Multichamber Implantable Devices: Clinical Data and Concepts for Future Development

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Summary

Several new methods of multichamber (biatrial, biventricular) cardiac pacing for intracardiac hemodynamic improvement and tachyarrhythmia prevention have been suggested in recent years. Biatrial, septal, and multifocal right atrial pacing clinically used in atrial fibrillation therapy, in particular to prevent atrial fibrillation paroxysms, appear to be an effective therapy in patients with tachy-brady syndrome and intra- or inter-atrial conduction disturbances. Today, biventricular, single-site left ventricular or multisite right ventricular pacing is a widely used therapy in patients with drug-refractory heart failure as well as in patients of the functional NYHA classes III or IV with intraventricular conduction dysfunction. Initial clinical results of prospective and randomized trials have demonstrated that in the next few years this alternative therapeutic approach will become established in heart failure patients as well as in patients with complicated, life-threatening arrhythmias. Only five years ago, multichamber implantable cardioverter-defibrillators were viewed as devices that might only be available in the distant future, but they are now widely used in everyday clinical practice. The combined hemodynamic and antiarrhythmic effect of electrical heart resynchronization facilitates improvement in the quality of life and a reduction in the number of implantable cardioverter-defibrillator therapy applications in heart failure patients.

Key Words

Multichamber implantable devices, atrial fibrillation/flutter electrotherapy, biatrial and biventricular pacing

Introduction

P-wave synchronous biventricular pacing is classically indicated for resynchronization of the heart. This electrotherapy approach might be effective in patients with atrial fibrillation (AF) associated with obvious heart failure (in this case, an atrioventricular (AV) block has developed). Many aspects concerning the heart chambers to be paced (atrial or ventricular pacing), on the one hand, and pacing adjustments, i.e., atrial or ventricular electrode positioning, on the other hand, are widely discussed in the literature. A considerable number of clinical cases with effective special single-site pacing (from the interatrial septum, left ventricular epicardial surface, right ventricular outflow tract, etc.) or multisite pacing (biatrial, biventricular, three- and four-chamber) is described elsewhere [1-7].

Atrial Fibrillation/Flutter Therapy and Prevention

Up to 50% of patients with persistent (stable) AF experienced an arrhythmia recurrence within 12 months after successful drug or electrical cardioversion [8-9]. In recent years, proarrhythmic effects of widespread antiarrhythmic drugs of the classes I and III, especially in patients with poor ejection fractions (EF), have lead to the extensive application of nonpharmacologic approaches to treat AF [10]. Until the mid 90s, the cardioverter-defibrillators "Metrix"-3000 and 3200 (InControl, USA) were successfully implanted. As an obligatory component, the implantable cardioverter-defibrillators (ICD) for atrial application included a three-lead system with right atrial coronary sinus (CS) shock coils and a ventricular lead to allow VVI pacing and R-wave synchronized shock discharge of 6 J. Even

though several hundred devices were implanted in patients with persistent AF , the ICDs for atrial application were not widely used because of painful shocks and AF recurrences during the first few minutes after pulse application in 15 – 30% of all cases.

The prospective randomized trials by Anderssen et al. in 1994 and 1997 proved that right atrial pacing reduces recurrences of AF and prolongs the period of time until chronic AF occurs in comparison with VVI pacing [11,12]. Multisite atrial pacing, including upper interatrial septum pacing, effectively resulted in the prevention of AF with a prolongation of "clear intervals" between AF episodes [6].

Saksena [2,13] and Prakash [3] demonstrated statistically insignificant but still evident trends towards AF episode reduction during multisite right atrial pacing (active fixation electrodes were implanted in the upper right atrium and near the CS ostium). Daubert et al. (1994) were the first to suggest biatrial pacing and demonstrated the benefit of this new electrotherapy mode in AF/atrial flutter (Afl) patients with interatrial block [14]. The mechanism of preventive multisite atrial pacing has not been completely studied. However, today a number of electrophysiologic and hemodynamic phenomena are worth mentioning, and we also have studied them in our clinical investigations. First of all, these are the decrease of the atrial pulse conduction time, the homogenization of the global right/left atrial excitation associated with atrial de- and repolarization, the elimination of functional block areas of pulse conduction, and reduction in the number of atrial extrasystoles [15]. While implanting the multichamber ICD, we observed a reduction in the number of extrasystoles that were the AF trigger before implantation. AV and interatrial delay optimization has improved intracardiac hemodynamics by achieving a reduction in left ventricular diastolic dysfunction, an increase of the EF, and a decrease in mitral valve regurgitation. This is also a very important factor in preventing atrial tachyarrhythmias.

At the Bakoulev Center, we were the first to use a three-chamber ICD (Tachos MSA, Biotronik) for biatrial pacing, atrial and ventricular cardioversion, and defibrillation in patients with life-threatening ventricular arrhythmias that were associated with the brady-dependent AF/Afl form [16]. Atrial flutter high frequency (50 Hz) pacing and AF paroxysm low-energy cardioversion in ICD patients provide not only arrhythmia termination, but also enable long-term disease

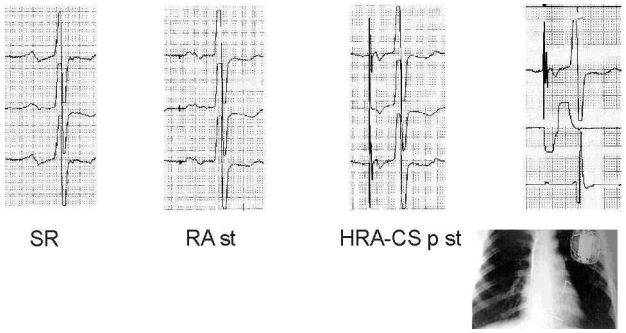

Figure 1. Surface ECGs of a multi-chamber implantable cardioverter-defibrillator patient at sinus rhythm (SR, P-wave duration = 145 ms), high right atrium pacing (RA st), and biatrial pacing (HRA-CS p st, P-wave duration = 90 ms).

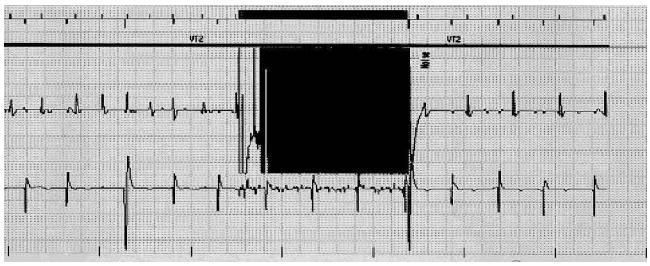

Figure 2. Atrial flutter termination by high frequency pacing (50 Hz). Upper tracing – atrial intracardiac electrogram (IEGM), lower tracing – right ventricular IEGM.

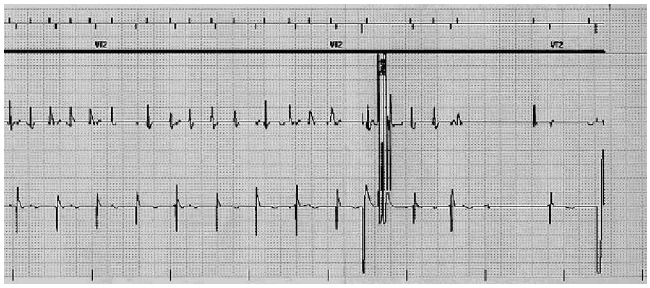

Figure 3. Atrial fibrillation (AF) therapy (cardioversion) with the aid of a 2-J discharge in a patient with ventricular tachycardia (VT)/ventricular fibrillation and paroxysmal AF. Sinus rhythm is restored by the discharge to terminate the AF paroxysm after a short period (1 s) of atrial tachycardia.

remission as assessed from the prolongation of the episode intervals (Figures 1, 2). The preventive aim of this pacing mode is to cause electrical, anatomical, and neurohumoral remodeling of atria.

The antiarrhythmic mechanisms of multisite and biatrial pacing could be related to atrial resynchronization, in particular to elimination of interatrial conduction blocks with retrograde activation delay of the left atri-

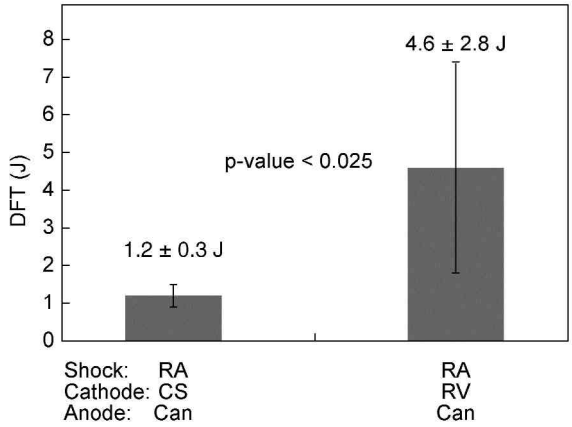

Figure 4. The atrial defibrillation threshold (DFT) with and without use of the coronary sinus (CS) lead. On the horizontal axis two lead configurations are presented. One configuration consists of the shock leads in the right atrium (RA), the cathode in the CS, and the implantable cardioverter-defibrillator housing (Can) as the anode. The mean atrial DFT for this configuration was 1.2 ± 0.3 J or significantly lower than for the other configuration with the shock coils in the right atrium (RA), the cathode in the right ventricle (RV) and the housing as the anode. Our clinical results have shown that only the lead position in the CS enables DFT reduction to 1 – 2 J.

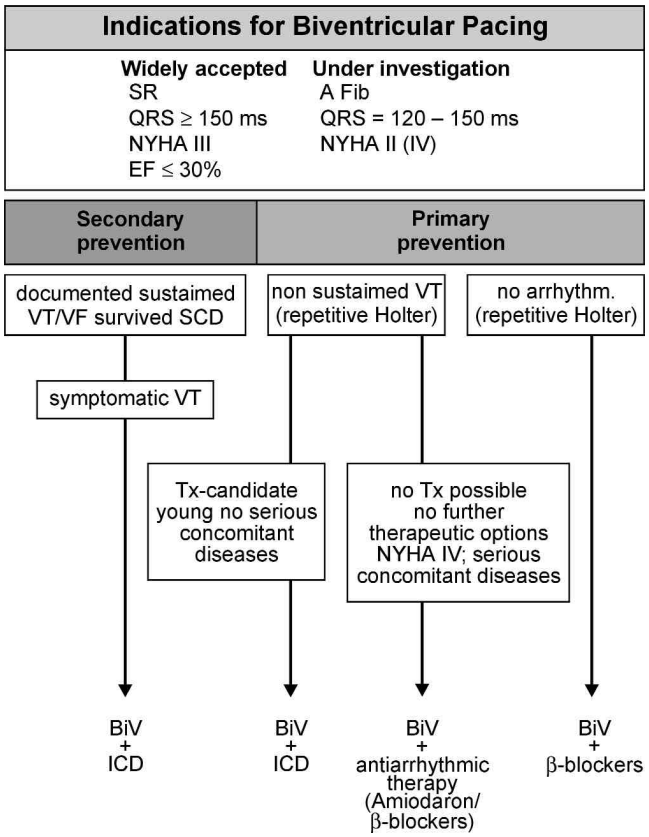

Figure 5. The algorithm suggested by Butter and Fleck [28] for biventricular pacing (BiV) summarizes our understanding of the indications for patients with congestive heart failure (CHF), i.e. ejection fraction (EF) £ 30%, NYHA functional class III, and QRS ³ 150 ms. Implantation of a three-chamber implantable cardioverter-defibrillator (ICD) with the biventricular pacing option is indicated for heart transplantation candidates with non-stable ventricular tachycardia and aggravating life-threatening ventricular arrhythmias and QRS ³ 150 ms. SR = Sinus rate; QRS = duration of the QRS-complex; EF = ejection fraction; Afib = Atrial Fibrillation. VT/VF = ventricular tachycardia/ventricular fibrillation; SCD = sudden cardiac death; Tx = treatment.

um, which is associated with a high incidence of atrial tachyarrhythmias [17]. Prakash et al. [3] observed in EPI trials that standard single-site pacing was associated with an increase in P-wave duration and appearance of a slow pulse conduction zone in the atria, and thus, an increasing activation time in the atria that enables re-entry formation. Experimental and clinical studies have demonstrated that dispersion of refractoriness or anisotropy in the atria is decreased by biatrial pacing, resulting in a homogenized atrial repolarization and a reduced probability of developing stable re-entry [18]. Our clinical trials have shown that left atrial pacing of a certain mode and cycle duration could eliminate hidden bigeminy and trigger activity in the pulmonary vein muscle in paroxysmal AF patients undergoing radiofrequency ablation of the pulmonary vein ostium. Overdrive pacing (P on T) reduces the number of early atrial extrasystoles and thus eliminates the AF trigger mechanism. Considering the role of pacing therapy in preventing paroxysmal AF one should take into account that anti-arrhythmic therapy (AAT) refractory AF is mediated by anatomic changes in the atria. Since "AF begets AF," the arrhythmia induces electrical and structural atrial remodeling. Tachyarrhythmia prophylaxis by means of multisite overdrive atrial pacing using special algorithms does not seem to be as effective because of recurrences of AF paroxysms. Termination of the "real" AF by means of rapid or super-rapid pacing, including 50-Hz pacing over a period of 2 – 10 s, was never documented in our AF electrotherapy studies. Up to 30% of ICD patients are known to have AF/Afl episodes, and the ratio increases up to 50% if one also takes into account the patients with heart failure and intraatrial block disturbances, sick sinus syndrome, etc. Atrial fibrillation is an independent risk factor of arrhythmic death and thromboembolism.

Clinical Experience on ICD (n = 111)			
Guardian	Telectronics	9	(8.57%)
Phylax 03	Biotronik	28	(26.7%)
Phylax 06	Biotronik	29	(27.6%)
Jewel PCD	Medtronic	8	(7.6%)
Phylax AV	Biotronik	22	(20.9%)
GEM™ DR	Medtronic	3	(0.9%)
Tachos DR	Biotronik	10	(6.7%)
Deikos A+	Biotronik	2	(0.9%)

Table 1. Several generations of implantable cardioverter-defibrillators (ICD) have been implanted at the A.N. Bakoulev Research Center.

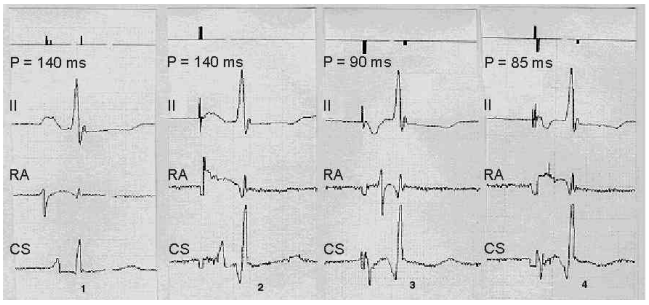

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Figure 6. Biatrial pacing in a patient with paroxysmal atrial fibrillation (AF). Surface ECG lead II, intracardiac electrogram in the high right atrium (RA) and the coronary sinus (CS) are shown. a) – sinus rhythm, b) right atrial pacing, c) coronary sinus pacing, d) biatrial pacing. Biatrial pacing in the AF patient with an interatrial conduction disturbance results in P-wave shortening from 140 ms to 85 ms. Thus, the atria are electrically and hemodynamically resynchronized and the number of AF paroxysms is reduced.

The clinical experience of the Bakoulev Center in implanting multichamber ICDs with the Af/Afl therapy option in patients with life-threatening ventricular tachyarrhythmia demonstrates that a statistically significant reduction in AF/Afl episodes can be achieved by preventive, atrial, multisite (biatrial) pacing, high-frequency pacing (ATP) in atrial flutter cases, and low-energy cardioversion in symptomatic, drug AAT resistant AF cases (Figures 1 – 4).

The majority of investigators recommend sinus rhythm restoration in persistent AF patients to improve their quality of life and reduce hospitalization [9,19]. Our clinical experience proves that sinus rhythm maintenance is the only way to achieve electrical and structural remodeling of the left atrium.

Though absolute implantation indications for the multisite atrial ICD system are not yet available, the majority of experts recommend applying the three-chamber ICD for the prevention of frequent AF paroxysms in patients with idiopathic and AAT refractory AF paroxysms under the condition that intra- and/or interatrial conduction disturbances are present (P-wave duration ≥ 120 ms).

Biventricular Pacing with a Multichamber ICD

Ventricular resynchronization is the main objective of biventricular pacing, which should be conducted with an optimized AV delay and in the P-synchronized mode at sinus rhythm. The benefits of intra- and interventricular resynchronization by pacing of the right ventricular apex-septum zone and of the left ventricular postero-lateral wall include not only a shorter QRS duration but also a prolongation of the ventricular end-diastolic filling period, segmental contraction improvement, and a decrease of the so-called septum de-synchronization in patients with left bundle-branch block (LBBB). Some authors used echo-Doppler and tissue echo-Doppler examinations and computer tomography to prove the benefits of biventricular pacing.

In 1994, Cazeau was the first to realize a four-chamber pacemaker implantation with a lead configuration including the usual set of right heart endocardial DDD pacing electrodes, a transvenous electrode for CS pacing, and a thoracoscopically implanted electrode for epicardial, left ventricular pacing [20]. While still in the hospital, the patient with terminal congestive heart failure (CHF), NYHA class IV, LBBB, a QRS duration of 200 ms, and first-degree AV block changed to NYHA class II with improved left ventricular diastolic and systolic functions as well as increased cardiac output. Unfortunately, up to 50% of the epicardial electrode implantations in patients with terminal CHF and NYHA class IV were associated with intra- and postoperative complications. In the late 1990s, many clinicians used only the transvenous implantation of special endocardial electrodes in the left ventricular venous system. Blanc et al. [21], Auriccio et al. [22], Kass et al. [23], Leclerq [24], and others have shown that biventricular and multisite pacing of the left ventricle raises blood pressure, lowers pulmonary block pressure, and prolongs the left ventricular end-diastolic fill-

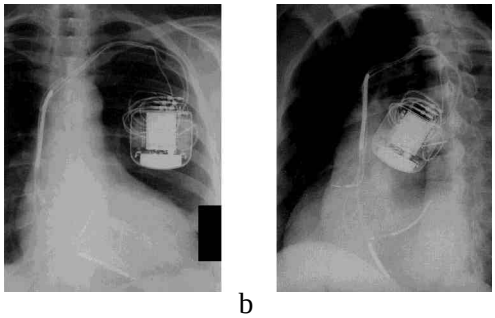

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Figure 7. X-ray picture of the patient with the three-chamber implantable cardioverter-defibrillator (Tachos DR, Biotronik); a) anterior projection; b) left anterior-lateral projection. The leads are implanted into the right atrium, the coronary sinus, and the right ventricle.

Parameters	Before ICD Implantation	BiV Pacing
QRS (ms)	172 ± 12	123 ± 17*
NYHA	III – IV (3.6)	II – III (2.2)*
LVD D (mm)	78.6	71.6
LVD S (mm)	66.2	61.4
EF (%)	24.5 ± 5.2	28.3 ± 6.2
Desynchronization	5	0*

*Table 2. Some clinical data of patients with congestive heart failure and ventricular tachycardia /ventricular fibrillation prior to and after the implantation of the three-chamber ICD Tachos MSV (Biotronik). Follow-up time 8.5 ± 5.6 months; * p-value < 0.05; n = 10; LVD D = left ventricular diastolic diameter; LVD S = left ventricular systolic diameter.*

ing time. There was no conclusive proof that the initial QRS duration is the cause of effective ventricular resynchronization. Nevertheless, the longer the initial QRS complex, the better is the hemodynamic result of biventricular pacing in CHF patients. The results of the INSYNC [25] randomized studies have demonstrated the benefit of biventricular pacing in CHF patients of the functional classes III and IV, including a statistically proven decrease in mean NYHA functional class, a longer mean distance covered during the 6-minute walk test, and an improved quality of life. The European multicenter, randomized crossover MUSTIC (Multisite Stimulation in Cardiomyopathy) study [4] confirmed improvement in both quality of life and functional status, as well as a decrease in hospitalization duration due to ventricular resynchronization [4]. The VENTAK-CHF trial in CHF patients with implanted ICDs having the biventricular pacing mode option [26] has demonstrated an actual decrease in the number of antitachycardia pacing and cardioversion therapies in response to ventricular tachycardias (VT) due to biventricular pacing. Walker et al. [27] also have shown a decrease in the number of ventricular extrasystoles, including double systoles of up to 50% during ventricular resynchronization. Today, no less than 15 randomized trials are being conducted worldwide. Among them are 6 trials concerning multichamber ICD implantation with a left ventricular pacing mode. The InSync ICD study is a prospective, randomized, multicenter study in CHF patients with ICD or pacemaker implantation indications. The COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure) trial is randomized with respect to three groups: biventricular pacing (group I), ICD (group II), and AAT only (group III). The PATH-CHF2 (ICD) and PACMAN (ICD) trials are aimed at primary sudden death prophylaxis on the background of ventricular resynchronization. In contrast, the VENTAC CHF, CONTAK CD, and MIRACLE ICD studies comprise patients with class I indications for ICD implantation, i.e., sec-

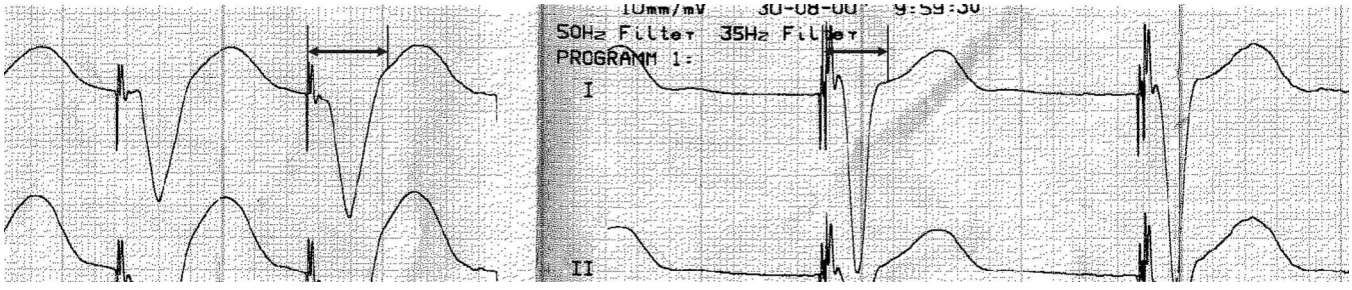

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Figure 8. Surface ECG of the congestive heart failure (CHF) patient at biventricular pacing (BiV). Biventricular pacing with the aid of the Corox LV lead (Biotronik) results in QRS shortening (panel b) when compared to conventional right ventricular pacing (panel a).

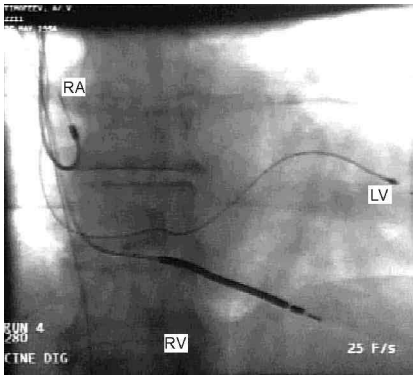

Figure 9. X-ray picture of leads in the patient with the three-chamber implantable cardioverter-defibrillator and the coronary sinus lead. The leads are positioned in the post-lateral vein (left ventricular venous system) to stimulate the left ventricle (LV), in the high right atrium (RA), and in the right ventricular apex (RV).

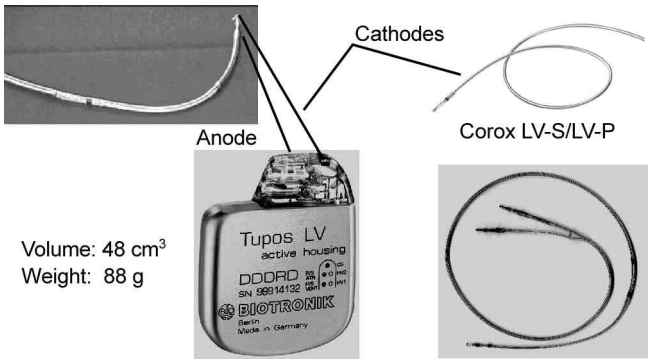

Figure 10. The three-chamber implantable cardioverter-defibrillator (Tupos LV, Biotronik) and the leads for synchronous biatrial and biventricular pacing (Corox LV-S/LV-P, Biotronik).

ondary sudden death prophylaxis and mortality in general will be analyzed in this group.

On the basis of ventricular resynchronization study results in CHF patients with life-threatening arrhythmias and ICD implantation indications, the following preliminary conclusions can be drawn:

- Ventricular resynchronization in patients with CHF and LBBB with QRS complexes > 150 ms has the potential to improve the quality of life and the NYHA functional class and in some cases to decrease the number of VT episodes and the number of ventricular extrasystoles.
- Left ventricular posterolateral and lateral zone pacing is preferable by means of transvenous electrodes effectively (up to 85 – 90%) positioned via the CS.

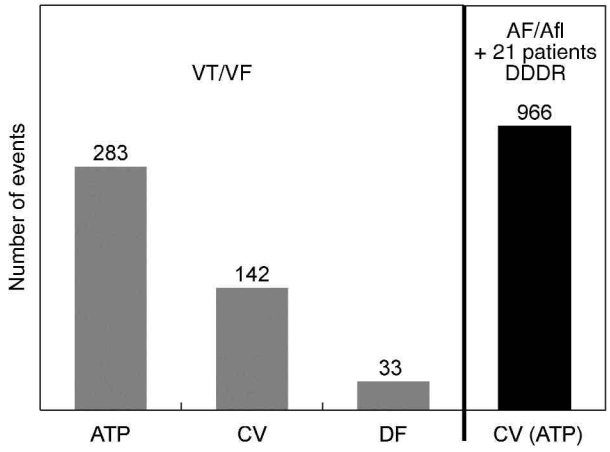

Figure 11. Type and number of ventricular tachycardia/ventricular fibrillation (VT/VF) and superventricular tachycardia, i.e., atrial fibriallation / atrial flutter (AF/Afl), therapies after multi-chamber implantable cardioverter-defibrillator implantation. ATP = anti-tachycardia pacing; CV = cardioversion; DF = defibrillation.

- The hemodynamic and functional effects of ventricular resynchronization are more impressive in sinus rhythm and LBBB patients. It remains to be proven whether the biventricular pacing mode is significantly effective in AF and right bundle-branch block patients.

Today, biventricular pacing can be recommended for patients with ICD implantation indications of the classes I or II, ischemic cardiomyopathy, NYHA functional classes II and III, LBBB, and QRS duration of more than 150 ms (Figure 5).

Clinical Results

The dual-chamber ICD Phylax AV (Biotronik) was successfully implanted in a subpectoral position in April 1996, and the three-chamber ICD with biatrial pacing option Tachos MSA (Biotronik), in January 2000 at the Bakoulev Center Moscow, which was the first implantation of its kind worldwide. Our overall clinical experience with ICDs includes 111 implantations (Table 1); in addition, multichamber ICDs have been implanted in 25 patients (17 male, mean age 50.2 ± 12.4 years).

Syncopes and the threat of sudden cardiac death due to VT/ventricular fibrillation (VF) paroxysms were the main indications for implantation. 22 patients (88.0%) needed physiologic pacing (AAI, DDD/R modes) to cure accompanying bradyarrhythmias and antiarrhyth-

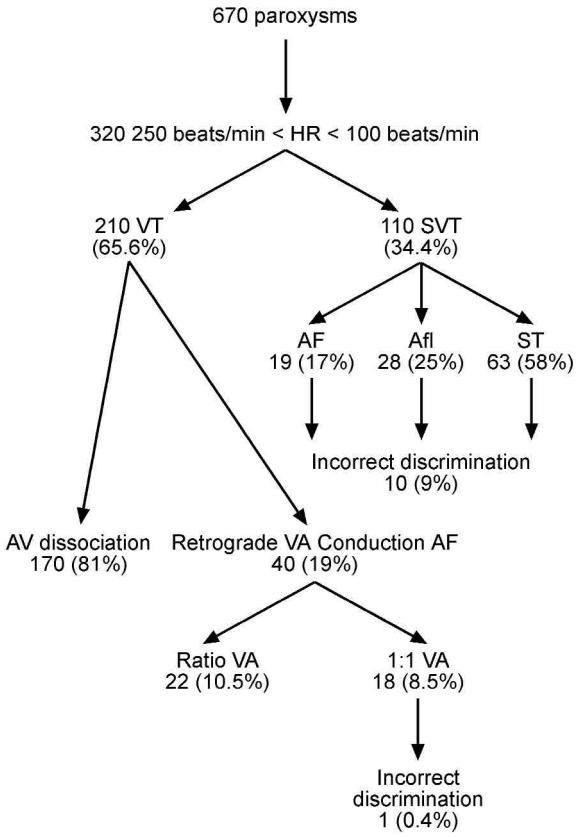

Figure 12. Analysis of the implantable cardioverter-defibrillator Holter ECG in 65 patients with superventricular and ventricular tachycardia paroxysms. From 320 paroxysms in the tachycardia zone (heart rate < 250 bpm), 11 events were classified incorrectly, which results in an efficacy of 96.2%. HR = heart rate; VT = ventricular tacycardia, SVT = supraventricular tacycardia; AF = Atrial fibrillation; Afl = atrial flutter; ST = Stable; AV = atrioventricular; VA = ventriculo-atrial.

mic drug induced bradycardia. Two of those patients had therapy-resistant AF paroxysms with recorded broad P-waves (130 – 140 ms) at sinus rhythm. They received lead systems for biatrial pacing to improve intraatrial conduction (P-wave duration = 90 ms) and to reduce the number of AF paroxysms (Figures 6, 7). Twenty patients (80%) had low EFs, 39.8 ± 9.2% on average. Fourteen patients in that group (56%) received DDD/DDDR pacing therapy, and the left-ventricular EF improved by 8.7 ± 5.6% due to individually adjusted AV delays. The implementation of physiologic pacing options in dual- and multi-chamber ICDs has significantly extended the possibilities of preventive drug therapy, thus decreasing the number of VT paroxysms in the whole group of patients.

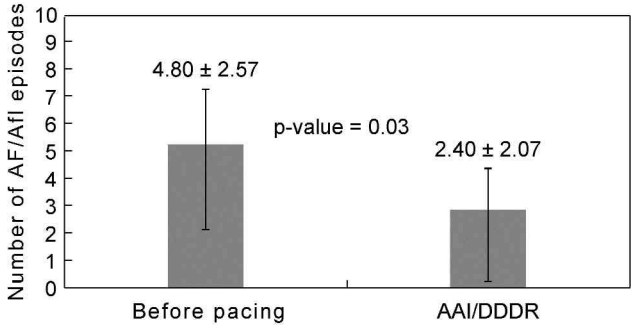

Figure 13. Atrial fibrillation / atrial flutter (AF/Afl) episodes in the group of patients with multichamber implantable cardioverter-defibrillators (ICD) prior to and after implantation. Mean values ± standard deviations.

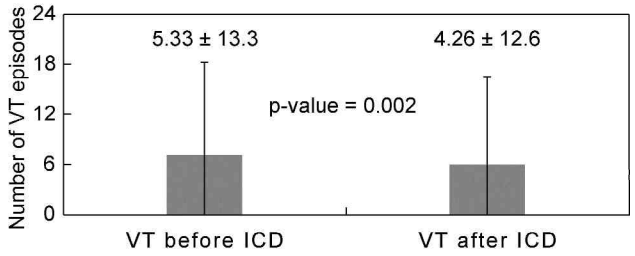

Figure 14. Ventricular tachycardia (VT) episodes in the group of patients with multichamber implantable cardioverter-defibrillators prior to and after implantation. Mean values ± standard deviations.

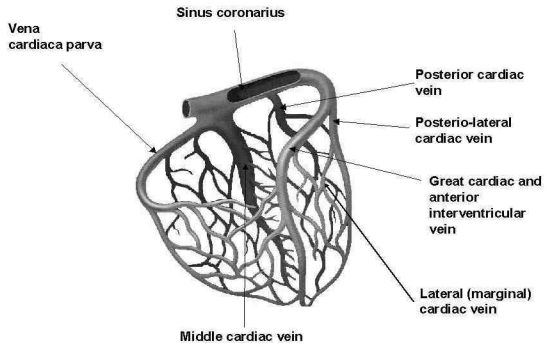

Figure 15. Anatomy of the coronary venous system. The resynchronization effect of biventricular pacing in congestive heart failure patients with left bundle branch block (duration of the QRS complex > 150 ms) is most pronounced with the left ventricular lead positioned in the posterior-lateral vein.

Together with B. Merkely [28] we have analyzed the results of 10 implantations of a three-chamber ICD (Tachos MSV, Biotronik) in CHF patients with a mean QRS duration of 172 ± 12 ms and life-threatening tachyarrhythmias (Table 2, Figures 8-10). The table demonstrates the QRS duration reduction (from 172 ± 12 ms

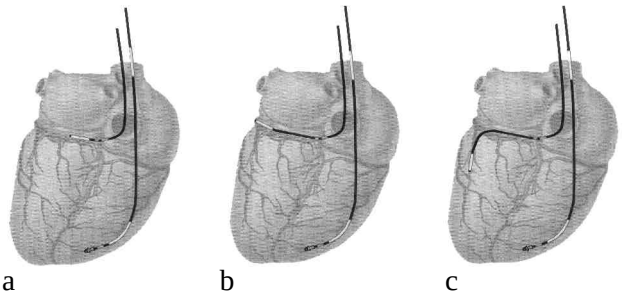

Figure 16. Different positions of the coronary sinus lead while applying the special three-phase shock: a) shock lead positioned in the proximal coronary sinus, b) shock lead positioned in the distal coronary sinus, c) shock lead positioned in the posterior-lateral cardiac vein. The lowest defibrillation threshold was experimentally achieved for the configuration shown in panel c.

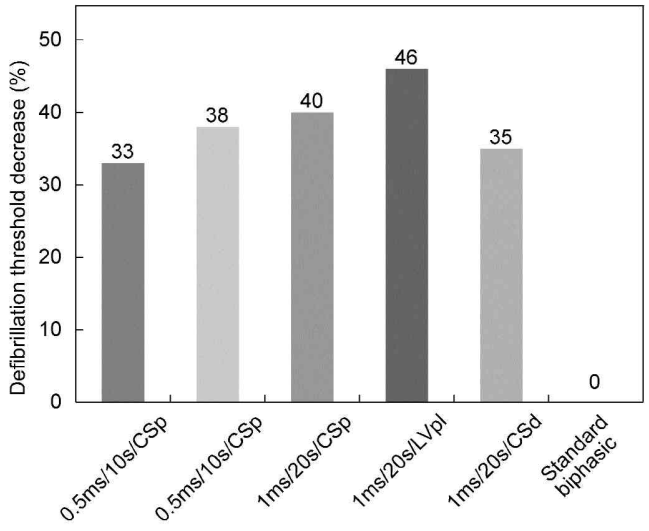

Figure 17. Defibrillation threshold decrease in % for the special three-phasic shock in comparison to the conventional biphasic shock (experimental data). The defibrillation threshold was optimal for the shock lead positioned in the posterior-lateral cardiac vein (LVpl, see Figure 16 c) with a 46% DFT decrease. CSp = proximal coronary sinus; CSd = distal coronary sinus.

to 123 ± 17 ms), and dynamics of the NYHA functional class and of the EF.

Figures 11 and 12 show the effectiveness of dual-chamber ICD application for VT/VF and supraventricular tachyarrhythmia therapy. The data summarize the results obtained from 25 patients who received Phylax AV and Tachos DR ICDs (Biotronik) at the Bakoulev Center (Figure 11). While the total number of VT/VF episodes was 458, the number of supraventricular AF/Afl episodes amounted to 966. Twenty-one patients received multichamber pacing therapy. We have analyzed 670 VT/VF episodes (Figure 12), of which 320 were in the tachycardia zone (heart rate < 250 bpm). Discrimination and, therefore, the delivered therapy were correct in 99.6% of the VT and 91% of the superventricular tachycardia (SVT) cases. The SMART algorithm (Biotronik) for VT/SVT discrimination was efficient in 96.2% of the cases.

Implantation of dual- and three-chamber ICDs results in a statistically relevant reduction of the episodes of AF/atrial tachycardia and of VT/VF therapies (Figures 13, 14). The number of AF/Afl episodes per patient decreased significantly from 4.8 to 2.4 (p-value = 0.03), and the number of VT episodes, from 5.3 to 4.2 (p-value = 0.002).

The resynchronization effect of biventricular pacing in CHF patients with the LBBB (QRS > 150 ms) is most pronounced with the left ventricular lead positioned in the posterior-lateral cardiac vein (Figure 15).

Another advantage of the third lead in the CS is the possibility of decreasing the ventricular defibrillation threshold (DFT), especially in patients with CHF and cardiomegaly. Different positions of the CS lead while applying a special three-phasic shock have been tested experimentally (Figure 16). The lowest DFT was achieved for a shock lead position in the posterior-lateral vein (see Figure 16 c). The experimental data and first clinical results prove a ventricular DFT reduction by 46% while applying the special three-phasic shock discharge in comparison to a conventional biphasic shock (Figure 17).

Conclusion

In the next two to three years, we will receive absolute confirmation of the effectiveness of multi-chamber ICDs in preventing SVT/VT and improving patients' quality of life and NYHA functional class, as has already been demonstrated in a number of prospective and randomized trials. Furthermore, statistically relevant data are needed to confirm reductions in mortality and postoperative complications due to the implantation of two or three endocardial leads. Today, multichamber (dual-chamber) ICDs range from 30 to 60% of the total number of ICD implantations in many hospitals worldwide. In the near future, additional medical research studies will show whether the application of more expensive three- and four-chamber ICDs will pay off.

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