# Final Results of the Observation Study of Biotronik Congestive Heart Failure Systems (BEATLE)

K. MALINOWSKI[1], G. JAKL[2], S. LÖSCHER[3], E. MEISEL[4], H. BONDKE[5], C. SCHAFFAR[6]

[1]Helios Klinikum, Aue, Germany;
[2]Wilhelminenspital der Stadt Wien, Wien, Austria;
[3]Klinik für Innere Medizin, Städtisches Klinikum, St. Georg, Leipzig, Germany;
[4]Praxiszentrum Herzkreislauf, Dresden, Germany;
[5]Medizinische Klinik, Charité Campus Mitte, Humboldt Universität Berlin, Berlin, Germany
[6]Biotronik GmbH & Co. KG, Erlangen, Germany

## Summary

*Severe congestive heart failure is often accompanied by interventricular conduction disturbances. In addition to optimal pharmacological therapy, numerous studies have shown the positive effect of cardiac resynchronization therapy (CRT) realized by biventricular pacing for patients with severe congestive heart failure. Patients improved in both exercise capacity and clinical symptoms. This article describes the final results of the BEATLE (Observation of Biotronik Congestive Heart Failure Systems) observation study, whose objective was to acquire initial experience with the Triplos LV pacemaker, the Tupos LV ICD, and the Corox LV coronary sinus lead family. Special emphasis was placed on the Corox LV-H lead with its optimized three-dimensional, helix-shaped fixation mechanism in the distal area of the lead. The BEATLE observation study was able to show that biventricular pacing via a coronary vein using the resynchronization systems described above can be conducted safely and successfully.*

## Keywords

Cardiac resynchronization therapy, biventricular pacing, chronic heart failure

## Introduction

Congestive Heart Failure (CHF) is a progressive disease with increasing incidence [1] and is characterized by decreased cardiac output. Today, CHF is already the most frequent diagnosis in patients over 65 years hospitalized for cardiovascular reasons [2]. The main causes of CHF are coronary heart disease, arterial hypertension, dilatative cardiomyopathy, and valvular heart defects. In addition to fatigue and significantly limited physical capacity, major clinical symptoms also include dyspnea during light physical activity as well as at rest. In the advanced stages of the disease, augmented peripheral and central hydroplexia (local circulation disturbances and clogging in the lymphatic system) occur.

Approximately 20% – 30% of patients with CHF also have a disturbance of the intraventricular conduction, distinguishable on the ECG as left bundle-branch block (LBBB) with a clear widening of the QRS complex. Asynchronous ventricular contraction is then shown on the echocardiograph. This asynchronicity of the left ventricular contraction causes an immediate worsening of the systolic function [3]. The objective of cardiac resynchronization therapy brought about through biventricular pacing is to normalize the contraction sequence, especially in the left ventricle, by synchronizing the right and left ventricular conduction. By optimizing the pacing interval between the atria and the ventricles, the atrioventricular (AV) delay, the function of the left ventricle improves [4,5]. Left ventricular pacing most often occurs through an endocardial lead that has been inserted into a coronary vein percutaneously. Cardiac resynchronization therapy provides a significant clinical benefit for a selected patient group [6-13].

The BEATLE (Observation of Biotronik Congestive Heart Failure Systems) observation study is a multi-center, prospective, uncontrolled clinical project with the objective of investigating the safety and efficacy of biventricular resynchronization therapy.

## Material and Methods

### Design

Included were patients with chronic heart failure and an indication for biventricular resynchronization therapy (after they had provided their written informed consent for data sharing). Excluded were patients with permanent atrial fibrillation. All patients also received individual optimal drug therapy. After the successful implantation of a resynchronization system, the patients underwent follow-up exams in the clinic before hospital discharge and at 6 weeks and 6 months after implantation. Additional follow-up exams in the clinic were also documented under the "special follow-up" category. The observation study's protocol did not stipulate any examinations that transcended the usual methods employed in typical clinical practice. The entire course of the therapy, including programming of the resynchronization system, was the responsibility of the attending physician.

### Patients

A total of 21 patients in five European centers were included in the BEATLE observation study. All patients demonstrated severe preoperative heart failure with an average NYHA class of 3.1 and a severely limited left ventricular ejection fraction of 28% on average (Tables 1 and 2). Heart failure, which was of ischemic origin in over half of the cases, caused shortness of breath for most patients. Other documented clinical symptoms included fatigue, edema, and chest pain. Drug therapy was tailored to each patient. Analysis of the surface ECG showed a significant widening of the QRS complex to an average of 150 ms; over half of the patients exhibited left bundle-branch block.

### Resynchronization Systems

Patients with ICD indication were treated with a Tupos LV; patients without such an indication received Triplos LV (both from Biotronik, Germany). Both resynchronization systems have a 3-channel header for the connection of bipolar right atrial and right

| | | |
|---|---|---|
| Age (years) | Mean ± SD | 70 ± 8 |
| | Range | 44 – 82 |
| Gender, male | | 16 (76%) |
| BMI | Mean ± SD | 28 ± 3 |
| | Range | 24 – 35 |
| Ischemic etiology | | 14 (67%) |
| NYHA Class | Mean ± SD | 3.1 ± 0.4 |
| | II - III | 4 (19%) |
| | III | 10 (48%) |
| | III - IV | 4 (19%) |
| | IV | 1 (5%) |
| | not documented | 2 (10%) |
| Symptoms | Shortness of breath | 16 (76%) |
| | Fatigue | 9 (43%) |
| | Peripheral edema | 8 (38%) |
| | Pulomnary edema | 5 (24%) |
| | Chest pain | 2 (10%) |
| Comorbidities | Diabetes mellitus | 7 (33%) |
| | Renal insufficiancy | 5 (24%) |
| | COPD | 2 (10%) |
| Pharmacological Therapy | ß-blockers | 16 (76%) |
| | Diuretics | 15 (71%) |
| | ACE-Inhibitors | 14 (67%) |
| | Spironolactones | 14 (67%) |
| | Digitalis | 12 (57%) |
| | Anticoagulants | 8 (38%) |
| | Nitrates | 7 (33%) |

*Table 1. Patient characteristics. SD = standard deviation, BMI = body mass index, COPD = chronic obstructive pulmonary disease.*

ventricular leads and a unipolar lead for pacing the left ventricle. When programming biventricular resynchronization, simultaneous, cathodal pacing of both ventricles is conducted according to the common-ring principle.

### Leads

The Corox LV-H and Corox LV-P coronary sinus leads (both Biotronik), which were investigated during the BEATLE observation study, have two different anchoring mechanisms to help fixate the lead in a coronary vein.

| ECG Analysis | Heart rate at rest (beats/min) | Mean ± SD Range | 75 ± 16 40 – 100 |
|---|---|---|---|
| | PR interval (ms) | Mean ± SD Range | 212 ± 37 175 – 300 |
| | QRS duration (ms) | Mean ± SD Range | 150 ± 25 110 – 200 |
| | Persistent AF | | 4 (19%) |
| | Paroxysmal AF | | 4 (19%) |
| | AV-Block III° | | 7 (33%) |
| | AV Block II° | | 2 (10%) |
| | AV Block I° | | 3 (14%) |
| | LBBB | | 13 (62%) |
| Echocardio-graphy | LVEF (%) | Mean ± SD Range | 28 ± 5 20 – 35 |

*Table 2. ECG analysis and echocardiographic measurement. LVEF = left ventricular ejection fraction, AF = atrial fibrillation, LBBB = left bundle-branch block, SD = standard deviation, AV = atrioventricular.*

| Resynchronization System | | Triplos LV | 10 |
|---|---|---|---|
| | | Tupos LV | 9 |
| LV lead | | Corox LV-H | 16 |
| | | Corox LV-P | 3 |
| RV lead | | Kainox | 8 |
| | | Merox | 3 |
| | | Polyrox | 2 |
| | | Synox | 2 |
| | | TIR | 1 |
| | | not documented | 3 |
| RA lead | | Y | 8 |
| | | Elox | 7 |
| | | YP | 2 |
| | | not documented | 2 |

*Table 3. Successfully implanted resynchronization devices (all Biotronik) and leads. LV = left ventricular, RV = right ventricular, RA = right atrial.*

The atraumatic fixation of the Corox LV-P is guaranteed by a curvature of the distal end. The Corox LV-H lead, however, has a three-dimensional helix-shaped fixation. Both these leads are optimally suited to cover the broad individual variability of coronary venous system characteristics. The implantation is performed through a stylet using the SCOUT implantation tool (Biotronik); the positioning of the lead can also be varied in the coronary venous system by partially retracting the stylet. Selection of the right atrial and right ventricular leads was determined by the attending physician.

**Results**

*Implantation*
All implantation procedures were performed by puncturing the subclavian vein, typically on the left side. Implantation on the right side was performed for only three patients, in whom an existing dual-chamber system was activated. Implantation of a resynchronization system was successfully conducted for 19 patients, which corresponds to an intraoperative success rate of 90%. Table 3 provides an overview of the successfully implanted resynchronization systems and the associated leads.
Both unsuccessful implantations were aborted, because the coronary sinus lead could not be fixated in any position with an adequate left ventricular pacing

threshold (< 3.5 V). On average, the implantation of the entire resynchronization system took 124 ± 39 min (80 – 255 min) with a fluoroscopy time of 24 ± 8 min (13 – 32 min).
The coronary sinus lead was successfully implanted in a lateral coronary vein in 10 patients, in a posterolateral coronary vein in two patients, in an anterolateral coronary vein in four patients, and in the great cardiac vein in one patient. In two cases, the final position of the left ventricular lead was not documented. Table 4 shows the intraoperatively measured lead parameters.

*Follow-up Period*
During the check-up of the implanted leads over the course of the follow-up period before discharge, slightly increased pacing thresholds were documented as compared to the intraoperative measurement (Table 5). The atrial threshold became normalized already at the 6-week postoperative follow-up, and the biventricular threshold at the 6-month postoperative follow-up. The NYHA class decreased from 3.1 ± 0.4 (2.5 – 4.0, preoperative) to 2.2 ± 0.4 (1.5 – 3.0, 6 weeks postoperatively) and 2.0 ± 0.3 (1.5 – 3.0, 6 months postoperatively). Due to biventricular resynchronization therapy, the QRS width was significantly ($p < 0.05$) reduced at all follow-up examinations (Figure 1).

|  |  | Right atrial | Right ventricular | Left ventricular | Biventricular |
|---|---|---|---|---|---|
| Threshold (V) | Mean | 1.1 | 0.8 | 1.0 | 1.5 |
|  | ± SD | 0.3 | 0.5 | 0.5 | 0.8 |
|  | Range | 0.6 – 1.7 | 0.3 – 2.2 | 0.4 – 2.0 | 0.4 – 2.9 |
| Sensing (mV) | Mean | 2.4 | 14.8 | 16.1 | 17.8 |
|  | ± SD | 1.0 | 6.5 | 6.3 | 7.0 |
|  | Range | 0.8 – 5.0 | 3.3 – 24.5 | 6.5 – 28.8 | 8.8 – 31.4 |
| Impedance (Ω) | Mean | 451 | 680 | 834 | 475 |
|  | ± SD | 61 | 190 | 164 | 191 |
|  | Range | 360 – 571 | 457 – 1048 | 560 – 1156 | 268 – 990 |

*Table 4. Lead parameters from intraoperative measurements. SD = standard deviation.*

|  |  | Pre-discharge | | 6-weeks postoperative | | 6-months postoperative | |
|---|---|---|---|---|---|---|---|
| Patients |  | 13 | | 16 | | 14 | |
|  |  | RA | BiV | RA | BiV | RA | BiV |
| Threshold (V) | Mean | 1.4 | 1.8 | 1.1 | 1.7 | 1.0 | 1.2 |
|  | ± SD | 1.1 | 0.8 | 0.4 | 0.8 | 0.3 | 0.5 |
|  | Range | 0.3 – 3.9 | 0.6 – 3.4 | 0.7 – 2.2 | 0.5 – 3.2 | 0.7 – 1.5 | 0.6 – 2.6 |
| Sensing (mV) | Mean | 1.8 | 9.3 | 2.1 | 10.0 | 2.1 | 12.6 |
|  | ± SD | 1.0 | 6.2 | 0.9 | 4.3 | 0.9 | 4.0 |
|  | Range | 0.5 – 4.3 | 2.6 – 25.3 | 0.7 – 3.9 | 2.8 – 17.0 | 0.8 – 3.8 | 4.8 – 18.6 |
| Impedance (Ω) | Mean | 346 | 348 | 354 | 367 | 357 | 404 |
|  | ± SD | 115 | 96 | 79 | 77 | 81 | 73 |
|  | Range | 229 – 600 | 239 – 530 | 220 – 490 | 250 – 550 | 239 – 480 | 287 – 520 |

*Table 5. Lead parameters from follow-up measurements. RA = right atrial, BIV = biventricular, SD = standard deviation.*

In the 6-month follow-up period, three cases of phrenic stimulation were observed, two of which could be terminated by reprogramming the resynchronization system. In the third case, the left ventricular lead (Corox LV-H) had to be repositioned.

Increases in the biventricular threshold were observed in the three patients; however, in each case dislocation of the left ventricular lead could be eliminated using an X-ray of the thorax. The resynchronization systems were correspondingly reprogrammed. In one case, a dislocation of the left ventricular lead (Corox LV-P) occurred; this lead was replaced by a Corox LV-H lead. One patient died three months after the implantation of a Tupos LV due to therapy-refractory ventricular tachycardias.

## Discussion

The BEATLE observation study showed that a safe and effective resynchronization therapy can be conducted with the systems employed. Further developments of implantation techniques for the left ventricular lead should aim to further decrease the implantation duration in order to minimize patient stress through operation. Both of the unsuccessful implantation attempts might be avoided in the future by expanding the lead portfolio to include leads with improved implantation properties, thus enabling more frequent implantation at sites with optimal pacing characteristics.

The implanted leads showed very good intraoperative electrical parameters, and the values measured during the follow-up period were also comparable to other published results [14]. The increased biventricular
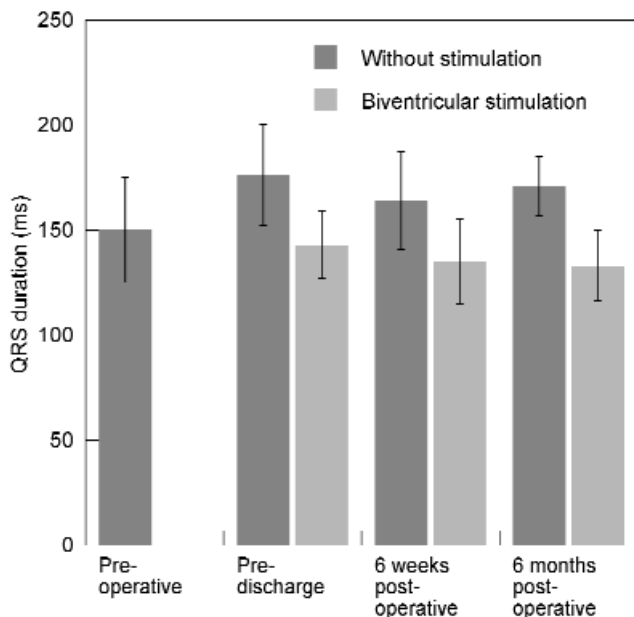
*Figure 1. Analysis of surface ECG during follow-up: QRS duration without stimulation and with biventricular stimulation. Shown are mean value ± standard deviation.*

thresholds observed during the 6-week follow-up show that when a lead is implanted in the coronary vein, there is a different healing response, as compared to leads that are anchored, for example, in the right atrium. The latter was proven during the discharge examination with a short-term increase in values; the values had normalized by the time of the next follow-up. The healing process of coronary sinus leads is slightly longer; however, after 6 months, the intraoperative level was reached again.

Over the course of 6 months, only one Corox LV-P lead was repositioned due to dislocation. No dislocations were observed with the Corox LV-H lead over the course of 6 months, and only one revision took place due to phrenic nerve stimulation. When these results are compared to published data regarding other leads, the Corox LV-H exhibits very stable fixation properties.

Due to the design of the project as an observation study, no examinations could be conducted that did not comply with the clinical standard. For this reason, it was not possible to gather information about the improvement of the patients' physical capacities, for example, as measured by a standardized exercise test.

However, the reduction of the NYHA class over the course of 6 months does provide evidence of the patients' decreased clinical symptoms. The reduction of the QRS width through biventricular pacing points to a normalization of the ventricular contraction sequence. More precise information would have been possible here if there had been a determination of the mechanical inter- and intraventricular delay.

## Conclusion

BEATLE showed that an equally safe and effective resynchronization therapy can be provided with Biotronik systems as with similar products on the market. The inclusion of an over-the-wire lead (Corox OTW) in the Corox lead family anticipates a possibly higher intraoperative success rate in the future.

## References

[1]   Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: Trends in incidence and survival in a 10-year period. Arch Intern Med. 1999; 159: 29-34.

[2]   Krumholz HM, Chen YT, Wang Y, et al. Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J. 2000; 139: 72-77.

[3]   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.

[4]   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. Circulation. 1999; 99: 2993-3001.

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

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

[7]   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.

[8]   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.

[9]   Le Franc P, Klug D, Lacroix D, et al. Triple chamber pacemaker for end-stage heart failure in a patient with a previously implanted automatic defibrillator. PACE. 1998; 21: 1672-1675.

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

[11] 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.

[12] Auricchio A, Stellbrink C, Sack S, et al. Chronic effect of hemodynamically optimized cardiac resynchronization therapy on patients with heart failure and ventricular conduction delay. J Am Coll Cardiol. 2002; 39: 2026-2033.

[13] Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002; 346: 1845-1853.

[14] Ricci R, Ansalone, Toscano S, et al. Cardiac resynchronization: materials, technique and results. The InSync Italian Registry. Eur Heart J. 2000; 2 (Suppl J): J6-J15.

**Contact**
Dr. Klaus Malinowski
Helios Klinikum Aue
Klinik für Innere Medizin I
Gartenstrasse 6
D-08280 Aue
Germany
Phone:  +49 (0) 3771 583 667
Fax:      +49 (0) 3771 581 343
E-mail: kmalinowski@aue.helios-kliniken.de