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Triple-site biventricular pacing in patients undergoing cardiac resynchronization therapy: a feasibility study

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Aims To evaluate implantation safety and efficiency of triple-site (double left–single right) cardiac resynchronization therapy (CRT) and to assess the outcome of this procedure.
Methods and results Twenty-six patients with New York Heart Association (NYHA) class III–IV, left ventricular ejection fraction (EF) $\leq$ 35%, and QRS $\geq$ 120 ms underwent triple-site CRT. Procedural course and complications were analysed. NYHA class, QRS duration, echocardiographic parameters, peak oxygen consumption (VO_2max), and 6 min walking distance (6MWD) were assessed at baseline and after 3 months. Responders were defined by survival, by no re-hospitalization for heart failure, and by >10% EF, VO_2max, and 6MWD increase. Implantation was successful in 22 patients (84.6%). Procedure duration (199.1 min) and fluoroscopy time (38.7 min) were higher than in standard procedures. Two clinically silent coronary sinus dissections occurred intra-operatively; one phrenic nerve stimulation and one pocket infection were observed during follow-up. After 3 months of CRT, a significant reduction ($P < 0.05$) of NYHA class, increment of VO_2max, 6MWD, EF, and improvement of indices of dyssynchrony were observed. Response rate in the studied group was 95.4%.
Conclusion Triple-site resynchronization appears to be a safe and efficient treatment method, with high response rate. Further studies are needed to evaluate the role of this pacing mode in CRT.

Introduction

Cardiac resynchronization therapy (CRT) has become a major breakthrough in the treatment of patients with symptomatic heart failure (HF), lowered ejection fraction (EF) of the left ventricle (LV), and disturbed intraventricular electrical conduction. However, in 20–40% of patients who fulfil the current criteria for CRT, no symptomatic improvement can be seen after the implementation of this method. Thus, any technique which could increase the response rate of this therapy would be of value for CRT candidates.

The first objective of our study was to evaluate both safety and procedural course of implantation procedures and the left ventricular leads' performance in patients undergoing triple-site resynchronization. The second objective was to investigate the effect of triple-site CRT on mid-term outcome of this procedure.

Methods

Patient selection

Inclusion criteria for CRT were symptomatic heart failure in New York Heart Association (NYHA) functional class III or IV, lowered left ventricular EF ($\leq$35%), sinus rhythm, and left bundle branch block (LBBB) with QRS width $\geq$ 120 ms. Between January and October 2006, 26 consecutive patients qualified to CRT underwent an implantation procedure with the intention to implant triple-site resynchronization device. Informed written consent was obtained from all patients participating in the study.

Implantation procedure and pacemaker settings

The implantation of the atrial and right ventricular lead (or defibrillation electrode in the patients receiving biventricular cardioverter–defibrillator) was performed in a conventional way into the high right atrium and the apex of the right ventricle, respectively, using a cut-down technique of a cephalic vein. The implantation of the LV lead was preceded by an angiography of the coronary sinus (CS) in every patient; the target veins were anterolateral, lateral branch, posterolateral branch of the CS, or median cardiac vein. After left-heart delivery system used to introduce

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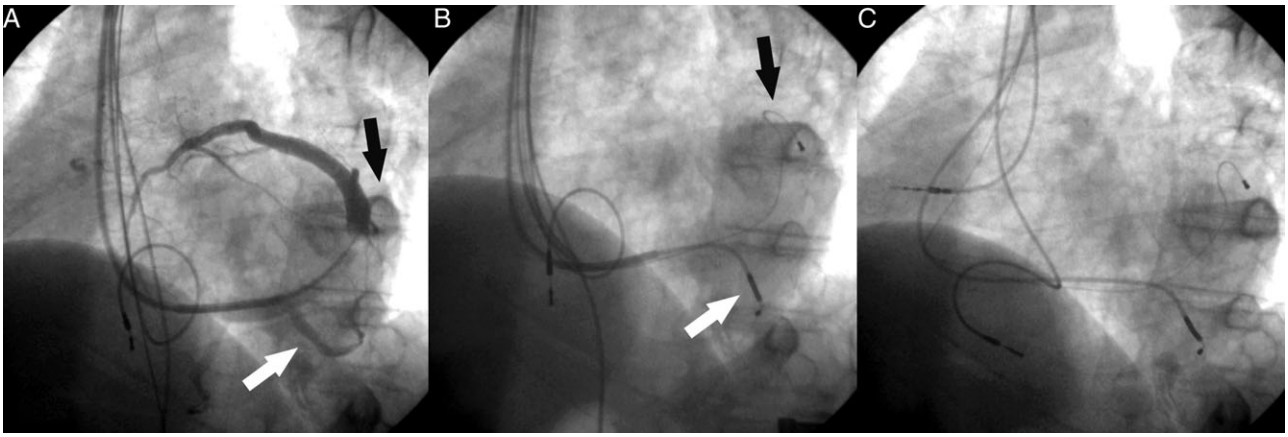

Figure 1 Intra-operative radiographs in the left-lateral oblique projection. (*A*) Angiography of the coronary sinus, showing anterolateral (black arrow) and posterolateral (white arrow) veins. (*B*) Implantation of the second left ventricular lead into the posterolateral cardiac vein. After withdrawal of the left-heart delivery system used to introduce the first left ventricular lead (black arrow), the second delivery system was introduced to the coronary sinus ostium; then the second lead was introduced (white arrow). (*C*) Final positions of the four leads.

the first left ventricular lead was withdrawn from the CS ostium, the second left-heart delivery system was introduced by the puncture of the subclavian vein, and the cannulation of the CS ostium was performed. The second left ventricular lead was introduced in the appropriate branch of CS with the intention to obtain as wide separation between the electrodes as possible (*Figure 1*). Decision on the type of lead used (unipolar vs. bipolar) was based on the diameter of accessible veins assessed visually by the operator during venography. Bipolar electrodes were generally implanted into large CS branches; unipolar leads were chosen if only narrow vessels were present. However, in order to allow future reprogramming of the left ventricular pacing polarity, attempts were made to implant at least one bipolar electrode in every patient. Then two left ventricular electrodes were connected with the use of Y-adaptor (Lead Adaptor 2827, Medtronic, Minneapolis, MN, USA), which is designed to connect two bipolar leads (or one bipolar and one unipolar lead) to one bipolar lead. Lead performance tests and high-amplitude current stimulation were performed using joined leads and unipolar split cathodal configuration. During threshold tests, the effectiveness of ventricular capture from both joined electrodes was verified using 12-lead ECG on the basis of tracings obtained previously during pacing through each lead separately (*Figure 2*). The procedures were accomplished with the implantation of the pacemakers InSync III or biventricular implantable cardioverter–defibrillator InSync Protect (Medtronic). All pacemakers were set on DDD mode with the lower rate of 60/min; pacing polarity was set on LV unipolar (or on LV tip-RV coil in cases of biventricular ICD). On the first postoperative day, each patient underwent optimalization of pacemaker settings under echocardiographic guidance. Atrioventricular delay was optimized for consistent ventricular capture and the most favourable diastolic filling pattern, using Doppler echocardiographic measurements of the transmitral flow.[1] Interventricular delay was set on the basis of the time-to-onset systolic myocardial velocity measurements performed with colour-coded tissue Doppler imaging (TDI), the settings were tailored to reduce septal-to-lateral wall motion delay (SLWMD) and anterior-to-inferior wall motion delay (AIWMD).[2]

Analysed data

Baseline data, intra-operative parameters, and remote results were obtained from medical records. Procedural data included:

(i) implantation success rate;
(ii) procedure duration, defined as door-to-door time;
(iii) fluoroscopy time;
(iv) intra-operative complications;
(v) acute LV leads performance tests—impedance, sensing, and pacing threshold.

The following parameters were collected at baseline:

(i) NYHA class;
(ii) QRS width measured as the maximum in leads II, V1, and V6;
(iii) Six minute walking distance (6MWD);
(iv) peak oxygen consumption during the stress test (VO_2max);
(v) echocardiographic measurements: end-diastolic volume (EDV); end-systolic volume (ESV), and EF of the LV were assessed using Simpson's method;
Interventricular delay (IVD) was calculated as the absolute difference between left and right ventricular pre-ejection periods, considered as the time interval between the QRS onset and the beginning of aortic or pulmonary flow, respectively. Septal-to-lateral wall motion delay and AIWMD were calculated using colour-coded TDI. Time-to-onset systolic myocardial velocities were measured as QRS to onset of systolic myocardial velocity at basal segments of lateral, septal, anterior, and inferior walls of the LV. Septal-to-lateral wall motion delay was calculated as the difference between the longest and the shortest time-to-onset myocardial velocities of the septum and lateral wall; anterior-to-inferior wall motion delay as the difference between time-to-onset myocardial velocities of the anterior and inferior wall;
(vi) medication.

All data, along with vital status and hospitalizations for exacerbated HF, were recorded again after 3 months postoperatively. A positive response to CRT at 3 months was considered as: (i) survival, (ii) no interim hospitalization for exacerbated heart failure, (iii) a $\geq$10% relative increase in EF, $\geq$10% relative rise in VO_2max, and $\geq$10% relative increase in 6MWD. Patients who have died, underwent hospitalization for HF, or did not reach a demanded level of improvement in any of the earlier-mentioned three parameters 3 months after CRT were considered as non-responders.

Statistical analysis

The software package Statistica (version 6.0, StatSoft Inc., Tulsa, OK, USA) was used for statistical analysis. Continuous data were expressed as mean $\pm$ SD, unless otherwise specified. Categorical variables were presented as number and percentage. Data were

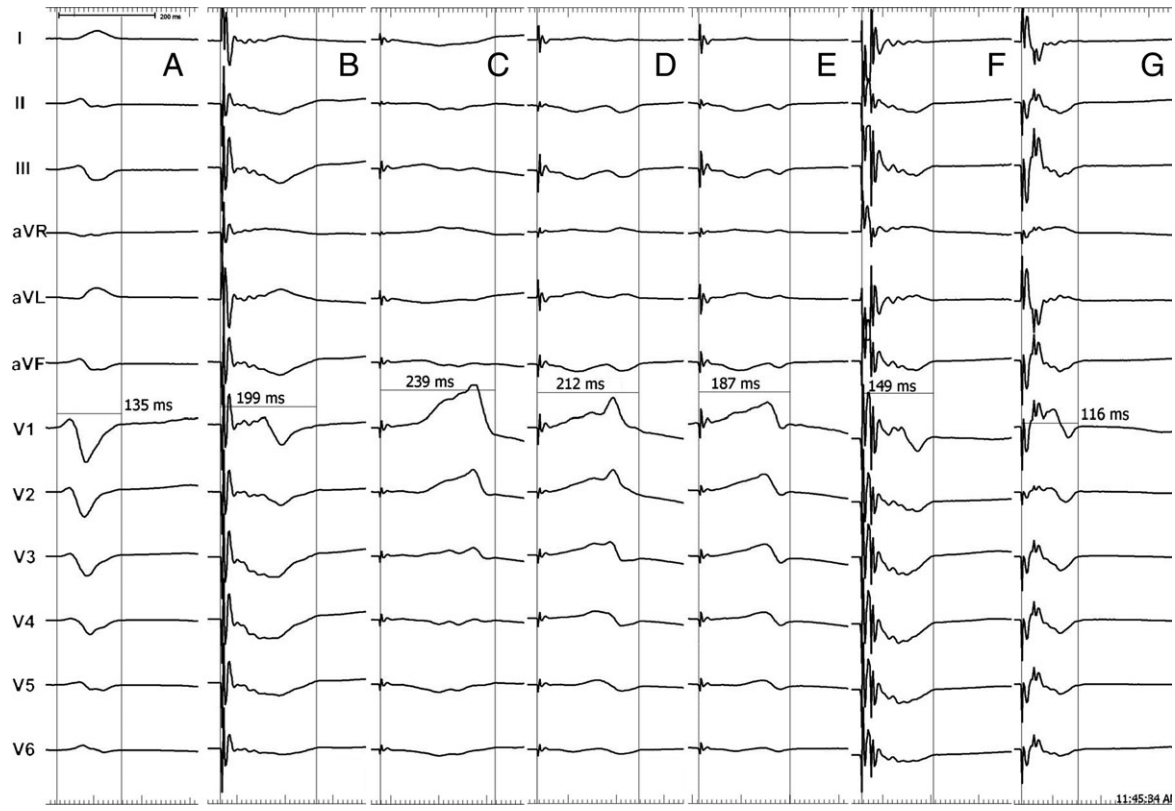

Figure 2 Twelve-lead electrocardiogram obtained intra-operatively in a patient implanted with triple-site resynchronization pacemaker. Of note is that in this patient, triple-site pacing was associated with shorter QRS than the standard biventricular pacing. (*A*) Sinus rhythm. (*B*) Right ventricular pacing. (*C*) Pacing through left ventricular lead in lateral vein. (*D*) Pacing from posterolateral vein. (*E*) Dual-site left ventricular pacing through Y-connected electrodes in lateral and posterolateral vein. (*F*) Conventional biventricular pacing from right ventricular electrode and the lead in lateral vein. (*G*) Triple-site (double left–single right) biventricular pacing.

compared using paired Student's *t*-test, and *P*-values <0.05 were considered statistically significant.

Results

Implantation course

The baseline characteristics of the analysed group is shown in *Table 1*. Triple-site pacemakers could be implanted successfully in 22 out of 26 patients (84.6%). The failure of the procedure in four patients was related to the absence of accessible CS branches (three subjects) and by phrenic nerve stimulation by the second LV lead (one patient); these patients received conventional resynchronization devices. Both the duration of procedure (199.1 $\pm$ 69.8 min) and the fluoroscopy time (38.7 $\pm$ 26.2 min) were longer than standard implantations of biventricular devices performed in our hospital (144 and 31 min, respectively).

Complications

The only intra-operative complications noted were CS dissections, which occurred in two patients (9.1%). The dissections remained clinically silent throughout the entire follow-up period. In one patient, signs of pocket infection have been observed 5 days after the implantation. In this case, the device and the electrodes were removed, specific antibiotic therapy was administered, and the triple-site pacemaker was implanted successfully using the contralateral side 2 weeks later. In one patient, phrenic nerve stimulation occurred during the follow-up period; reprogramming of the pacemakers abolished the symptoms.

Left ventricular lead performance

The impedance of Y-connected leads used in the study group was lower compared with standard left ventricular electrodes implanted into the CS tributaries during conventional resynchronization therapy. In six patients, the impedance of joined LV leads measured acutely was $<250\,\Omega$, and the current needed to capture the ventricle in this subgroup was significantly higher than in the subgroup with LV lead impedance $\geq 250\,\Omega$ (median 5.8 vs. 1.5 mA, respectively, $P < 0.001$). During the follow-up period, in two of these six patients, the impedance increased to the acceptable level (450 and 613 Ω), but in three patients it remained low, and in one, it fell below 200 Ω. In these four patients, the pacemakers were reprogrammed to bipolar split cathodal stimulation (split LV tip- common LV ring), and this resulted in increased LV leads impedance and led to the reduction of current needed to capture the ventricle. Procedural details and leads performance data are shown in *Table 2*.

Table 1 Baseline characteristics of study group

Age (years)	58.5 ± 9.0
Female gender (%)	9 (34.6)
Ischaemic HF aetiology (%)	11 (42.3)
Comorbidities (%)	
Diabetes	7 (26.9)
Arterial hypertension	9 (34.6)
COPD	1 (3.8)
CRF	1 (3.8)
Pre-discharge data[a]	
Medication (%)	
Beta-blocker	20 (90.9)
ACE-I/ARB	21 (95.4)
Spironolactone	20 (90.9)
Loop diuretic	19 (86.3)
Digoxin	13 (59.1)
ICD implanted (%)	5 (22.7)
LV electrode position (%)	
Anterolateral branch	8 (36.4)
Lateral branch	17 (77.3)
Posterolateral branch	11 (50)
MCV	7 (31.8)
Types of joined LV leads (%)	
Unipolar + bipolar	18 (81.8)
Unipolar + unipolar	3 (13.6)
Bipolar + bipolar	1 (4.5)
Pacemakers settings	
Sensed/paced AV delay (ms)	89.1 ± 23.3/ 80.9 ± 25.5
VV delay (ms)	21.6 ± 25.7
In 18 patients with LV electrodes on adjacent walls (ms)[b]	25.5 ± 26.9
In 4 patients with LV electrodes on opposite walls (ms)[c]	4.0 ± 0
LV paced first (%)	20 (90.9)

[a]Values calculated for 22 patients implanted successfully with triple-site resynchronization pacemaker.

[b]Values calculated for patients with electrodes in lateral and anterolateral branch, lateral and posterolateral branch, both electrodes in lateral branch or in posterolateral branch of CS and median cardiac vein.

[c]Values calculated for patients with electrodes in anterolateral and posterolateral branch of CS or median cardiac vein.

HF, heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; ACE-I, angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker; MCV, middle cardiac vein; AV, atrioventricular.

Clinical, electrocardiographic, and echocardiographic outcomes after triple-site cardiac resynchronization therapy

No deaths occurred during follow-up; one patient (4.5%) underwent hospitalization for HF exacerbation during the observation period. After 3 months of triple-site resynchronization, significant reduction ($P < 0.05$) of NYHA class (by 1.3 class), increment of VO_2max (2.8 mL/kg/min), 6MWD (101.5 m), decrease of left ventricular volumes, EF increase (8.9%), and improvement of indices of dyssynchrony were observed in the study group. Triple-site pacing did not result in a significant ($P > 0.05$) QRS shortening. The combined criterion of a positive response has been fulfilled in 21 subjects (95.4% of all successfully implanted patients). Data on remote outcome after triple-site CRT are depicted in *Table 3*.

Table 2 Implantation procedural course and left ventricular leads performance

Success rate (%)	22/26 (84.6)
Procedure duration (min)	199.1 ± 69.8
Fluoroscopy time (min)	38.7 ± 26.2
Complications (%)	4 (18.2)
Intra-operative complications	2 (9.1)
CS dissection	2 (9.1)
Remote complications	2 (4.5)
Pocket infection	1 (4.5)
Phrenic nerve stimulation	1 (4.5)
Complication leading to re-operation (%)	1 (4.5)
Acute LV lead performance	
Threshold (V/0.4 ms)	1.3 ± 0.6
R-wave amplitude (mV)	18.8 ± 7.5
Impedance (Ω)	608.5 ± 317.8
Patients with LV lead impedance < 250 Ω (%)	6 (27.3)
Remote LV lead performance	
Threshold (V/0.4 ms)	1.31 ± 0.5
Impedance (Ω)	595.1 ± 281.3
Patients with LV lead impedance < 250 Ω (%)	4 (18.2)

Table 3 Clinical, electrocardiographic, and echocardiographic outcomes at baseline and 3 months after triple-site cardiac resynchronization therapy

	Baseline	Three months after CRT	*P*-value
NYHA class	3.2 ± 0.4	1.9 ± 0.5	<0.05
QRS width (ms)	168.6 ± 18.3	155.8 ± 33.9	0.09
EDV (mL)	259.8 ± 74.1	220.1 ± 72.6	<0.05
ESV (mL)	194.6 ± 67.6	148.4 ± 61.5	<0.001
EF (%)	25.6 ± 5.9	34.5 ± 8.3	<0.001
IVD (ms)	64.5 ± 25	20.7 ± 18.7	<0.001
SLWMD (ms)	72.4 ± 40.8	19.1 ± 39.9	<0.001
AIWMD (ms)	61.6 ± 31.1	17.0 ± 20.6	<0.001
VO_2max (mL/kg/min)	12.9 ± 4.3	15.7 ± 5.2	<0.001
6MWD (m)	277.4 ± 94.5	378.9 ± 85.3	<0.001

Discussion

Since its first use in 1994,[3] CRT has been accepted as a treatment option in some patients with heart failure. In this group of patients, resynchronization can not only improve clinical status and quality of life, but also, as shown by CARE-HF trial, it is considered as a life-saving therapy.[4,5] However, up to 40% of patients who fulfil the current criteria for resynchronization do not benefit from this method of treatment.[5–10] We have, therefore, used triple-site biventricular pacing in an attempt to improve the outcome of resynchronization. Bifocal stimulation of the right ventricle as a safe and attractive alternative to biventricular pacing has been also proposed.[11–13] However, recently published study by Lane *et al.*[14] showed that this mode of stimulation was inferior to conventional resynchronization in terms of reduction of intra- and interventricular dyssynchrony. Multifocal pacing of the LV in patients undergoing CRT has been reported in few studies only. Pappone *et al.*[15] found that dual-site pacing was superior to single-site LV pacing in terms of acute haemodynamic performance of the

ventricle and electrical synchrony. To our knowledge, triple-site ventricular pacing in patients with heart failure has been reported by case reports studies only. Sassara *et al.*[16] demonstrated that dual-site left–single-site right ventricular stimulation was a feasible and effective method of treatment in patient with indications for CRT. Acosta *et al.*[17] reported on patient implanted with standard CRT device, in whom an upgrade to triple-site resynchronization pacemaker exerted anti-arrhythmic effect. Encouraged by these case studies, we have now analysed the series of consecutive patients and found that implantation of the triple-site device, although more time-consuming and technically difficult, is a safe procedure, which can be performed in the majority of CRT candidates. Interestingly, the only implantation failure encountered in our study was related to an unfavourable morphology of CS. This suggests that the assessment of venous anatomy with appropriate visualization techniques prior to this procedure can be particularly helpful. Implantation duration and fluoroscopy exposure, although higher than in the standard CRT procedures performed in our institution, still remained acceptable for the patient and the operator. Complication rates in our group were similar to the published data.[5–8] Our results indicate also that triple-site resynchronization may be beneficial in terms of improvement of subjective and objective heart failure indices during mid-term observation. In order to monitor the effectiveness of triple-site resynchronization, we used a composite, clinically echocardiographic criteria of positive response, as previously described.[9,18] This approach was used because echocardiographic parameters do not always correlate closely with the clinical outcome, and the functional status may be influenced by a placebo effect in up to 40% of patients.[6] The composite criterion of positive response has been reached by 21 out of 22 successfully implanted patients and this response rate was higher to those found in many studies investigating the effects of conventional CRT.[5–10] Similarly, analysing the effects of standard resynchronization in our centre, we found that among 27 patients implanted in 2005, only 17 (63%) fulfilled the criteria of positive response used in the current study after 3 months of conventional CRT. Therefore, our data suggest that triple-site pacing can be more effective than conventional biventricular resynchronization in selected groups of HF patients. Mechanisms responsible for the beneficial effect of this mode of pacing remain uncertain; however, they may be attributed to the wide anatomical separation of LV leads and more physiological excitation pattern. Spatial orientation of two LV electrodes can also theoretically solve the problem of conduction through the intramuscular line of block or slow conduction seen in the hearts of patients with LBBB.[19,20] These conduction disturbances, which change the activation front unfavourably during pacing, were suggested to be responsible for the lack of resynchronization in cases of the 'wrong' positioning of LV lead.[20] Two LV pacing leads could potentially overcome these shortcomings. Further studies are required to elucidate electrophysiological mechanisms involved in the therapeutic effect of triple-site resynchronization. Our patients presented with sinus rhythm and therefore we had to use four electrodes for resynchronization. Because currently available CRT devices have three pacing channels, we decided to split the LV channel into two separate electrodes using Y-adaptor. This modification resulted in unfavourable alteration of the electrical characteristics of joined LV leads (lower impedance with resulting higher current consumption). Similar effect of the split cathodal pacing had been reported previously and has to be kept in mind when using the Y-adaptor because it can lead to the loss of capture and/or premature depletion of the battery.[21,22] This drawback can be eliminated in the future should devices with four independent channels become available.

Although our data indicate that triple-site pacing seems to be a safe method, it can be associated with the higher rate of complications than standard CRT owing to the complexity of the procedure, multiple electrodes, and the specific circuit used to pace LV. This method carries also potentially some risk of late adverse events, which have not been observed in the current study because of the short follow-up period. Thus, it is crucial to narrow the indications of this technique to those patients who will really benefit from it. Therefore, performing the intra-operative echocardiographic assessment of ventricular synchrony during the standard CRT and in cases of insufficient resynchronization, implanting the second left ventricular lead may be advisable. This acute assessment could also be helpful in the selection of the optimal LV pacing sites in patients in whom multiple accessible CS branches are present.

Limitation of the study

When considering triple-site CRT, one has also to take into consideration other serious limitations of this method. The ability to implement multiple-site CRT is strictly dependent on CS anatomy. The usage of multiple electrodes is more time-consuming and exposes both the patient and the operator to excessive fluoroscopy. Furthermore, additional electrodes may potentially increase the risk of lead-related complications (dislocation, damage of the lead, infection, and vein thrombosis). Therefore, until the data from larger studies are available, this method cannot be recommended as a routine procedure. However, implantation of triple-site pacemaker in case of insufficient effect of standard resynchronization assessed acutely with the use of intra-operative echocardiography or upgrading to double left-single right pacemaker in patient who did not respond to conventional CRT during the long-term follow-up may become a promising option in the near future.

This study is a retrospective, single-centre observational analysis with a relatively short follow-up period, and this could have potentially influenced the results. Triple-site pacing strategy was not compared with standard resynchronization therapy; therefore, our analysis should be considered as a feasibility study which provides only some preliminary data on the effectiveness of this type of CRT. We suggest that further trials are needed to evaluate a potential therapeutic role of multiple-site pacing in HF patients.

Conclusions

Our data indicate that triple-site pacing is a technically feasible method with low complication-rate. This mode of pacing is highly effective in improving subjective and objective indices in HF patients. Further studies are needed to identify patient subsets, which will benefit most from this

mode of pacing, and to assess whether triple-site resynchronization can increase response rate to CRT.

Conflict of interest: none declared.

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