

# Efficacy of cardiac resynchronisation therapy in the treatment of end-stage inotrope-dependent heart failure patients

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## Abstract

**Background and aim:** Currently, cardiac resynchronisation therapy (CRT) is recommended only for New York Heart Association (NYHA) class IV ambulatory patients. However, some recent reports have suggested that CRT could also be beneficial for end-stage inotrope-dependent heart failure (HF) NYHA class IV patients. In this report, we summarise the results of CRT implantation in a group of 11 HF inotrope-dependent patients who were not candidates for urgent orthotopic heart transplantation (OHT).

**Methods and results:** Between August 2006 and June 2011, 11 end-stage inotrope-dependent HF patients with wide QRS complex, ineligible for urgent OHT, were implanted with CRT in the Silesian Centre for Heart Diseases in Zabrze. Dependence on inotropic therapy was defined as an inability to stop the infusion of the drug without the occurrence of hypotension, oligo- or anuria and/or hypoxaemia. All patients were successfully implanted with CRT and subsequently weaned from inotropes in a median time of two (1–17) days. Mean QRS duration shortened from  $190 \pm 34$  ms at baseline to  $142 \pm 25$  ms ( $p < 0.001$ ) after the procedure. Average left ventricular ejection fraction increased from  $19 \pm 4\%$  to  $25 \pm 4\%$  ( $p < 0.001$ ). All patients were discharged from hospital. Median hospital stay after the procedure was ten (5–56) days. During the median follow-up of 1,212 (182–2,048) days, four patients died (one due to arrhythmic storm, three others due to progressive pump failure). During that period, 57 adequate device interventions occurred in three patients, including 52 therapies in one fatal case.

**Conclusions:** CRT can be an alternative for end-stage inotrope-dependent HF patients with wide QRS who are ineligible for urgent heart transplantation.

**Key words:** cardiac resynchronisation therapy, heart failure, inotrope dependence

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## INTRODUCTION

According to the current European Society of Cardiology (ESC) guidelines, ambulatory New York Heart Association (NYHA) class IV patients can become candidates for cardiac resynchronisation therapy (CRT) only if they have been in a stable clinical condition for at least three months before implantation [1, 2]. End-stage inotrope-dependent heart failure (HF) patients have an extremely poor prognosis, with a one year survival rate of 6% to 30% [3, 4]. Ventricular assist devices or urgent heart transplantation are the only alternative and generally accepted therapeutic options in this group

of patients [1, 2]. However, cardiac transplantation is available only for the minority of patients due to the lack of heart donors as well as the common presence of many orthotopic heart transplantation (OHT) contraindications. To date, the clinical value of CRT in patients requiring continuous inotropic support remains uncertain [5–7]. Recently, two retrospective reports have shown a substantial benefit of CRT in end-stage inotrope-dependent HF patients [8, 9].

In this report, we present our CRT experience in 11 consecutive NYHA class IV, end-stage inotrope-dependent HF patients who were not eligible for OHT.

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## METHODS

### Study population

From August 2006 to June 2011, we identified 11 consecutive NYHA class IV, end-stage inotrope-dependent HF patients. Five of them had a history of cardiac surgery. To minimise a selection bias, we reviewed all 494 CRT recipients who were implanted between the beginning of 2006 and the end of 2011. Out of these subjects, we finally found 11 patients (nine men and two women) who required inotropic support during implantation procedure. In eight patients, the aetiology of underlying cardiomyopathy was ischaemic. All five patients with a history of cardiac surgery underwent coronary artery bypass surgery. Four of them had simultaneous mitral valve surgery (three mitral valve restrictive valvuloplasty, one mitral valve replacement), and three surgical ventricular remodelling of left ventricle. All patients before CRT implantation were evaluated for urgent heart transplantation and ultimately disqualified due to either irreversible pulmonary hypertension (seven patients) or age over 65 years with concomitant comorbidities (four patients). Baseline characteristics of study patients are summarised in Table 1. Dependence on intravenous inotropic therapy was defined as the inability to stop or decrease the dose of drugs without the occurrence of hypotension (systolic blood pressure < 90 mm Hg), oligo- or anuria (< 20 mL/h) and/or hypoxaemia. Eight out of 11 patients were infused with dobutamine with a median dose of 8.5 µg/kg/min i.v. (4–12 µg/kg/min), five of them additionally with dopamine (median 3, range 2–5 µg/kg/min), and one of them also with norepinephrine (1.3 µg/min i.v.). Three out of 11 patients were infused with dopamine alone with

a median dose of 5 µg/kg/min (3–8 µg/kg/min) i.v. Two out of 11 analysed patients required additionally an intra-aortic balloon pump (IABP) support at the time of CRT implantation. The characteristics of inotropic support are summarised in Table 2. All patients were informed as to the severity of their clinical status and, after obtaining a written, informed consent, implanted with a CRT-D device.

### Implantation of CRT-D device

Before the procedure, all patients received a light sedation and oxygen that was continued during the implantation. Arterial blood pressure and basic vital parameters were continuously monitored by the accompanying anaesthesiologist. Intravenous inotropic agents and IABP were continued during the whole procedure and 12 h after at the same doses.

All leads were routinely implanted transvenously, the atrial and right ventricular leads were positioned in the high right atrium and the apex of right ventricle, respectively. In eight cases of biventricular pacing one left ventricular lead was placed into the lateral or postero-lateral cardiac vein on the basis of obtained coronary sinus venogram. In three cases of triple site biventricular pacing, two left ventricular leads were placed into the lateral or postero-lateral and anterior or antero-lateral vein and connected with Y connector as described before [10].

### Follow-up

QRS duration, echocardiographic parameters (left ventricular ejection fraction [LVEF], end diastolic volume [EDV], end systolic volume [ESV]) and clinical assessment were obtained

Table 1. Baseline characteristics of study population

Patient number	Age [years]	Male gender	Ischaemic aetiology	Diabetes	History of CS	LBBB	QRS [ms]	LVEF [%]
1	61		√		√	√	200	22
2	69	√	√				210	17
3	34	√					220	18
4	68	√	√		√		160	12
5	54	√	√			√	220	16
6	73	√	√	√			160	19
7	77	√		√		√	210	20
8	62	√	√	√	√	√	170	18
9	67	√		√		√	190	18
10	71		√		√	√	160	30
11	65	√	√	√	√		185	18
Mean ± SD	63.7 ± 12.6						190 ± 34	19 ± 4
n		9	8	5	5	6		
Per cent		82%	72%	45%	45%	55%		

CS — cardiac surgery; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction

Table 2. Characteristics of inotropic support of analysed patients

Patient number	Dopamine [ $\mu\text{g}/\text{kg}/\text{min}$ ]	Dobutamine [ $\mu\text{g}/\text{kg}/\text{min}$ ]	Norepinephrine [ $\mu\text{g}/\text{min}$ ]	Intra-aortic balloon pump
1	3	8	0	√
2	0	9	4	
3	3	0	0	
4	2	4	1.3	√
5	2	10	0	
6	5	5	0	
7	8	0	0	
8	5	0	0	
9	5	5	0	
10	0	12	0	
11	0	10	0	

in a 48 h period before implantation, directly before hospital discharge and at the routine follow-up outpatient visits scheduled every three months. Additionally, all information about ventricular and supraventricular arrhythmic events were obtained from the device memory during the follow-up visits. Three patients with new devices were provided with remote monitoring supervision.

### Statistical analysis

All continuous data was expressed as mean and standard deviation. Data was analysed using a Statistica 8 statistics package (StatSoft Poland). One way ANOVA and Newman-Keuls post hoc tests were applied for the analysis of continuous variables. P value < 0.05 was considered significant.

### RESULTS

All patients were successfully implanted with a CRT-D device without any haemodynamic deterioration during the procedure. No serious postprocedural complications were observed except for two small pocket haematomas in patients who required IABP support during the procedure and were therefore on continuous heparin infusion. These haematomas resolved spontaneously. Rapid haemodynamic amelioration allowed the withdrawal of inotrope and IABP support gradually within the median time of two (1–17) days. This improvement was accompanied by an increase of average LVEF from  $19 \pm 4\%$  at baseline to  $25 \pm 4\%$  ( $p < 0.001$ ) before hospital discharge without further improvement during the follow-up (Fig. 1A). However, although a visible trend towards decreased left ventricle volumes was observed, neither EDV nor ESV lowered statistically significantly immediately after CRT implantation or during the follow-up period (Figs. 1B, C). Mean QRS shortened from  $190 \pm 34$  ms at baseline to  $142 \pm 25$  ms after implantation ( $p < 0.001$ ) without further improvement during the three months of follow-up (Fig. 1D). All patients

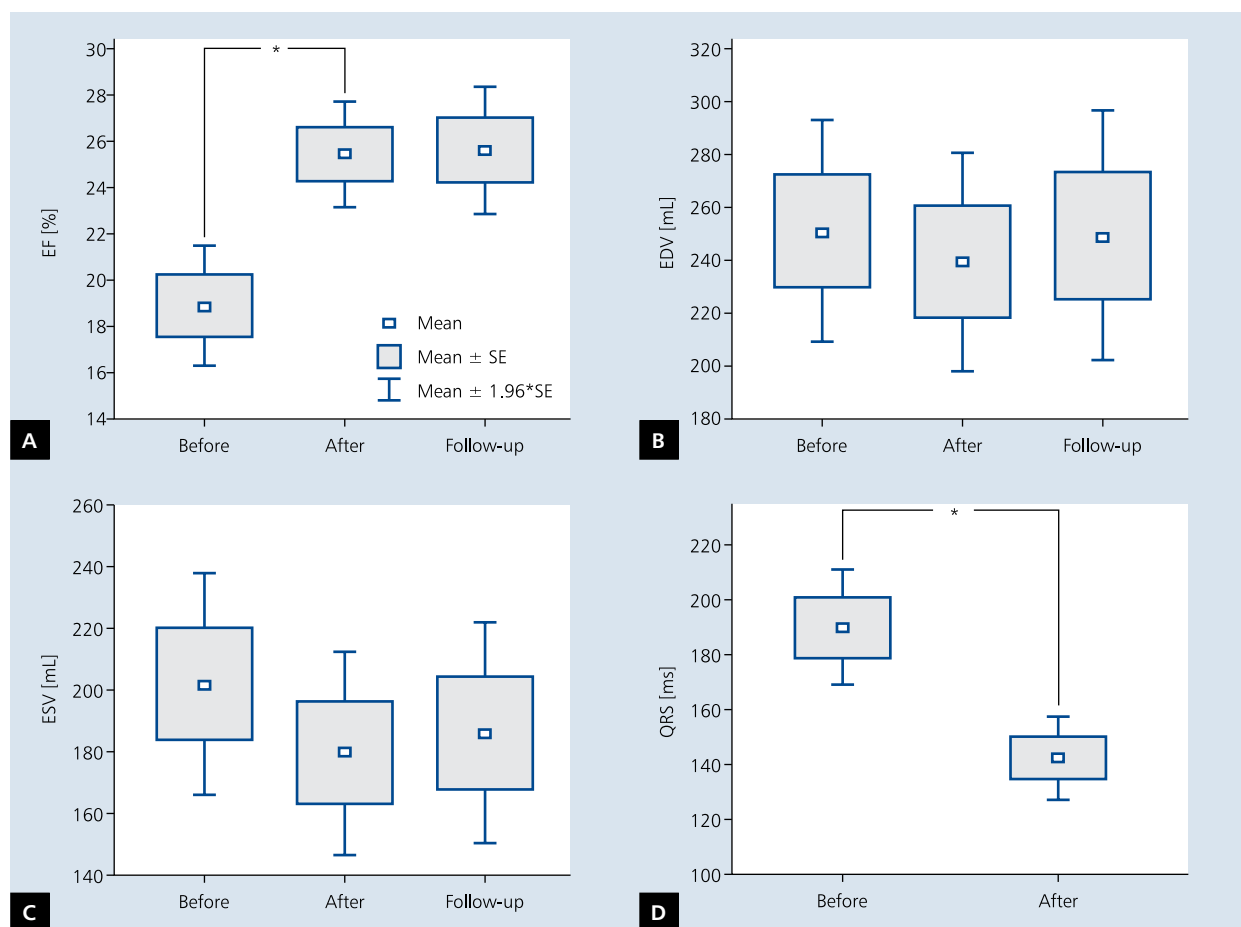
were discharged from hospital. Median hospital stay after the procedure was ten (5–56) days. During the mean follow-up of 1,212 (182–2,048) days, four patients died. One patient died due to arrhythmic storm and three due to progressive pump failure (Fig. 2). One patient was hospitalised within this period due to recurrent, drug resistant ventricular tachycardia/ventricular fibrillation (VT/VF) and died 182 days after the procedure during the second episode of arrhythmic storm. As a result of CRT implantation, the median NYHA class decreased from initial class IV to III at the time of hospital discharge and no further improvement in NYHA has been observed during the follow-up period.

Analysis of device memory revealed 57 adequate implantable cardioverter defibrillator interventions (55 antitachycardia pacing and two shocks) due to VT/VF in three patients, including 52 therapies in one fatal case and numerous recurrent, asymptomatic paroxysmal atrial fibrillation episodes in three patients. The median CRT pacing was 99% (96–99%).

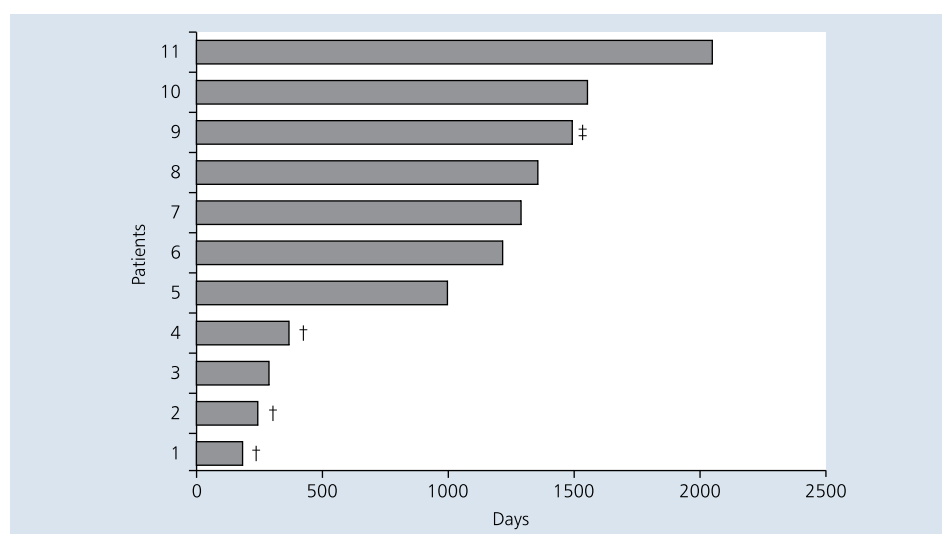
### DISCUSSION

In the present paper, we have shown the effectiveness of cardiac resynchronisation in a group of 11 end-stage inotrope-dependent HF patients. The implantation of CRT devices made it possible to wean all patients from the support of inotropes and stabilise their clinical status at a level sufficient for hospital discharge. Current ESC guidelines do not recommend the implantation of CRT in unstable NYHA class IV patients [1, 2]. This is a result of a lack of evidence of such a therapy in this group of patients, mainly because these patients commonly did not meet the inclusion criteria of the large clinical trials evaluating the effectiveness of CRT.

To the best of our knowledge, the success rate and effectiveness of CRT in such a population of patients have been evaluated retrospectively only by a few authors. Interestingly, two recent works suggested that CRT can be safe and effec-



**Figure 1.** Changes of echocardiographic parameters and QRS duration before and after cardiac resynchronisation therapy (CRT) implantation, and after three months of follow-up. Significant differences are marked by an asterisk ( $p < 0.05$ ); **A.** Ejection fraction (EF) rose significantly immediately after CRT implantation, but no further improvement was observed. This is consistent with a lack of positive remodelling during the follow-up. Neither end diastolic volume (EDV) nor end systolic volume (ESV) changed (**B, C**); **D.** QRS width shortened significantly after CRT implantation; SE — standard error



**Figure 2.** Follow-up time for particular patients. All patients who died due to 'pump failure' died relatively shortly after cardiac resynchronisation therapy implantation; † patient died due to pump failure; ‡ patient died due to arrhythmic storm

tive in end-stage inotrope-dependent HF patients [6, 7]. Our results support this observation and extend it over a longer perspective. Acute haemodynamic effect caused by biventricular pacing has been already presented in several reports [11–13]. However, an increase of cardiac output as a result of an improvement of atrio- and inter-ventricular asynchrony and prolongation of the left ventricle filling time is likely to be limited by the availability of viable, contracting heart muscle. Improvement of contractility during echocardiographic dobutamine test has been postulated to be a predictor of efficacy of CRT [14–16]. Relative haemodynamic stabilisation of end-stage HF patients dependent on continuous catecholamine infusion can be an equivalent of positive response to dobutamine. Because long-time catecholamine infusion may lead to tolerance due to desensitisation of the beta-adrenergic pathway [17, 18], it seems that implantation of CRT should be considered relatively early in the course of sustained inotropic therapy. The long delay between beginning inotropic infusion and device implantation could explain the discouraging results of previous attempts of CRT for terminally advanced HF patients [3, 19]. In the analysis by Cowburn et al. [6], all ten patients who required inotropic support and underwent CRT implantation in  $11 \pm 6$  days after beginning of inotrope infusion were weaned from inotropic support and survived to hospital discharge. Additionally, Herweg et al. [8] showed that also patients who were on longstanding, outclinic inotropic therapy benefited from CRT and were successfully weaned from inotropic support with 100% survival during the follow-up period ( $1,088 \pm 284$  days). In our analysis, the median time between the beginning of catecholamine infusion and CRT implantation was 25 (11–36) days, and thus the drug tolerance induction seems to be unlikely.

Current ESC guidelines recommend the use of left ventricular assist devices (LVAD) for end stage HF patients despite poor long-term survival. However, the results of the REMATCH study showed that two year survival of patients with pulsatile flow LVAD was only 23% [20]. For continuous flow left ventricle assist devices, the two year survival rate reached 58% [21]. Thus, the survival of end-stage inotrope-dependent HF patients with CRT seems to be similar to that after LVAD implantation. It should be noted that the lack of improvement after CRT in these patients does not exclude the implantation of LVAD in the future.

### Limitations of the study

The significance of our results is limited by the small number of patients and the lack of randomisation. However, for this terminally ill population of patients, the organisation of a randomised trial would be difficult to justify on ethical grounds.

## CONCLUSIONS

We suggest that CRT may be used for the treatment of patients with end-stage inotrope-dependent HF.

**Conflict of interest:** AS, RL, OK — consultant fee from Medtronic and Biotronik.

## References

- Dickstein K, Cohen-Solal A, Filippatos G et al.; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail*, 2008; 10: 933–989.
- Dickstein K, Vardas PE, Auricchio A et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. *Eur Heart J*, 2010; 31: 2677–2687.
- Gorodeski EZ, Chu EC, Reese JR et al. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. *Circ Heart Fail*, 2009; 2: 320–324.
- Hershberger RE, Nauman D, Walker TL et al. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. *J Card Fail*, 2003; 9: 180–187.
- Konstantino Y, Iakobishvili Z, Arad O et al. Urgent cardiac resynchronization therapy in patients with ecompensated chronic heart failure receiving inotropic therapy. A case series. *Cardiology*, 2006; 106: 59–62.
- Cowburn PJ, Patel H, Jolliffe RE et al. Cardiac resynchronization therapy: an option for inotrope-supported patients with end-stage heart failure? *Eur J Heart Fail*, 2005; 7: 215–217.
- James KB, Militello M, Barbara G, Wilkoff BL. Biventricular pacing for heart failure patients on inotropic support: a review of 38 consecutive cases. *Tex Heart Inst J*, 2006; 33: 19–22.
- Herweg B, Ilercil A, Cutro R et al. Cardiac resynchronization therapy in patients with end-stage inotrope-dependent class IV heart failure. *Am J Cardiol*, 2007; 100: 90–93.
- Milliez P, Thomas O, Haggui A et al. Cardiac resynchronisation as a rescue therapy in patients with catecholamine-dependent overt heart failure: results from a short and mid-term study. *Eur J Heart Fail*, 2008; 10: 291–297.
- Lenarczyk R, Kowalski O, Kukulski T et al. Triple-site biventricular pacing in patients undergoing cardiac resynchronization therapy: a feasibility study. *Europace*, 2007; 9: 762–767.
- Brecker SJ, Xiao HB, Sparrow J, Gibson DG. Effects of dual-chamber pacing with short atrioventricular delay in dilated cardiomyopathy. *Lancet*, 1992; 340: 1308–1312.
- Nishimura RA, Hayes DL, Ilstrup DM et al. Effect of dual-chamber pacing on systolic and diastolic function in patients with hypertrophic cardiomyopathy. Acute Doppler echocardiographic and catheterization hemodynamic study. *J Am Coll Cardiol*, 1996; 27: 421–430.
- 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: 1825–1823.
- Muto C, Gasparini M, Neja CP et al. Presence of left ventricular contractile reserve predicts midterm response to cardiac resynchronization therapy: results from the LOw dose DObutamine study.

- tamine stress-echo test in Cardiac Resynchronization Therapy (LODO-CRT) trial. *Heart Rhythm*, 2010; 7: 1600–1605.
15. Ciampi Q, Pratali L, Citro R et al. Identification of responders to cardiac resynchronization therapy by contractile reserve during stress echocardiography. *Eur J Heart Fail*, 2009; 11: 489–496.
  16. Ypenburg C, Sieders A, Bleeker GB et al. Myocardial contractile reserve predicts improvement in left ventricular function after cardiac resynchronization therapy. *Am Heart J*, 2007; 154: 1160–1165.
  17. Bristow MR, Hershberger RE, Port JD et al. Beta-adrenergic pathways in nonfailing and failing human ventricular myocardium. *Circulation*, 1990; 82 (2 Suppl.): I12–I25.
  18. Colucci WS, Leatherman GF, Ludmer PL, Gauthier DF. Beta-adrenergic inotropic responsiveness of patients with heart failure: studies with intracoronary dobutamine infusion. *Circ Res*, 1987; 61 (4 Part 2): I82–I86.
  19. Auricchio A, Abraham WT. Cardiac resynchronization therapy: current state of the art: cost versus benefit. *Circulation*, 2004; 109: 300–307.
  20. Rose EA, Gelijns AC, Moskowitz AJ et al. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*, 2001; 345: 1435–1443.
  21. Slaughter MS, Rogers JG, Milano CA et al. HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med*, 2009; 361: 2241–2251.

## Skuteczność terapii resynchronizującej w leczeniu pacjentów ze schyłkową niewydolnością serca zależnych od leków inotropowych

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### Streszczenie

**Wstęp i cel:** Aktualnie terapia resynchronizująca jest zalecana jedynie „ambulatoryjnym” pacjentom z niewydolnością serca (HF) w IV klasie wg NYHA. Ostatnie doniesienia sugerują jednak, że może być ona również korzystna dla pacjentów w końcowej fazie HF zależnych od leków inotropowych. W niniejszym doniesieniu przedstawiono wyniki implantacji układów resynchronizujących w grupie 11 pacjentów z końcową HF zależnych od leków inotropowych.

**Metody i wyniki:** Do analizy włączono 11 pacjentów z szerokimi zespołami QRS, zależnych od leków inotropowych, niekwalifikujących się do natychmiastowego przeszczepienia serca, u których między sierpniem 2006 a czerwcem 2011 r. implantowano układ resynchronizujący w Śląskim Centrum Chorób Serca w Zabrzu. Zależność od terapii resynchronizującej została zdefiniowana jako niemożność zaprzestania infuzji leków inotropowych bez wystąpienia hipotonii, oligo- lub anurii albo hipopksemii. Implantacja układów resynchronizujących powiodła się u wszystkich pacjentów. Również u wszystkich osób możliwe było odstawienie wlewno leków inotropowych z medianą 2 (1–17) dni. Średni czas QRS skrócił się z wyjściowych  $190 \pm 34$  ms do  $142 \pm 25$  ms ( $p < 0,001$ ). Średnia wartość frakcji wyrzutowej lewej komory wzrosła z  $19 \pm 4\%$  do  $25 \pm 4\%$  ( $p < 0,001$ ). Wszyscy pacjenci zostali wypisani ze szpitala. Mediana pobytu po implantacji układu resynchronizującego wynosiła 10 (5–56) dni. W trakcie obserwacji, której mediana wynosiła 1212 (182–2048) dni 4 pacjentów zmarło (1 z powodu burzy arytmicznej, 3 z powodu niewydolności serca jako pompy). W tym czasie miało miejsce 57 adekwatnych interwencji wszczepionych urządzeń obejmujących 52 interwencje w przypadku burzy elektrycznej zakończonej zgonem.

**Wnioski:** Terapia resynchronizująca może być alternatywą dla pacjentów z szerokimi zespołami QRS w końcowym stadium HF, zależnych od wlewno leków inotropowych.

**Słowa kluczowe:** schyłkowa niewydolność serca, zależność od leków inotropowych, terapia resynchronizująca

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