the apical two-chamber view) (12)

*Myocardial performance (Tei) index* = (RR interval − RV filling time − RV ejection time)/RV ejection time (13)

*Tricuspid regurgitation* was quantified using the usual four-grade scale

*RV maximum +dP/dt* was estimated from the initial slope of the tricuspid regurgitation jet at blood velocities between 1 and 3 m/s in six of eight patients

*RV fractional area of change* = (RV end-diastolic − RV end-systolic area)/RV end-diastolic area as measured from the apical four-chamber view

**Table 1.** Patients

| Pt. No. | Age (yrs) | Diagnosis | Previous Surgical Procedures | Concurrent Surgical Procedures | NYHA Functional Class | Baseline Rhythm | QRS (ms) | LV Lead | RV Lead |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 13 | TGA, VSD | Senning, patch, PA banding | PA debanding | II | RBBB | 140 | — | RAS, RPL |
| 2 | 10 | CTGA, VSD, TV regurgitation | — | Patch, TV plasty | II | 3°AVB/DDD | 140 | LAL | RAL, RPL |
| 3 | 22 | TGA | Senning | — | II | 3°AVB/DDD | 180 | LMVS | RAL, RPL |
| 4 | 12 | TGA, VSD | Senning, patch | PA banding | II | 3°AVB/DDD | 190 | LMVS | RL |
| 5 | 29 | TGA | Mustard | — | III | 1°AVB, RBBB | 150 | LMVS | RL, RP |
| 6 | 18 | CTGA, VSD, PS, TV regurgitation | Patch, TV replacement, LV-PA conduit | — | II | 3°AVB/DDD | 180 | LVA | RL |
| 7 | 9 | CTGA, TV regurgitation | — | TV replacement | II | 3°AVB/DDD | 170 | LL | RL |
| 8 | 7 | DORV, ventricular inversion | Kawashima | Pacing lead revision | II | 3°AVB/DDD | 140 | LVA | RL |

Anatomic nomenclature is used for lead positions.
AVB = atrioventricular block; CTGA = congenitally corrected transposition of great arteries; DDD = conventional DDD pacing; DORV = double outlet right ventricle; Kawashima = intracardiac correction according to Kawashima; LAL = left anterolateral; LL = left lateral; LMVS = left mid-ventricular septum; LV = left ventricle; LVA = left ventricular apex; NYHA = New York Heart Association; PA = pulmonary artery; PS = pulmonary stenosis; RAL = right anterolateral; RAS = right anteroseptal; RL = right lateral; RP = right posterior; RPL = right posterolateral; RV = right ventricular; TGA = transposition of great arteries; TV = tricuspid valve; VSD = ventricular septal defect.

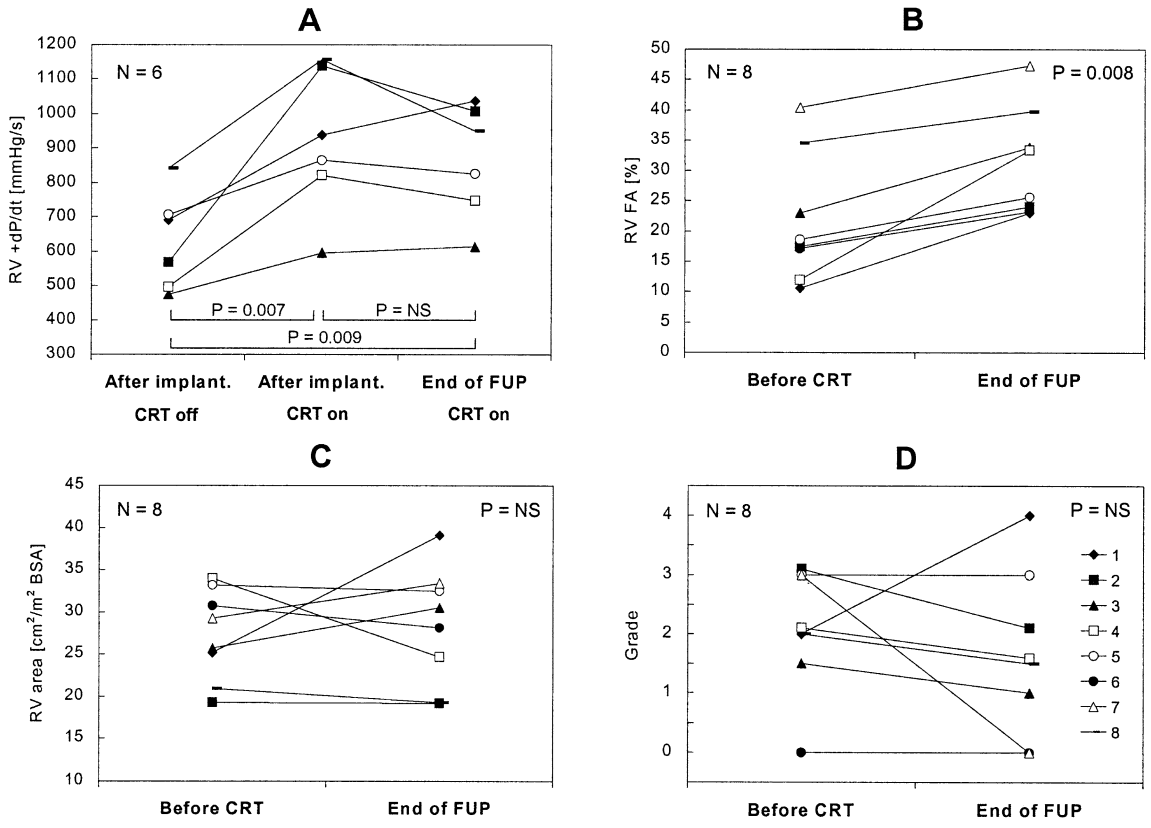


**Figure 1.** Mid-term hemodynamic changes associated with cardiac resynchronization therapy (CRT). **(A)** Right ventricular maximum +dP/dt. Statistical significance by one-way repeated measures analysis of variance and paired *t* tests. **(B)** Right ventricular fractional area of change (RV FA). **(C)** Right ventricular end-diastolic area. **(D)** Grade of tricuspid valve regurgitation. **Symbols** indicate individual patients according to Table 1. BSA = body surface area; FUP = follow-up on CRT; implant. = implantation.

Radionuclide ventriculography was performed after a median of 3.8 months (range 0.2 to 6.8 months) of CRT using a technique described elsewhere (14), and RV ejection fraction was measured. Each study was performed twice using a single dose of isotope at CRT off and on.

**Statistics.** SigmaStat for Windows Version 3.0 (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Data were

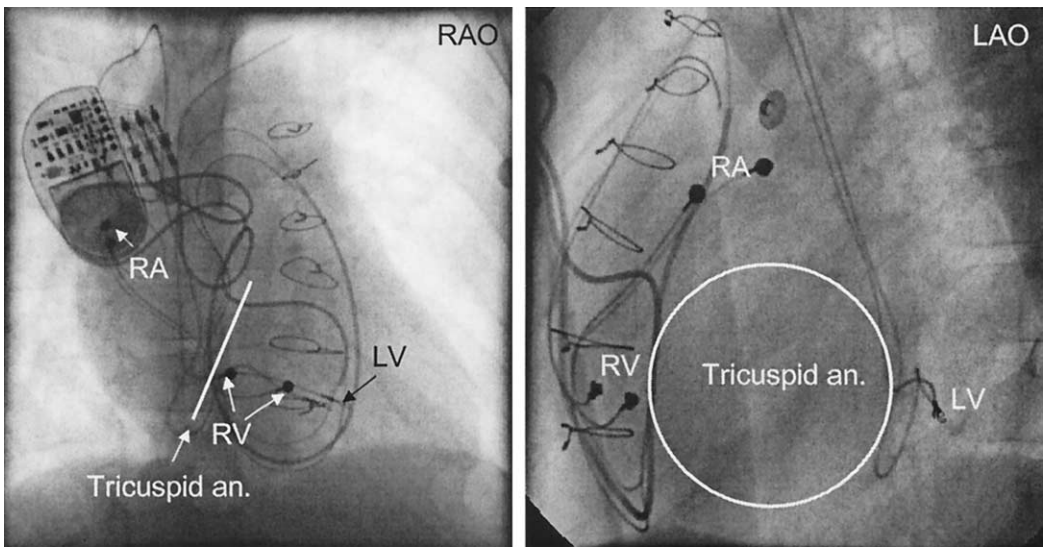


**Figure 2.** Mixed lead system in a patient after the Senning procedure for transposition of great arteries (Patient #4) (Table 1). Two pre-existing unipolar ventricular leads (one is abandoned) are implanted transvenously at left ventricular mid-septum (LV). A bipolar epicardial lead is placed through the thoracotomy at the right ventricular free wall (RV) with good spatial separation of the RV and LV leads across the right ventricle. Presumed position of the tricuspid annulus is indicated. LAO = left anterior oblique projection; RA = right atrial lead; RAO = right anterior oblique projection.

**Table 2.** Acute Hemodynamics Effects of CRT

| Parameter | CRT Off Mean (SD) | CRT On Mean (SD) | % Change | p Value |
|---|---|---|---|---|
| QRS interval (ms) | 161 (21) | 116 (22) | −28.0 | 0.002† |
| Interventricular mechanical delay (ms) | median60 | median50 | −16.7 | 0.047‡ |
| Dyssynchrony index (ms) | 138 (59) | 64 (21) | −53.6 | 0.042† |
| RV filling time (% RR) | 45.1 (6.5) | 50.0 (6.1) | 10.9 | 0.002† |
| Tei index | median0.65 | median0.60 | −7.7 | 0.008‡ |
| RV +dP/dt (mm Hg/s) | 630 (142) | 919 (211) | 45.9 | 0.007† |
| Aortic VTI (cm) | 17.2 (6.2) | 18.4 (6.8) | 7.0 | 0.028† |
| RV EF (%)* | 41.5 (8.1) | 45.5 (6.4) | 9.6 | 0.04† |

*Measured at a median of 3.8 months after initiation of CRT; †paired *t* test; ‡Wilcoxon signed rank test.
CRT = cardiac resynchronization therapy; EF = ejection fraction; RR = RR interval; RV = right ventricular; SD = standard deviation; VTI = velocity-time integral.

expressed as means ± standard deviations or medians, whichever is applicable with regard to normal distribution (Kolmogorov-Smirnov test). One-way repeated measures analysis of variance and paired *t* test (for normally distributed data) or the Wilcoxon signed rank test were used to evaluate intra-individual changes in continuous variables. A p value of $<0.05$ was considered as significant.

## RESULTS

All implantation attempts were successful and were performed without major complications. Pacing thresholds were acceptable. Ventricular activation times at the sites of RV lead implantation referenced to the beginning of the baseline QRS complex equaled 77 ± 21% of QRS interval at CRT off, confirming the placement of these leads in areas of late activation. The Y adapter failure occurred in one patient, resulting in an interrupted connection to the systemic ventricular lead after nine months of therapy (Patient #2) (Table 1). Cardiac resynchronization therapy was associated with beneficial acute changes in systolic and diastolic RV function and improved RV +dP/dt, fractional area of change, and New York Heart Association functional classification in the mid-term (Tables 2 and 3, Fig. 1). Interventricular mechanical delay decreased in six of seven patients, and tissue Doppler imaging confirmed improved RV contraction synchrony in four of five patients, in whom evaluations were possible (Table 2). Tricuspid valve regurgitation was, however, not significantly influenced by CRT alone and increased despite successful resynchronization in one Senning patient after concurrent pulmonary artery debanding (Patient #1) (Table 1, Fig. 1).

## DISCUSSION

Systemic RV patients are at increased risk of developing heart failure (5), need for conventional pacemaker therapy (5,15), and frequently lack transvenous pacing access to the systemic ventricle. After a previous case report (16), this is the first study documenting a positive effect of CRT for either spontaneous or pacing-induced RV desynchronization in this population. The results correspond with those reported for patients with idiopathic or ischemic dilated cardiomyopathy and normal cardiac anatomy (17). However, tricuspid valve regurgitation did not decrease following CRT in a similar way as functional mitral regurgitation (18). Thus, concurrent tricuspid valve interventions may be a necessary adjunct to CRT in patients with severe regurgitation and, in fact, may be facilitated by the improvement in RV function achieved by resynchronization. Impaired myocardial blood flow reserve was described after the atrial switch procedure (19) and proposed as a potential mechanism for RV dysfunction. As CRT is known to decrease myocardial oxygen consumption (20) while increasing the efficiency of ventricular contraction, it may decrease stress-related ischemia and produce another positive long-term effect specific to the systemic RV population.

Conventional RV pacing-induced LV desynchronization has been recently shown to lead to LV dysfunction (21,22), which can be improved by upgrading to biventricular stimulation (23,24). A report on patients with a systemic RV or single ventricle (5) described higher incidence of conventional pacemaker therapy in those with overt heart failure (68.0% vs. 17.1%, $p < 0.001$) and in victims of heart failure (62% vs. 25%, $p < 0.005$, numbers were recalculated by the authors from available data). In our study, LV

**Table 3.** Mid-Term Changes Associated With CRT

| | Prior to CRT Mean (SD) | End of Follow-Up Mean (SD) | % Change | p Value |
|---|---|---|---|---|
| TV regurgitation (grade) | 2.1 (1.0) | 1.6 (1.4) | — | NS† |
| RV end-diastolic area ($cm^2/m^2$ BSA) | 27.3 (5.4) | 28.4 (7.0) | 4.0 | NS† |
| RV fractional area of change (%) | median18.1 | median29.5 | 63.0 | 0.008‡ |
| NYHA functional class | 2.0 | 1.3 | — | 0.008‡ |

BSA = body surface area; NS = not significant; other abbreviations and footnotes as in Tables 1 and 2.

pacing-induced RV desynchronization was a more frequent indication for CRT than right bundle-branch block, and both indications showed similar results.

This study has several limitations, including small sample size, methodological difficulties with longitudinal evaluation of RV size and function, combination with surgery potentially influencing ventricular function (although all patients showed a clear acute hemodynamic effect of CRT regardless of concurrent surgery), and the use of two RV leads in a subset. Criticism may also arise regarding the inclusion of two patients with marginally decreased RV function, who underwent "preventive" CRT at the occasion of other necessary cardiac surgery. The relatively high mean RV ejection fraction of the whole group may, however, already be the result of reverse remodeling, as radionuclide studies were performed at a median of 3.8 months after initiation of resynchronization therapy.

Despite all mentioned limitations, we believe that CRT is a promising adjunct to the treatment of systemic RV failure in young patients. Attaching CRT to other necessary cardiac surgical procedures may be a good basis for a proactive approach to the prevention of RV failure in this high-risk population.

**Reprint requests and correspondence:** Dr. Jan Janoušek, Kardiocentrum, University Hospital Motol, V úvalu 84, 150 06 Prague, Czech Republic. E-mail: jan.janousek@lfmotol.cuni.cz.

## REFERENCES

1. Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. Heart 2001;85:438–43.
2. Webb CL, Jenkins KJ, Karpawich PP et al. Congenital Cardiac Defects Committee of the American Heart Association Section on Cardiovascular Disease in the Young. Collaborative care for adults with congenital heart disease. Circulation 2002;105:2318–23.
3. Bolger AP, Coats AJ, Gatzoulis MA. Congenital heart disease: the original heart failure syndrome. Eur Heart J 2003;24:970–6.
4. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. Am J Cardiol 2000;86:1111–6.
5. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. Circulation 2002;105:1189–94.
6. Boucek MM, Edwards LB, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: Sixth Official Pediatric Report—2003. J Heart Lung Transplant 2003;22:636–52.
7. Janoušek J, Vojtovič P, Hučín B, et al. Resynchronization pacing is a useful adjunct to the management of acute heart failure after surgery for congenital heart defects. Am J Cardiol 2001;88:145–52.
8. Zimmerman FJ, Starr JP, Koenig PR, Smith P, Hijazi ZM, Bacha EA. Acute hemodynamic benefit of multisite ventricular pacing after congenital heart surgery. Ann Thorac Surg 2003;75:1775–80.
9. Dubin AM, Feinstein JA, Reddy VM, Hanley FL, Van Hare GF, Rosenthal DN. Electrical resynchronization: a novel therapy for the failing right ventricle. Circulation 2003;107:2287–89.
10. Kindermann M, Frohlig G, Doerr T, Schieffer H. Optimizing the AV delay in DDD pacemaker patients with high degree AV block: mitral valve Doppler versus impedance cardiography. Pacing Clin Electrophysiol 1997;20:2453–62.
11. Cleland JG, Daubert JC, Erdmann E, et al., CARE-HF Study Steering Committee and Investigators. The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end points. Eur J Heart Fail 2001;3:481–9.
12. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2003;91:684–8.
13. Williams RV, Ritter S, Tani LY, Pagoto LT, Minich LL. Quantitative assessment of ventricular function in children with single ventricles using the Doppler myocardial performance index. Am J Cardiol 2000;86:1106–10.
14. Reich O, Voriskova M, Ruth C, et al. Long-term ventricular performance after intra-atrial correction of transposition: left ventricular filling is the major limitation. Heart 1997;78:376–81.
15. Walker F, Siu SC, Woods S, Cameron DA, Webb GD, Harris L. Long-term outcomes of cardiac pacing in adults with congenital heart disease. J Am Coll Cardiol 2004;43:1894–901.
16. Rodriguez-Cruz E, Karpawich PP, Lieberman RA, Tantengco MV. Biventricular pacing as alternative therapy for dilated cardiomyopathy associated with congenital heart disease. Pacing Clin Electrophysiol 2001;24:235–7.
17. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. Circulation 2003;108:2596–603.
18. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol 2003;41:765–70.
19. Singh TP, Humes RA, Muzik O, Kottamasu S, Karpawich PP, Di Carli MF. Myocardial flow reserve in patients with a systemic right ventricle after atrial switch repair. J Am Coll Cardiol 2001;37:2120–5.
20. Nelson GS, Berger RD, Fetics BJ, 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;102:3053–9.
21. Tantengco MV, Thomas RL, Karpawich PP. Left ventricular dysfunction after long-term right ventricular apical pacing in the young. J Am Coll Cardiol 2001;37:2093–100.
22. Wilkoff BL, Cook JR, Epstein AE, et al., Dual Chamber and VVI Implantable Defibrillator Trial Investigators. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002;288:3115–23.
23. Baker CM, Christopher TJ, Smith PF, Langberg JJ, Delurgio DB, Leon AR. Addition of a left ventricular lead to conventional pacing systems in patients with congestive heart failure: feasibility, safety, and early results in 60 consecutive patients. Pacing Clin Electrophysiol 2002;25:1166–71.
24. Janousek J, Tomek V, Chaloupecky V, Gebauer RA. Dilated cardiomyopathy associated with dual-chamber pacing in infants: improvement through either left ventricular cardiac resynchronization or programming the pacemaker off allowing intrinsic normal conduction. J Cardiovasc Electrophysiol 2004;15:470–4.