Cardiac resynchronization therapy : determinants of patient outcome and emerging indications
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Chapter 16

Requirement for coronary sinus lead interventions and effectiveness of endovascular replacement during long-term follow-up after implantation of a resynchronization device

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ABSTRACT

Background: The aim of this study was to assess the requirement for coronary sinus (CS) lead intervention after cardiac resynchronization therapy (CRT) and to evaluate the effectiveness of endovascular replacement.

Methods: All patients receiving a CRT device with CS lead in the Leiden University Medical Center in the period from 1999 to 2007 were prospectively evaluated and followed. Five hundred and seventy-seven patients were successfully implanted with a CRT device. Nine (1.6%) patients were lost to follow-up. The remaining 568 patients were included in the analysis.

Results: During a median follow-up time of 645 days (inter-quartile range, 260–1148), 7% of the patients required a CS lead intervention. Cause of the intervention was an elevated threshold (n = 13), loss of capture (n = 20), or intractable phrenic nerve stimulation (n = 6). Fifteen patients (38%) required a CS lead intervention before first scheduled follow-up (2 months after implantation). Thirteen patients (33%) warranted a CS lead intervention more than 6 months after implantation. The first endovascular replacement was successful in 86% (32 of 37), whereas a second endovascular approach failed in 66% (2 of 3).

Conclusions: The long-term requirement for CS lead interventions is 7%. Endovascular repositioning or replacement is successful in the majority of cases

INTRODUCTION

Cardiac resynchronization therapy (CRT) plays an important role in the treatment of advanced heart failure in patients with cardiac dyssynchrony. Biventricular pacing has a positive effect on mortality, exercise tolerance, quality of life, and number of heart failure-related hospitalizations.[1–5] Furthermore, a significant clinical improvement, as measured by a change in New York Heart Association (NYHA) functional class, occurs in 70–80% of the patients receiving resynchronization therapy.[6–8] The clinical non-response in 20–30% of all CRT recipients is the most important setback in the use of CRT. Further important complicating factors are the success rate of coronary sinus (CS) lead positioning, which is 88–96% in large trials,[3,8,9] and the occurrence of CS lead dysfunction in 5–10% of the patients during follow-up.[9,10] However, currently available follow-up data are often limited to 6 months following CRT implantation. Endovascular placement of the CS lead in a branch of the CS is the approach of first choice. However, this technique has a number of setbacks and is not applicable to all patients because of CS anatomy, coronary vein anatomy, phrenic nerve stimulation (PNS), and/or dislocation of the CS lead.[11] In all cases of CS lead failure, the clinician has three options of intervening: (i) endovascular replacement; (ii) replacement of the endovascular lead by an epicardial lead by means of a (minimally invasive) surgical implant; or (iii) trans-septal or trans-apical approach.[12-14] The current study evaluated the incidence and causes of the requirement for CS lead intervention and the effectiveness of endovascular replacement.

METHODS

Patients

All 577 patients receiving a CRT device with CS lead in the Leiden University Medical Center in the period from 1999 to 2007 were prospectively evaluated and followed. Patients in whom it was not possible to implant a CS lead during the initial procedure were excluded from the current analysis. Eligibility for CRT was based on the standard guidelines and included advanced heart failure, depressed left ventricular ejection fraction (LVEF <35%), and wide QRS complex (>120 ms).[15]

Device implantation

A CS venogram was obtained using a balloon catheter, followed by the insertion of the CS lead into one of the posterolateral veins through an 8-F guiding catheter. The following CS lead models were used: Easytrak, Easytrak 2, and Acuity manufactured by Boston Scientific [Natick, MA, USA (formerly, Guidant, St Paul, MN, USA)]; Attain and Attain-SD manufactured by Medtronic Inc. (Minneapolis, MN,USA); Aescula by St Jude Medical (St Paul, MN, USA); and the Enpath by Enpath Medical Inc. (Minneapolis, MN, USA). The right atrial and right ventricular leads were positioned conventionally. All leads were connected to a dual-chamber CRT or CRT-defibrillator (CRT-D) device of the following models: Contak TR, Contak CD, or Contak Renewal, Guidant Corp.; Insync III, Insync CD, Insync III Marquis, or Insync Sentry, Medtronic Inc.; and Epic or Atlas, St Jude Medical. Procedural success was accomplished when pulse generator and the three leads were positioned without complications. Before patient discharge, all leads were systematically screened for adequate functioning. This included testing for pacing threshold, sensing, and lead impedance. Additionally, possible presence of PNS was ruled out.

Follow-up

All devices and leads were technically assessed at 3–6 months intervals. In case of loss of capture at maximum output, increase of threshold to sub-maximal (>5.5 V/1.0 ms) values, or intolerable PNS, a chest roentgenogram was made to evaluate whether gross dislodgement of the CS lead had occurred. In case of PNS, all effort was made to prevent its occurrence, using different technical settings. In the Dutch healthcare system, all patients are followed by the implanting centre. Since periodical follow-up was performed every 3–6 months, patients with more than 6 months of missing data were considered as lost to follow-up.

Left ventricular lead intervention

Before admittance for repositioning of the CS lead, the retrograde venogram of the CS made at first CS lead implant was reevaluated in order to assess CS anatomy and to predict the probability of successful endovascular replacement of the CS lead. After repositioning or replacement of the CS lead in an area with a good threshold and sensing, the occurrence of PNS was tested by pacing with high output (10 V). In case of PNS with low output pacing, the CS lead was repositioned to a better location. Furthermore, the CS lead position after replacement was compared with its position after the initial implantation. Endovascular repositioning or replacement of the CS lead was performed by an electrophysiologist at our centre.

Statistical analysis

Continuous data are expressed as mean and standard deviation or range, median and first and third quartile where appropriate; nominal data are presented as numbers and percentages. Comparison of data was performed with the Student's t-test for unpaired data and χ^2 tests with the Yates correction when appropriate. Non-normally distributed data (NYHA functional class) were compared using the Mann–Whitney U-test. Cumulative incidences were analyzed by the method of Kaplan Meier. Death or heart transplantation was counted as censoring events. For all tests, a p-value <0.05 was considered significant.

RESULTS

Patient characteristics

During the study period, 596 patients were implanted with a CRT device. Five hundred seventy-seven patients (97%) successfully received a CS lead. Nine (1.5%) patients were lost to follow-up. The remaining 568 patients were included in the analysis. One hundred thirty-four patients died (n = 130) or underwent heart transplantation (n = 4) with their lead still intact at last follow-up. Median follow-up time was 645 days (inter-quartile range, 260–1148). Implanted leads consisted mostly of models manufactured by Boston Scientific (n = 365) or Medtronic (n = 185). The majority of patients (80% men, mean age 66 years, range 36–87 years) had ischemic heart disease (60%) and a poor LVEF (25±8%). Leads were connected to a CRT only device in 10% (n = 56) or CRT-D device in 90% (n = 512). All data are summarized in Table 1.

Table 1. Patient characteristics

Variable	All CS lead (n = 568)	CS lead requiring intervention (n = 39)	p-value
Age (years)	66 ± 10	64 ± 11	0.1
Male gender	452 (80%)	30 (77%)	0.7
Ischemic cardiomyopathy	343 (60%)	18 (46%)	0.1
LVEF (%)	25 ± 8	24 ± 9	0.4
NYHA class II /III / IV	105 / 420 / 43	9 / 30 / 0	0.4
QRS duration (ms)	159 ± 32	164 ± 31	0.3
Medication			
Diuretics	500 (88%)	36 (92%)	0.4
ACE inhibitors	507 (89%)	36 (92%)	0.5
Spironolactone	272 (48%)	19 (49%)	0.9
Beta-blockers	372 (66%)	27 (69%)	0.6
Amiodarone	141 (25%)	11 (28%)	0.6
CRT-D	512 (90%)	33 (85%)	0.2

CRT-D = cardiac resynchronization therapy-defibrillator; CS = coronary sinus; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association

Requirement for coronary sinus lead intervention

During follow-up, 39 (7%) patients required CS lead intervention. Median time to this event was 85 days (inter-quartile range, 35–211 days). Patients with a CS lead, needing intervention, showed no significant differences in clinical parameters (Table 1). The incidence of surgical CS

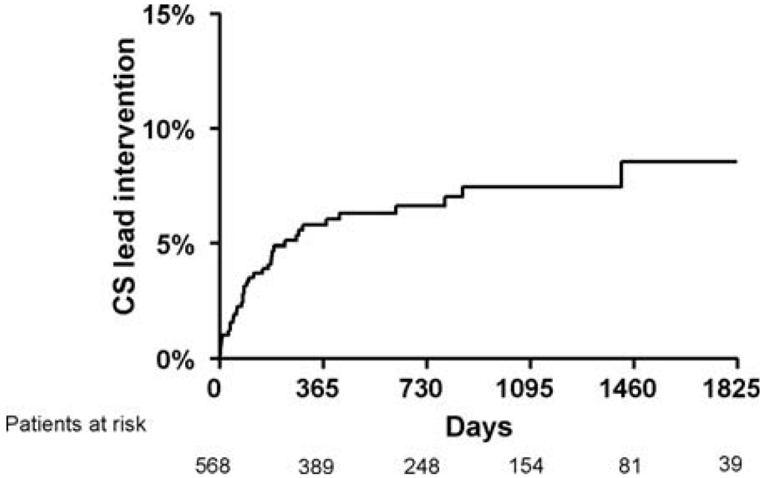

Figure 1. Cumulative requirement for coronary sinus lead intervention.

lead intervention was found to be 3.3/100 patient-years (95% CI, 2.3–4.5/100 patient-years). Cumulative event-rate (Figure 1) at 1 year was 5.8% (95% CI, 1.9–9.7), at 2 years 6.6% (95% CI, 2.3–10.9), and at 5 years 8.6% (95% CI,2.2–14.9). Additionally, no technical failure of the CS lead was observed. In case of re-intervention, no difficulties were encountered during the removal of CS leads, which was performed by traction. In six (15%) cases, requirement of CS lead intervention was based on the occurrence of intractable PNS. The remaining cases of CS lead intervention were diagnosed by findings during periodical examination. In 20 (51%) patients, a complete loss of capture was found, and in 13 (33%) cases, the intervention was warranted due to an elevated threshold >5.5 V/0.5 ms. In the 20 cases of complete loss of capture and consequently loss of biventricular pacing, 13 patients (65%) had experienced an increase in heart failure symptoms. In addition, dislocation could be verified on roentgenogram in 14 of 20 (70%) cases of complete loss of capture. In the remaining 25 cases, no sign of dislodgement was visible on roentgenogram.

Elevated thresholds, causing the need for lead intervention, occurred longest after implantation with a median duration of 180 days (inter-quartile range, 4–376 days),whereas complete loss of capture occurred after the shortest period of time (median 83 days; inter-quartile range, 55–174)(Table 2). The shorter time to diagnosis and the fact that 14 of 20 (70%) cases of lead dysfunction could be verified on roentgenogram imply a more severe dislodgement in the patients with a complete loss of capture. Fifteen patients (38%) required a CS lead intervention before first scheduled follow-up 2 months after implantation. Thirteen patients (33%) were indicated for CS lead intervention more than 6 months after implantation. It is of note that one patient required a CS lead intervention because of a severely elevated threshold 1415 days after implantation (Figure 2).

Table 2. Reasons for the requirement of coronary sinus lead intervention

	Reason for intervention, n	Median time to intervention, days (1st–3rd quartile)
Total	39 (100%)	85 (35-211)
Elevated threshold	13 (33%)	180 (4-376)
Loss of capture	20 (51%)	83 (55-174)
Phrenic nerve stimulation	6 (15%)	83 (16-167)

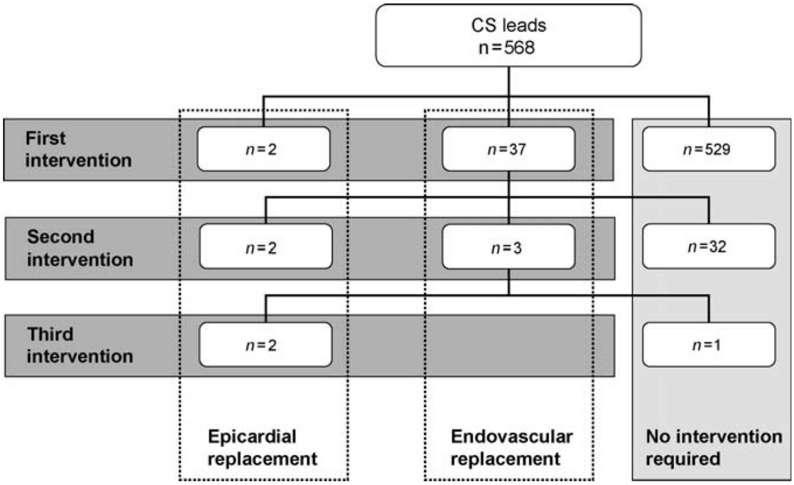

Figure 2. Flow-chart of the requirement and type of coronary sinus lead intervention.

Endovascular replacement

Of the 39 patients warranting CS lead re-intervention, two directly received an epicardial left ventricular (LV) lead because of unfavorable CS anatomy. In 37 patients, endovascular replacement was attempted of which 86% (n = 32) were successful during follow-up. In these patients, a median of 867 days (inter-quartile range, 647–1123 days) of stable long-term biventricular pacing was achieved after repositioning. The remaining five patients needed a second intervention during further follow-up. In two of these patients, clinicians chose to implant an epicardial lead because of unfavorable CS anatomy and the experience during the previous attempt. In three patients, a (second) attempt of endovascular replacements was made in which the rate of success was 33% (n = 1). This patient demonstrated adequate biventricular pacing during a follow-up of 1574 days after the second replacement. The two patients with an unsuccessful second attempt for endovascular intervention both received an epicardial lead. It is of note that the same branch of the CS could be used in 21of 37 (57%) first attempts at endovascular intervention and most leads were placed at the posterolateral region. Of the 37 performed first endovascular CS lead replacements, the old lead was re-used 11 (30%) times. Cases in which leads could be re-used, occurred a shorter period after the initial implantation (re-use of lead: 126±128 days after implantation vs. usage of a new lead: 213±311 days after implantation, $p = 0.05$). The angiographic study, performed at CS lead intervention, demonstrated changes in coronary venous anatomy, such as occlusion or narrowing of the initially used branch, in six cases. In the three cases of second attempts for endovascular replacements, the clinician chose to use a new lead in every case.

DISCUSSION

The current study aimed to specifically describe the need for CS lead intervention during long-term follow-up and to assess the successfulness of endovascular repositioning. The main findings of the current study can be summarized as follows: (i) endocardial CS lead performance during long-term follow-up is excellent; (ii) replacement or repositioning was necessary in 7% of patients; (iii) cases in which evaluation of the CS venogram favored an attempt of endovascular replacement of the CS lead had a success rate of 86% (32 of 37) at first attempt and 33% (1 of 3) in second attempt; (iv) 33% (n = 13) of CS lead interventions were made more than 6 months after implantation; (v) in case of clinical or technical evidence for CS lead malfunction, only 36% (n = 14) could be verified on roentgenogram.

Although CRT has become an established treatment in patients with advanced heart failure, clinical use of biventricular pacing still has to cope with some serious setbacks. Firstly, 20–30% of implanted patients do not show clinical improvement.[6–8] Secondly, implantation of a biventricular system succeeds only in 88–96% of patients,[3,8,9] and finally, during follow-up, the need for CS lead intervention is warranted in 5–10% of implantedpatients.[9,10] Since endovascular replacement of the CS lead is the least invasive (in contrast to epicardial placement), the current study sought to evaluate the incidence and causes of the requirement of CS lead intervention and the effectiveness of endovascular replacement.

During follow-up, high thresholds, complete loss of capture, or intractable PNS prevented adequate left ventricular pacing in 7% of our population. Compared with other device-related complications, this is a substantial number of cases requiring an invasive procedure to resolve. To replace a CS lead, the clinician has to find the best side branch of the CS, which can be assessed by reevaluation of the retrograde venogram of the CS, made at the initial implantation. Due to more experience and improved technical possibilities, there is a high success rate in the initial endovascular implantation of CS lead into one of the branches of the CS.[1,8] Our data show that in case of a subsequent CS lead intervention, the endovascular approach is successful in 86% of cases, making it a very reasonable therapeutic option to restore biventricular pacing and its accompanying beneficial effects.

Coronary sinus lead dislodgement can occur shortly after implantation but was seen as late as 4 years after implantation. Although the median follow-up in our population was 645 days (inter-quartile range, 260–1148), there might well be an underestimation of the percentage CS lead dislodgements. This is also shown in our analysis of the cumulative incidence, which can reach up to 8.6% 5 years after implantation. The same underestimations likely to have occurred in some large studies with relatively short follow of less than 1 year.[3,8] Only the CARE-HF study has a comparable long mean follow of 29.4 months and also showed a 6% CS lead dislodgement, results comparable to our CRT population.[16]

Phrenic nerve stimulation is tested during implantation by high voltage pacing (up to 10 V). Nevertheless, chronic PNS is reported in up to 12% of CRT recipients.[8] During follow-up, PNS can also arise de novo because of changes in body position or (micro) dislodgement of the CS lead. Changing the pacing output and/or pacing configuration can resolve the problem most of the time but repositioning of the CS lead is necessary in some cases. In our population, only six patients (1.3%) needed a CS lead replacement due to intolerable PNS, which is 15% (6/39) of all patients with CS lead failure.

Three patients underwent a successful second endovascular replacement but during further follow-up, two of them needed an epicardial lead placement after renewed CS lead malfunction. A second replacement procedure should therefore be carefully evaluated. However, the number of patients receiving a secondary replacement in this study is limited. In total, six patients received an epicardial LV lead without complications peri-procedural or during follow-up. Nevertheless, taking in account the invasiveness and time consumption of an epicardial approach and the 86% effectiveness of the endovascular approach, clinicians should favor the endovascular. It is of note that before intervening, all cases in the current study were reevaluated by venogram of the CS to determine the possibility of endovascular replacement.

Conclusion

The long-term requirement for CS lead interventions is 7%.Endovascular repositioning or replacement is successful in the majority of cases.

REFERENCES

1. Abraham WT, Fisher WG, Smith AL et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-1853.
2. Auricchio A, Stellbrink C, Sack S et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;39:2026-2033.
3. Bristow MR, Saxon LA, Boehmer J et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-2150.
4. Gras D, Leclercq C, Tang AS et al. Cardiac resynchronization therapy in advanced heart failure the multicenter InSync clinical study. *Eur J Heart Fail* 2002;4:311-320.
5. Linde C, Leclercq C, Rex S et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUltisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002;40:111-118.
6. Bardy GH, Lee KL, Mark DB et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-237.
7. Bradley DJ, Bradley EA, Baughman KL et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;289:730-740.
8. Young JB, Abraham WT, Smith AL et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *JAMA* 2003; 289:2685-2694.
9. Gras D, Bocker D, Lunati M et al. Implantation of cardiac resynchronization therapy systems in the CARE-HF trial: procedural success rate and safety. *Europace* 2007;9:516-522.
10. Leon AR, Abraham WT, Curtis AB et al. Safety of transvenous cardiac resynchronization system implantation in patients with chronic heart failure: combined results of over 2,000 patients from a multicenter study program. *J Am Coll Cardiol* 2005;46:2348-2356.
11. Albertsen AE, Nielsen JC, Pedersen AK et al. Left ventricular lead performance in cardiac resynchronization therapy: impact of lead localization and complications. *Pacing Clin Electrophysiol* 2005;28:483-488.
12. Leclercq F, Hager FX, Macia JC, Mariottini CJ, Pasquie JL, Grolleau R. Left ventricular lead insertion using a modified transseptal catheterization technique: A totally endocardial approach for permanent biventricular pacing in end-stage heart failure. *Pacing Clin Electrophysiol* 1999;22: 1570-1575.
13. Szili-Torok T, Foldesi C, Kardos A, Szekely A, Kassai I. A novel approach for endocardial resynchronization therapy: transapical implantation of left ventricular pacing lead. *Heart Rhythm* 2008;5: S96.
14. van Gelder BM, Scheffer MG, Meijer A, Bracke FA. Transseptal endocardial left ventricular pacing: an alternative technique for coronary sinus lead placement in cardiac resynchronization therapy. *Heart Rhythm* 2007;4:454-460.
15. Epstein AE, DiMarco JP, Ellenbogen KA et al. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;51:e1-e62.

16. Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-1549.