Cardiac Resynchronization in Congestive Heart Failure

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Summary

Treating congestive heart failure will represent an increasingly important problem in the field of cardiology for the next years. Parallel to the rising life expectancy, in part due to improved cardiologic therapy options, incidence and prevalence of congestive heart failure are gradually rising. In the course of progressive heart failure, conduction disturbances arise in about 35 % of the patients, with 90 % of them suffering from a left bundle branch block. Cardiac resynchronization is a new therapeutic approach attempting to remedy the effects of these conduction disturbances by simultaneous right- and left-ventricular pacing with optimized AV delay. Though several studies already showed an increase in functional capacity, as well as an improvement in quality of life with cardiac resynchronization therapy, data regarding the most important endpoint, the improvement in morbidity and mortality, are still missing. This article covers a review of the clinical experiences with biventricular pacing and a critical analysis of open questions.

Key Words

Congestive heart failure, cardiac resynchronization, biventricular stimulation

Introduction

In the next years, treating congestive heart failure will constitute an increasingly important problem in the field of cardiology. Parallel to the rising life expectancy, in part due to improved cardiologic therapy options, e.g., treatment of acute coronary syndroms, incidence and prevalence of congestive heart failure are gradually rising. Currently, they affect about 4 % of the total European population [1]. Despite great progress in the drug treatment of congestive heart failure, especially through the use of ACE-inhibitors, the renaissance of the aldosterone antagonist, and the increasing importance of ß-blocker therapy [2-5], many patients remain substantially impaired in their quality of life as well as their prognosis [6,7]. The 5-year survival rate is only about 30 %, mainly due to the risk of sudden cardiac death [8].

In the course of progressive congestive heart failure, conduction disturbances arise in about 35 % of the patients, mainly in the form of left bundle branch blocks (LBBB) and – to a varying degree – of atrioventricular (AV) blocks [9]. Several studies have documented a correlation between the severity of LBBB (as expressed by the QRS width in the surface ECG) and the extent of left-ventricular dysfunction [10-12]. In addition, a wide QRS complex is an independent risk factor for mortality in patients with congestive heart failure [13-15]. To a lesser degree, such worsening of prognosis also applies to the presence of AV blocks [16,17].

Functional Significance of the AV Delay and First Approaches of Pacemaker Therapy for Congestive Heart Failure

Together with the prolongation of the AV conduction – the formation of an AV block I – a presystolic mitral insufficiency occurs, leading to a hemodynamically unfavorable reduction of left-ventricular filling time [18]. Very short AV delays, on the other hand, are also cutting diastolic filling time, because of the premature

mitral valve closure due to the early rise in ventricular pressure, leading to an interruption of the atrial contribution to diastolic filling [19]. The probably optimal AV delay lies between 100 and 125 ms, though considerable interindividual variations can be found [20,21].
Partially preceding these findings, as early as at the beginning of the 90 s the hypothesis was conceived that an improvement of myocardial hemodynamics and, consequently, of the clinical symptoms in heart failure patients could be achieved by optimizing (or just shortening) the AV conduction with conventional dual-chamber pacing (DDD). Early observational studies demonstrated promising results [22-26], which could not be confirmed by the following randomized trials [27-29]. Among the reasons for these diverging results, most likely the heterogeneity of study populations regarding their electrophysiologic characteristics (i.e., the presence of conduction disturbances) was the most important one. In addition, by creating an artificial LBBB with conventional right-ventricular pacing, adverse hemodynamic effects could have been provoked in the studied heart failure patients. Later on, better defined study populations showed, that hemodynamic improvement can be expected in patients with AV block I [30], or should be evaluated by individual invasive testing [31]. Interestingly, another recent study described the at first sight paradox effect, that only patients with a preexisting LBBB would hemodynamically profit from purely right-ventricular pacing [32]. The authors explain the reduction of asynchronous contraction with a shortening of the left-ventricular activation time by right-ventricular-apical pacing compared to the delayed intrinsic conduction in LBBB patients.
Pacing site might also be of crucial importance in right-ventricular pacing. Some studies reported hemodynamic superiority of right-ventricular septal pacing compared to the conventional right-ventricular-apical pacing [33,34]. However, these controversial data are regarded with the according criticism in a recent review of pacemaker therapy in congestive heart failure [35].

Functional Significance of Intraventricular Conduction Disturbances and Definition of Cardiac Resynchronization

More than 90 % of all heart failure patients with ventricular conduction disturbances have LBBB. As early as 1968, the negative hemodynamic effects caused solely by the presence of LBBB were demonstrated by phono- and mechanocardiographical means [36]. Considerably later, the underlying mechanisms of the hemodynamic deterioration were detected by echocardiographic studies [37,38]: *inter*ventricular asynchrony – between the right and left ventricle due to a delayed left-ventricular contraction – and *intra*ventricular asynchrony – within the left ventricle due to a delayed activation of the lateral wall – are leading to an asynchronous septal movement, a reduction of the diastolic filling time, a prolongation of isovolumetric relaxation and contraction time as well as duration of mitral regurgitation, with resulting reduction of overall contractility (Figure 1, panel a – c).
Cardiac resynchronization is the attempt to remedy the effects of conduction disturbances by simultaneous right- and left-ventricular pacing with optimized AV delay, using sequential biventricular pacemaker therapy (Figure 1, panel d – e).

Cardiac Resynchronization

First Clinical Experiences and Acute Electrophysiologic-Hemodynamic Studies

The first case reports describing a potential benefit of additional left-ventricular pacing in symptomatic congestive heart failure with LBBB were published in 1994 [39]. Cazeau described a patient with severe heart failure and advanced conduction disturbance (NYHA IV, LBBB with 200 ms QRS width, AV block I with 200 ms), who experienced a dramatic clinical improvement (NYHA II, recompensation with 17 kg weight loss) by "four-chamber pacing" (i.e., conventional right-ventricular DDD pacing, transvenous left-atrial pacing via the coronary sinus, and thoracoscopically inserted epicardial left-ventricular pacing).
Subsequently, a surgical study with 18 patients, following elective aorto-coronary bypass operation, was able to document the hemodynamic advantage of temporary epicardial atrio-biventricular pacing with an increase in cardiac output (CO) and a reduction in systemic vascular resistance [40]. These results are even more remarkable, given that no heart failure patients with ventricular conduction disturbances were included in the studied patient group. Another early french study provided further insight into possible positive hemodynamic effects in congestive heart failure, reporting acute improvements with increase in CO, and decrease in pulmonary-capillary wedge pressure [41].

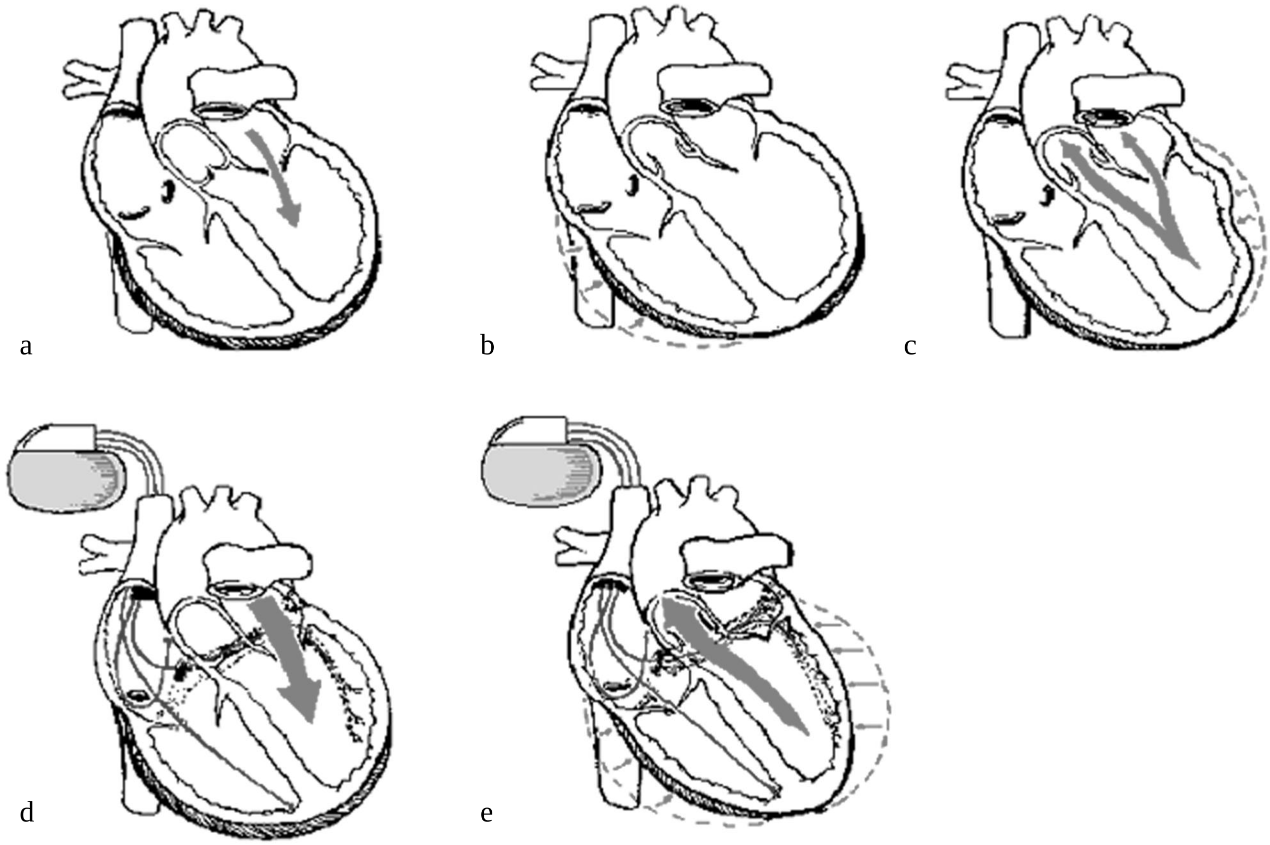

Figure 1. Mechanisms of ventricular asynchrony and cardiac resynchronization: Panel a) reduced diastolic filling; panel b) right-ventricular contraction; panel c) delayed left-ventricular contraction with concomitant mitral regurgitation; panel d) improved diastolic filling time with biventricular pacing; panel e) improved cardiac output with biventricular pacing.

However, due to placement of epicardial left-ventricular leads by limited thoracotomy also a 50 % peri- and post-operative mortality in this critically ill patient group with severe heart failure and partial catecholamine dependency. Subsequently, several electrophysiologic-hemodynamic acute studies underlined the benefit of cardiac resynchronization for myocardial hemodynamics in congestive heart failure and discovered further pathophysiologic mechanisms [42-44]. Blanc [42] showed an increase in arterial blood pressure with concomitant reduction of pulmonary-capillary wedge pressure and pulmonary V wave, reflecting the reduction of mitral valve insufficiency. Figure 2 shows an echocardiographic example of an acute reduction in mitral insufficiency by biventricular pacing. Auricchio [43] demonstrated, an acute improvement of diastolic filling time in nine heart failure patients in 1997. The acute effects of epicardial left-ventricular pacing in 27 patients enrolled in the PATH-CHF study (Pacing Therapies in Congestive Heart Failure) were published in 1999 [20]. Based on this data, the authors postulate that only heart failure patients with pronounced conduction delays (QRS

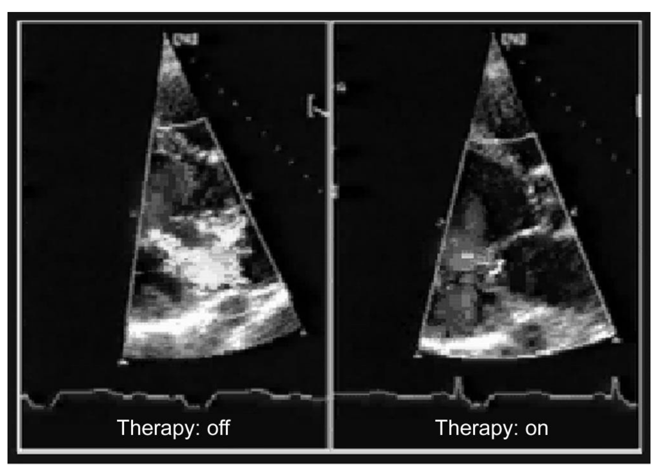

Figure 2. Reduction of mitral regurgitation with biventricular pacing (echocardiographic example, parasternal long axis view).

widths > 150 ms) would respond to therapy with hemodynamic improvement. In the same year, Kass [21] drew similar conclusions, after showing with pressure-volume curves, that only left- or biventricular pacing results in an improvement in relation to the QRS width. In contrast to these findings, Leclercq [44] presented data one year earlier, that the improvement in CO by left- or biventricular pacing is not related to QRS width, but to the reduced left-ventricular function.

Transvenous Lead Placement and Permanent Biventricular Pacing

Since surgical left-ventricular lead implantation via limited thoracotomy was associated with a considerable morbidity and mortality in heart failure patients, other possibilities of left-ventricular pacing were investigated. In 1994, Bai [45] published the case reports of two patients with conventional pacemaker indication and successful permanent pacing via coronary sinus leads. Conventional right-ventricular lead implantation was not possible because of the existence of a mechanical tricuspid valve or phrenic nerve stimulation, respectively.

In view of these results, attempts were made to achieve cardiac resynchronization with a completely transvenous system (Figure 3). First experiences with this new therapeutic approach could be presented already in 1998 [46]. During the same year, the initial results of the INSYNC trial, an open non-randomized Canadian-European study evaluating the effects of biventricular pacing on the functional capacity and quality of life in NYHA III/IV patients were published [47]. The results showed a significant improvement in NYHA class, 6-minutes hall-walk distance and quality of life within the first 3 months. Left-ventricular lead placement was successful in 84 %. The same group published data on possible positive predictive parameters regarding the improvement of functional capacity in 1999 [48]. They postulated that a clinical improvement with biventricular pacing correlates to the amount of QRS narrowing with therapy and not to the baseline QRS width. An example is given in Figure 4.

Recently, the results of the MUSTIC trial (Multisite Stimulation in Cardiomyopathy), an european multicenter singleblind, randomized, cross-over controlled study were presented [49]. In addition to functional capacity and quality of life, hospitalization rate improved significantly with cardiac resynchronization.

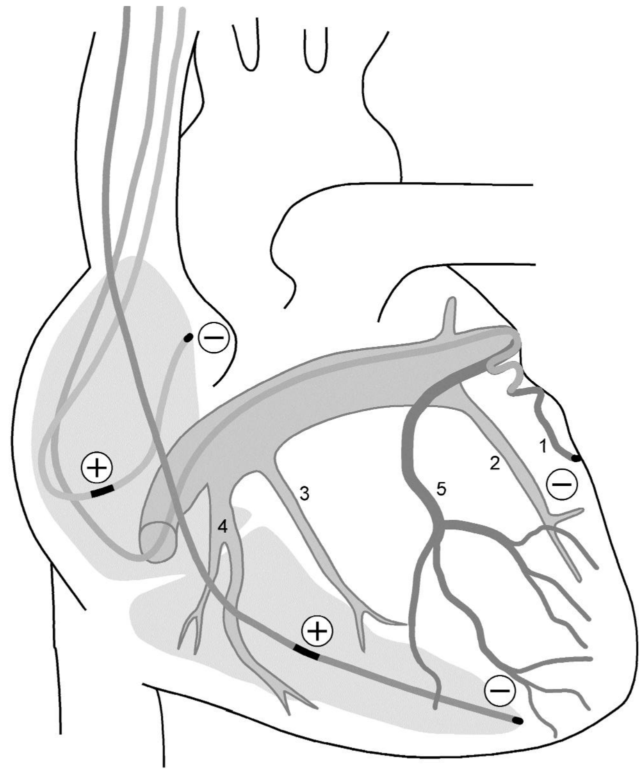

Figure 3. Coronary sinus anatomy and lead position: (1) Lateral (marginal) cardiac vein; (2) postero-lateral cardiac vein; (3) posterior cardiac vein; (4) middle cardiac vein; (5) great cardiac and anterior interventricular vein. The supposed optimal left-ventricular pacing site is (1) and (2) for left-bundle branch-block-like conduction abnormalities.

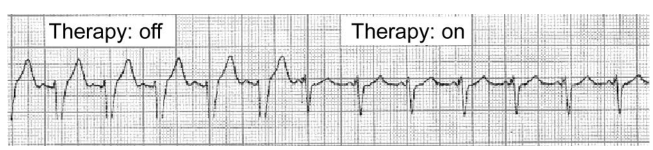

Figure 4. Reduction of QRS width with biventricular pacing.

Further evidence suggests, that aside from hemodynamic improvement, cardiac resynchronization might also contribute to a stabilization of the electrical activity with a reduction of ventricular ectopies and tachyarrhythmias [50,51]. The sub-study of the VENTAK-CHF trial (heart failure patients with implanted cardioverter-defibrillator and biventricular pacing [52]) showed a significant reduction of therapy deliveries due to ventricular tachyarrhythmias under cardiac resynchronization [50]. Parallel,Walker reported a 50 % reduction of ventricular ectopies with active pacing [51].

Optimization of the AV Delay, Technical Difficulties, and Resynchronization During Chronic Atrial Fibrillation

One difficulty in optimizing cardiac resynchronization therapy is the evaluation of the hemodynamic changes in relation to AV delay and left-ventricular pacing site. As already mentioned before, mostly invasive parameters, such as CO, aortic pressure amplitude, velocity of systolic pressure increase, or pulmonary-capillary wedge pressure and V wave have been employed so far [21,30,31,42,43]. Since these parameters are not useful for optimizing pacing parameters in clinical routine settings, non-invasive methods have been investigated. Doppler echocardiography has become established as the method of choice, mostly applying improvement in mitral flow profile for optimizing AV delay. Ritter originally published an equation for determination of the optimal AV delay in abstract form, which has been confirmed and validated subsequently [53]. Figure 5 shows an example of optimizing the diastolic filling time with this method. In parallel, other echocardiographic parameters, such as end-diastolic volume measurement, velocity time integrals over the mitral and aortic valves, and newer indices ("myocardial performance index") were studied, but had only been published in abstract form so far (e.g., Kerwin et al. Circulation AHA Suppl. 2000; Abs 1563). However, a completely new echocardiographic method – tissue velocity imaging – appears to be particularly promising in regard to screen patients with asynchronous contraction mode and to optimize AV-delay.

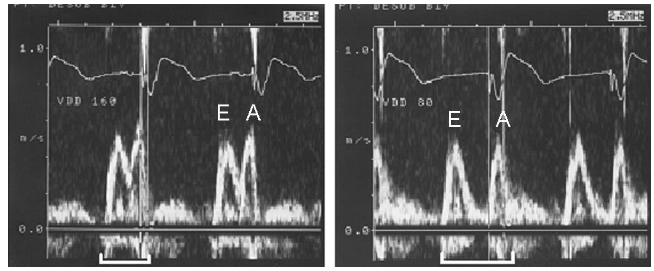

Figure 5. Echocardiographic transmitral flow Doppler measurements. Prolongation of diastolic filling time with AV-optimization and biventricular pacing: Long AV-delay with short filling time and almost fusion of mitral E and A wave, and optimized AV-delay with improved filling time and normal E and A wave.

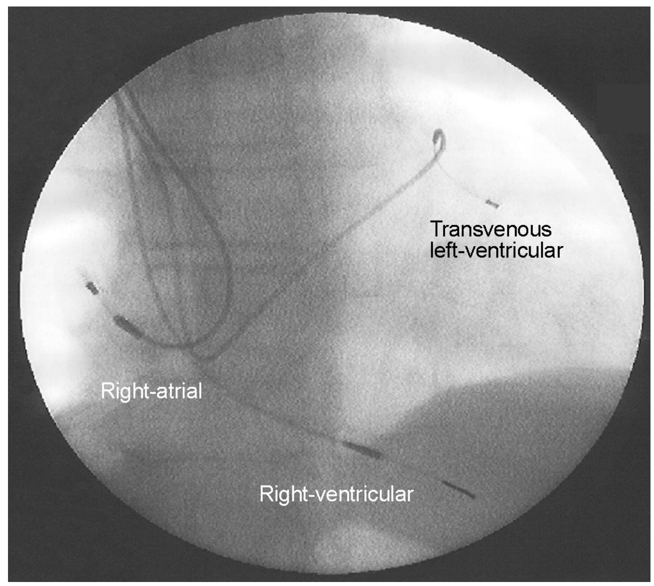

Figure 6. Chest X-ray showing a left atrial lead, a right apical lead and a coronary sinus lead.

No final statement has yet been made regarding the optimal left-ventricular pacing site; nevertheless, the postero-lateral or lateral position should produce the best results (Figure 3). The PATH-CHF II study tries to answer questions concerning the impact of different left-ventricular pacing sites, alone or in combination with right-ventricular sites, on hemodynamic performance in LBBB as well as right bundle branch block (RBBB) type conduction delays [54]. In patients with RBBB an anterior interventricular vein lead placement is attempted. This implies that a precise lead positioning is desirable. However, with the current lead technology this cannot be accomplished in all cases, due to the limited controllability and the considerable anatomical variability of the coronary sinus. In our own patient population, we were able to achieve an internationally comparable primary implantation success of 85 %. A postero-lateral or lateral lead position was achieved in 90 % of all cases (Figure 6). These fairly encouraging primary results can, however, only be accomplished with a considerable time expenditure (implantation time up to 4 hours) using the currently available lead material. Coronary sinus injuries are a rare complication, and mostly resolves without long-term sequelae [55]. In view of these facts, further development of the lead systems has become a primary concern. To this end, mainly guide wire technologies, comparable to the interventional cardiology setting, are under investigation. First positive experiences with an "over the wire" system as well as a "side wire" system were recently reported [56,57]. However, ongoing development and improvement of lead performance for optimizing implantation success seems mandatory.

Another frequently occurring rhythm disturbance in the development of congestive heart failure is chronic atrial fibrillation. Whether patients with intraventricular conduction delay and atrial fibrillation will profit from only resynchronizing ventricular activation, without the possibility to optimize AV delay, has not yet been sufficiently clarified. First data point towards a hemodynamic profit for these patients, too [58-60]. However, to guarantee consistent pacemaker stimulation, the intrinsic AV conduction has to be permanently suppressed by His-bundle ablation. Recent data from the atrial fibrillation group of the MUSTIC trial, presented at the ESC in Amsterdam in August 2000, show a smaller benefit for patients with atrial fibrillation compared to patients with sinus rhythm regarding quality of life and hospitalization rate.

Ongoing Studies About Cardiac Resynchronization and Future Perspectives

Currently, several large-scale multicenter studies are trying to establish this promising therapeutic approach as a new form of therapy for heart failure patients with associated conduction disturbances. First data from the MIRACLE trial (Multicenter InSync Randomized Clinical Evaluation), a large-scale randomized, double-blind parallel controlled study in the USA, have been presented at the 50th annual session of the American College of Cardiology. In addition to the improvement in functional capacity and quality of life, a reduction of mitral insufficiency and heart volume, as well as an increase in left-ventricular ejection fraction occurred. Furthermore neurohormone and cytokine levels will be assessed. Two other randomized, double-blind multicenter studies also compare functional capacity, quality of life, and hemodynamic improvement in heart failure patients with intraventricular conduction delay (> 120 ms), either without conventional pacemaker indication (VIGOR-CHF) or in combination with an ICD implantation (VENTAK-CHF). The InSync ICD trial is a prospective, randomized, multicenter trial with heart failure patients without conventional indication for ICD or pacemaker implantation. All patients receive the device and will be randomized to either resynchronization therapy on or off. After 6 months all patients will be programmed "on". Besides functional capacity, echocardiographic assessment of hemodynamics, neurohormone levels, antitachycardia therapy delivery and survival will be secondary endpoints. The COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure) trial is a three armed study investigating the benefit of biventricular pacing or biventricular pacing with ICD backup in addition to optimized medical therapy compared to medical therapy alone. Finally, the recently started european randomized, controlled trial, CARE-HF (Cardiac Resynchronization in Heart Failure), tries to answer questions regarding mortality and morbidity reduction with cardiac resynchronization, by comparing 400 heart failure patients with optimized medical therapy to 400 patients with additional biventricular stimulation.

Conclusion

The attempt to reestablish cardiac resynchronization by biventricular pacing is a new and promising therapeutic approach in heart failure patients with intraventricular conduction disturbances. Currently, positive therapeutic effects with increase in exercise capacity and improvement in quality of life have been published and repeatedly confirmed for patients with preserved sinus rhythm and LBBB-like conduction delay. Still unsolved or only partially answered are questions regarding the benefit of cardiac resynchronization in chronic atrial fibrillation and RBBB-like conduction delays. Regarding the patient selection, only a few and not undisputed parameters have been published. Future studies for precise characterization of the patient who will profit from cardiac resynchronization are therefore of primary importance in order to avoid unnecessary, expensive, and potentially complication-harboring operations. Finally, unambiguous data concerning the benefit in morbidity and mortality with this new therapy for heart failure patients are still missing, but should be provided by the ongoing large-scale, double blind trials in the near future.

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References

[1] Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left-ventricular dysfunction in the general population; The Rotterdam Study. Eur Heart J. 1999; 20: 447-455.

[2] Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987; 316: 1429-1435.

[3] Effect of enalapril on survival in patients with reduced left-ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991; 325: 293-302.

[4] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999; 353: 9-13.

[5] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999; 341: 709-717.

[6] Dracup K, Walden JA, Stevenson LW, et al. Quality of life in patients with advanced heart failure. J Heart Lung Transplant. 1992; 11: 273-279.

[7] Doval HC, Nul DR, Grancelli HO, et al. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA). Lancet. 1994; 344: 493-498.

[8] Ho KK, Pinsky JL, Kannel WB, et al. The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol. 1993; 22: 6A-13A.

[9] De Maria R, Gavazzi A, Recalcati F, et al. Comparison of clinical findings in idiopathic dilated cardiomyopathy in women versus men. The Italian Multicenter Cardiomyopathy Study Group (SPIC). Am J Cardiol. 1993; 72: 580-585.

[10] Murkofsky RL, Dangas G, Diamond JA, et al. A prolonged QRS duration on surface electrocardiogram is a specific indicator of left-ventricular dysfunction. J Am Coll Cardiol. 1998; 32: 476-482.

[11] Eriksson P, Hansson PO, Eriksson H, et al. Bundle-branch block in a general male population: the study of men born 1913. Circulation. 1998; 98: 2494-2500.

[12] Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: a study of all incident cases in Olmsted County, Minnesota, in 1991. Circulation. 1998; 98: 2282-2289.

[13] Cianfrocca C, Pelliccia F, Nigri A, et al. Resting and ambulatory ECG predictors of mode of death in dilated cardiomyopathy. J Electrocardiol. 1992; 25: 295-303.

[14] Aaronson KD, Schwartz JS, Chen TM, et al. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997; 95: 2660-2667.

[15] Shamim W, Francis DP, Yousufuddin M, et al. Intraventricular conduction delay: a prognostic marker in chronic heart failure. Int J Cardiol. 1999; 70: 171-178.

[16] Xiao HB, Roy C, Fujimoto S, et al. Natural history of abnormal conduction and its relation to prognosis in patients with dilated cardiomyopathy. Int J Cardiol. 1996; 53: 163-170.

[17] Schoeller R, Andresen D, Buttner P, et al. First- or second-degree atrioventricular block as a risk factor in idiopathic dilated cardiomyopathy. Am J Cardiol. 1993; 71: 720-726.

[18] Ishikawa T, Kimura K, Nihei T, et al. Relationship between diastolic mitral regurgitation and PQ intervals or cardiac function in patients implanted with DDD pacemakers. PACE. 1991; 14: 1797-1802.

[19] Ronaszeki A, Denef B, Ector H, et al. Influence of short atrioventricular delay on late diastolic transmitral flow and stroke volume. Angiology. 1992; 43: 32-39.

[20] Auricchio A, Stellbrink C, Block M, 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: 2993-3001.

[21] Kass DA, Chen CH, Curry C, et al. Improved left-ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation. 1999; 99: 1567-1573.

[22] Hochleitner M, Hortnagl H, Ng CK, et al. Usefulness of physiologic dual-chamber pacing in drug-resistant idiopathic dilated cardiomyopathy. Am J Cardiol. 1990; 66: 198-202.

[23] Hochleitner M, Hortnagl H, Fridrich L, et al. Long-term efficacy of physiologic dual-chamber pacing in the treatment of end-stage idiopathic dilated cardiomyopathy. Am J Cardiol. 1992; 70: 1320-1325.

[24] Hochleitner M. Pacemaker therapy in heart failure. Wien Med Wochenschr. 1998; 148: 134-136.

[25] Auricchio A, Sommariva L, Salo RW, et al. Improvement of cardiac function in patients with severe congestive heart failure and coronary artery disease by dual chamber pacing with shortened AV delay. PACE. 1993; 16: 2034-2043.

[26] Brecker SJ, Xiao HB, Sparrow J, et al. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. Lancet. 1992; 340: 1308-1312.

[27] Gold MR, Feliciano Z, Gottlieb SS, et al. Dual-chamber pacing with a short atrioventricular delay in congestive heart failure: a randomized study. J Am Coll Cardiol. 1995; 26: 967-973.

[28] Innes D, Leitch JW, Fletcher PJ. VDD pacing at short atrioventricular intervals does not improve cardiac output in patients with dilated heart failure. PACE. 1994; 17: 959-965.

[29] Linde C, Gadler F, Edner M, et al. Results of atrioventricular synchronous pacing with optimized delay in patients with severe congestive heart failure. Am J Cardiol. 1995; 75: 919-923.

[30] Nishimura RA, Hayes DL, Holmes DR Jr, et al. Mechanism of hemodynamic improvement by dual-chamber pacing for severe left-ventricular dysfunction: an acute Doppler and catheterization hemodynamic study. J Am Coll Cardiol. 1995; 25: 281-288.

[31] Sack S, Franz R, Dagres N, et al. Can right-sided atrioventricular sequential pacing provide benefit for selected patients with severe congestive heart failure? Am J Cardiol. 1999; 83: 124D-129D.

[32] Garrigue S, Barold SS, Valli N, et al. Effect of right-ventricular pacing in patients with complete left bundle branch block. Am J Cardiol. 1999; 83: 600-604, A608.

[33] Buckingham TA, Candinas R, Attenhofer C, et al. Systolic and diastolic function with alternate and combined site pacing in the right ventricle. PACE. 1998; 21: 1077-1084.

[34] Schwaab B, Frohlig G, Alexander C, et al. Influence of right-ventricular stimulation site on left-ventricular function in atrial synchronous ventricular pacing. J Am Coll Cardiol. 1999; 33: 317-323.

[35] Peters RW, Gold MR. Pacing for patients with congestive heart failure and dilated cardiomyopathy. Cardiol Clin. 2000; 18: 55-66.

[36] Baragan J, Fernandez-Caamano F, Sozutek Y, et al. Chronic left complete bundle-branch block. Phonocardiographic and mechanocardiographic study of 30 cases. Br Heart J. 1968; 30: 196-202.

[37] Xiao HB, Lee CH, Gibson DG. Effect of left bundle branch block on diastolic function in dilated cardiomyopathy. Br Heart J. 1991; 66: 443-447.

[38] Grines CL, Bashore TM, Boudoulas H, et al. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation. 1989; 79: 845-853.

[39] Cazeau S, Ritter P, Bakdach S, et al. Four chamber pacing in dilated cardiomyopathy. PACE. 1994; 17: 1974-1979.

[40] Foster AH, Gold MR, McLaughlin JS. Acute hemodynamic effects of atrio-biventricular pacing in humans. Ann Thorac Surg. 1995; 59: 294-300.

[41] Cazeau S, Ritter P, Lazarus A, et al. Multisite pacing for end-stage heart failure: early experience. PACE. 1996; 19: 1748-1757.

[42] Blanc JJ, Etienne Y, Gilard M, et al. Evaluation of different ventricular pacing sites in patients with severe heart failure: results of an acute hemodynamic study. Circulation. 1997; 96: 3273-3277.

[43] Auricchio A, Salo RW. Acute hemodynamic improvement by pacing in patients with severe congestive heart failure. PACE. 1997; 20: 313-324.

[44] Leclercq C, Cazeau S, Le Breton H, et al. Acute hemodynamic effects of biventricular DDD pacing in patients with end-stage heart failure. J Am Coll Cardiol. 1998; 32: 1825-1831.

[45] Bai Y, Strathmore N, Mond H, et al. Permanent ventricular pacing via the great cardiac vein. PACE. 1994; 17: 678-683.

[46] Daubert JC, Ritter P, Le Breton H, et al. Permanent left-ventricular pacing with transvenous leads inserted into the coronary veins. PACE. 1998; 21: 239-245.

[47] Gras D, Mabo P, Tang T, et al. Multisite pacing as a supplemental treatment of congestive heart failure: preliminary results of the Medtronic Inc InSync Study. PACE. 1998; 21: 2249-2255.

[48] Alonso C, Leclercq C, Victor F, et al. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol. 1999; 84: 1417-1421.

[49] Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med. 2001; 344: 873-880.

[50] Higgins SL, Yong P, Sheck D, et al. Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy. Ventak CHF Investigators. J Am Coll Cardiol. 2000; 36: 824-827.

[51] Walker S, Levy TM, Rex S, et al. Usefulness of suppression of ventricular arrhythmia by biventricular pacing in severe congestive cardiac failure. Am J Cardiol. 2000; 86: 231-233.

[52] Saxon LA, Boehmer JP, Hummel J, et al. Biventricular pacing in patients with congestive heart failure: two prospective randomized trials. The VIGOR CHF and VENTAK CHF Investigators. Am J Cardiol. 1999; 83: 120D-123D.

[53] Kindermann M, Frohlig G, Doerr T, et al. Optimizing the AV delay in DDD pacemaker patients with high degree AV block: mitral valve Doppler versus impedance cardiography. PACE. 1997; 20: 2453-2462.

[54] Stellbrink C, Auricchio A, Butter C, et al. Pacing therapies in congestive heart failure II study. Am J Cardiol. 2000; 86: K138-K143.

[55] Walker S, Levy T, Paul VE. Dissection of the coronary sinus secondary to pacemaker lead manipulation. PACE. 2000; 23: 541-543.

[56] Walker S, Levy T, Rex S, et al. Initial results with left-ventricular pacemaker lead implantation using a preformed "peel-away" guiding sheath and "side-wire" left-ventricular pacing lead. PACE. 2000; 23: 985-990.

[57] Auricchio A, Klein H, Tockman B, et al. Transvenous biventricular pacing for heart failure: can the obstacles be overcome? Am J Cardiol. 1999; 83: 136D-142D.

[58] Etienne Y, Mansourati J, Gilard M, et al. Evaluation of left-ventricular based pacing in patients with congestive heart failure and atrial fibrillation. Am J Cardiol. 1999; 83: 1138-1140, A1139.

[59] Leclercq C, Victor F, Alonso C, et al. Comparative effects of permanent biventricular pacing for refractory heart failure in patients with stable sinus rhythm or chronic atrial fibrillation. Am J Cardiol. 2000; 85: 1154-1156, A1159.

[60] Hubmann M, Vestner J, Ruppert T, et al. Acute improvement of left-ventricular functions by biventricular pacing in a patient with dilated cardiomyopathy and permanent atrial fibrillation - a case report. Prog Biomed Res. 2000; 5: 37-40.

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