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First clinical evaluation of an atrial haemodynamic sensor lead for automatic optimization of cardiac resynchronization therapy

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Aims One option to improve cardiac resynchronization therapy (CRT) responder rates lies in the optimization of pacing intervals. A haemodynamic sensor embedded in the SonRtip atrial lead measures cardiac contractility and provides a systematic automatic atrioventricular and interventricular delays optimization. This multi-centre study evaluated the safety and performance of the lead, up to 1 year.

Methods and results A total of 99 patients were implanted with the system composed of the lead and a CRT-Defibrillator device. Patients were followed at 1, 3, 6, and 12 months post-implant. The primary safety objective was to demonstrate that the atrial lead complication free rate was superior to 90% at 3-months follow-up visit. A lead handling questionnaire was filled by implanting investigators. Lead electrical performances and the performance of the system to compute AV and VV delays were evaluated at each study visit over 1 year. The complication free rate at 3 months post-implant was 99.0% [95%CI 94.5–100.0%], $P < 0.001$. Electrical performances of the lead were adequate whatever the atrial lead position and remained stable over the study period. The optimization algorithm was able to compute AV and VV delays in 97% of patients, during >75% of the weeks.

Conclusion The atrial lead is safe to implant and shows stable electrical performance over time. It therefore offers a promising tool for automatic CRT optimization to further improve responder rates to CRT.

Keywords Peak endocardial acceleration • SonRtip atrial lead • Cardiac resynchronization therapy • Atrioventricular delay optimization • Interventricular delay optimization

Introduction

Cardiac resynchronization therapy (CRT) has broadly been shown to improve symptoms and exercise tolerance, to improve quality of life, to reduce morbidity, and mortality.[1–3] However, about one-third of patients receiving CRT are considered to be non-responders.[4] Besides optimization of left-ventricular lead position or treatment of supraventricular tachycardia, optimization of device programming can improve responder rates.[5,6] Optimization of atrioventricular (AV) and interventricular (VV) delays has been

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suggested using different techniques, including echocardiography, device-based algorithms, and other methods.[7] However, some of these methods, like Ritter's formula,[8] are time consuming and require suitable equipment. Furthermore, the individual optimal AV and VV delay of one patient may vary over time[9] necessitating frequent optimization of intervals. Device-based algorithms might overcome these obstacles by optimizing the AV and VV delays both automatically and periodically. Several algorithms based on intracardiac electrogram (IEGM) have been developed for delays optimization to date including Smart AV Delay™ (Boston Scientific Corporation),[10] QuickOpt™ (St Jude Medical)[11] and AdaptivCRT™ (Medtronic).[12]

For continuous haemodynamic measurement, the SonR haemodynamic sensor has been introduced for long-term measurement of cardiac contractility. The method is based on the peak endocardial acceleration (PEA) principle which is the mechanical acceleration of the heart and was shown to correlate with left-ventricular dP/dt_{max}.[13,14] PEA-based algorithms were validated for optimization of AV and VV delays in dual chamber pacing and CRT[15–17] and were recently shown to improve the rate of responders to CRT in a pilot study.[18] Of note, the sensor used in these studies was located at the tip of a right-ventricular pacemaker lead. Since current guidelines state that most of the patients having an indication for CRT will also be considered for primary prophylactic implantable cardioverter/defibrillator (ICD) therapy, the sensor technology was embedded in a novel atrial lead to permit the implantation of a right-ventricular defibrillation lead. This study was the first to investigate this novel atrial active fixation lead. The primary endpoint was the safety of the lead at 3 months, while secondary endpoints included lead handling and electrical performances, up to 1 year.

Methods

Study design

This was a European prospective, multi-centre, non-randomized, longitudinal study designed to assess the safety and effectiveness of the SonRtip atrial lead. The study was conducted in accordance with the Declaration of Helsinki. National or local Ethics Committee approved the study protocol for each centre. All patients gave written informed consent.

Patients included had to fulfil the criteria for a CRT-D implantation according to current guidelines[19] and were implanted the atrial lead. Patients with incessant ventricular tachycardia/ventricular fibrillation or an implanted pacemaker that was not going to be explanted or otherwise disabled were excluded from this study.

Patients were followed in the study until the primary endpoint period at 3 months and could agree to continue in a registry phase until 12 months. Right-atrial (RA) lead electrical performances and data on the ability to determine optimal CRT timings were collected at implantation, pre-hospital discharge (PHD), 1-month (M1), 3-months (M3), 6-months (M6), and 12-months (M12) follow-up. Pacing threshold was measured either at 0.35 ms or at 0.50 ms, at investigators' discretion. Adverse events were reported throughout the study and investigators assessed their relationship with the investigational device.

Study objectives

The primary safety objective of the study was to demonstrate that the atrial lead complication free rate, i.e. freedom from complications directly attributed to the lead, was superior to 90% at 3-months follow-up visit.

Secondary objectives included lead handling feedback by the physician at implant, atrial electrical performances (pacing threshold, pacing impedance, and sensing), sensor signal and capacity of the system to compute AV and VV delays whatever the position of the lead in the right atrium, up to 1 year. Additionally, adverse events were collected throughout the study duration.

Implanted devices

Enrolled patients were implanted the SonRtip™ RA lead (Sorin CRM SAS, Clamart, France) and the PARADYM™ RF SonR CRT-D 9770 (Sorin CRM SAS, Clamart, France). The choice of the RV and the LV leads were left at the discretion of investigators.

The SonRtip lead is an endocardial, straight, bipolar, active fixation pacing lead with an integrated acceleration sensor. The lead is inserted in the right atrium and attached to the atrial wall by a fixed screw. The fixed helix is coated with polyethylene glycol (PEG) to prevent damage while advancing the lead through the venous anatomy. This coating is completely dissolved within 4 min once inserted into the blood stream. Fixation is achieved by applying 4 (max. 6) clockwise turns to the whole lead.

The implanting physician completed a questionnaire on lead handling after each implant procedure. Each parameter had to be rated as 'easy', 'acceptable', or 'poor'.

Sensor capacity to adjust AV and VV delays

The CRT optimization using the algorithm has been described previously.[15] In brief, the system uses the signal amplitude variations in different AV and VV delays to calculate the optimized timings automatically, updating AV and VV intervals weekly. In this study, optimal delays were recorded for evaluation, but not applied to the patient, once calculated.

Statistical analyses

Analyses were performed on patients with successful implantation of an atrial lead. Continuous variables are presented as mean $\pm$ standard deviation (SD) or as median [Q1–Q3] according to the distribution of the variable. Categorical variables are summarized as frequencies and percentages.

For the primary objective, a required sample size of 89 patients was estimated under the hypothesis of an expected success of 97% to reach a power of 80%. Adjusted with a potential rate of 10% lost to follow-up, the inclusion of 99 patients was necessary for the study. Fisher's exact test was performed to compare the rate obtained at 3 months with 90% (primary safety endpoint of the study). The 95% confidence interval of this rate was also calculated.

Electrical performance parameters stability were evaluated by testing intra-patient differences between M3 and M12 study visits using a Student's *t*-test for parametric parameters and a Wilcoxon test for non-parametric parameters. Patients with atrial fibrillation were excluded from the lead amplitude analysis. The PEA signal amplitude was analysed by atrial lead position (comparison between the

median PEA signal in the appendage position vs. the one measured in the other positions) using a Wilcoxon test, at 12-month follow-up. The percentage of patients in whom AV and VV delays could be computed by the device was categorized by percentage of weeks [<25%, (25–75%), and >75%] over 1 year. Moreover, this distribution was compared between lead positions (appendage vs. all other positions) using a Fisher's exact test.

Statistical analyses were performed on the frozen study database using SAS, version 9.2 (SAS Institute, Cary, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Study population

Between 2 November 2010 and 6 May 2011, 100 patients were enrolled in 21 centres in France, Germany, Spain, and the Netherlands. Lead implantation was not possible in one patient due to vein fibrosis. Since no other atrial lead implantations were attempted in this patient, he terminated the study before implantation and was not considered for the analysis. Therefore, 99 patients were successfully implanted with the CRT-D device and connected to the atrial lead under investigation (analysed population). Patients were 68.3 ± 9.2 years old in average, 73% male, with mild-to-severe heart failure NYHA functional class II, III, or IV (42, 49, and 3% respectively), mainly implanted for primary prophylactic ICD indication (91.9%), with a mean left-ventricular ejection fraction of 26.3 ± 6.6%. Baseline characteristics are shown in *Table 1*.

Two patients terminated the study before the 3-months follow-up: in one patient, the system had to be explanted due to system infection 5 weeks after implantation and the other patient died of heart failure before the 3 months follow-up. Therefore, a total of 97 patients were followed-up at 3 months and 91 patients (96.8%) remained in the study up to 12 months. Between 3 and 12 months, two patients were lost to follow-up and four patients died. The mean study duration was 359 ± 53 (range 23–427) days.

Table 1 Baseline characteristics

Parameters, *n* (%)	*n* = 99
Demographics	
Age (mean ± SD, in years)	68.3 ± 9.2 years
Male gender	72 (72.7)
BMI (mean ± SD, in kg/m^2)	27.1 ± 4.5 kg/m^2
Implant indication	
Primary prophylactic indication	91 (91.9)
Secondary prophylactic indication	8 (8.1)
NYHA functional class	
I	3 (3.0)
II	42 (42.4)
III	49 (49.5)
IV	3 (3.0)
Left-ventricular ejection fraction	26.3 ± 6.6
Heart failure aetiology	
Ischaemic	54 (54.6)
Non-ischaemic	45 (45.5)
Valvular disease	
Mitral	31 (31.0)
Aortic	8 (8.0)
Tricuspid	13 (13.0)
Conduction disorders	
AVB—1st degree	13 (13.1)
AVB—2nd degree	6 (6.1)
AVB—3rd degree	5 (5.1)
Sinus dysfunction	6 (6.1)
Paroxysmal AA (flutter or fibrillation)	20 (20.2)
Persistent AA (flutter or fibrillation)	9 (9.1)
Associated conditions	
Arterial hypertension	52 (52.5)
Diabetes mellitus	32 (32.3)
Renal failure	15 (15.2)

AA, atrial arrhythmia; AVB, atrioventricular block; BMI, body mass index; SD, standard deviation.

Lead implantation

The atrial lead was positioned in the appendage (66.7%), the lateral wall (24.2%), the septum (3.0%), or the anterior wall (6.1%).

Mean implantation time from lead introduction to sleeve fixation was 6.2 ± 4.0 (range 0.3–30.0) min, excluding 4 min for sugar tip (PEG coating) dissolution. While the tested lead was successfully implanted in 97 patients with the initial lead, a second lead was needed for two patients. For one patient the PEG coating protecting the screw was absent; for the second patient, the investigator had difficulties to manoeuvre the lead in the atrium and experienced limited torque transmission. The second attempt was successful in both patients.

Most investigators rated all parameters of lead handling at implant as easy or acceptable. More detailed results on the lead handling questionnaire are presented in *Figure 1*.

Primary objective, complication free rate at 3 months

The complication free rate at 3 months post-implant was 99.0% [95%CI: 94.5–100.0%], $P < 0.001$. We observed one atrial lead dislodgement possibly related to the lead the day after the implant; a reintervention occurred the day after and the atrial lead was repositioned without necessitating a lead change. No other serious adverse events or adverse events related to the atrial lead were reported.

Electrical performances

At implant, median [Q1; Q3] pacing threshold was 0.75 V [0.50; 0.75 V] at 0.35 ms and 0.50 V [0.50; 1.00 V] at 0.50 ms. Mean lead impedance was 504 ± 128 Ω (range 415–536 Ω, median 474 Ω). The P-amplitude was 3.0 ± 1.8 mV (range 0.4–6.1 mV, median 2.7 mV). *Figure 2* presents pacing threshold, lead impedance, and P-amplitude evolution with time. There was no difference in median pacing threshold between M3 and M12: 0.00 V [−0.25; 0.00 V] at 0.35 ms ($P = 0.157$) and 0.00 V [−0.25; 0.00 V] at 0.50 ms ($P = 0.090$). Mean amplitude and impedance also remained stable from M3 to M12 [mean difference ± SD (95%CI) amplitude: −0.2 ± 1.1 mV (−0.4; 0.1 mV), $P = 0.126$; and impedance: 2.3 ± 55.0 Ω (−9.2; 13.8 Ω), $P = 0.691$].

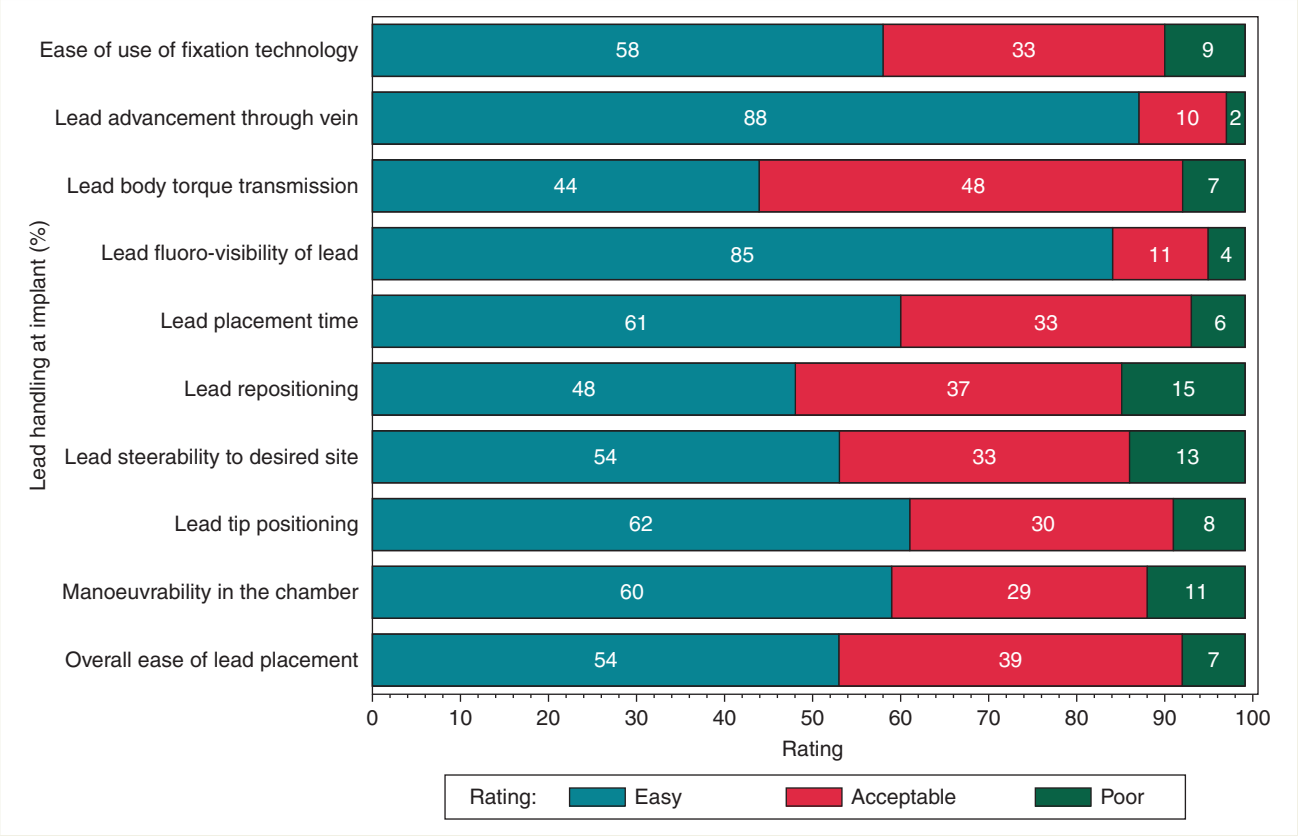

Figure 1 Results of the questionnaire on SonRtip atrial lead handling. Investigators were asked to rate different lead handling characteristics using a scale from easy, acceptable to poor compared with two models they are used to implant. The handling results were based on the 99 implanted SonRtip leads and the feedback of 41 different investigators.

Haemodynamic signal recorded by the lead

Amplitude of the PEA signal ranged between 0.06 and 2.56 g, over the whole study. *Figure 3* presents the mean evolution of the signal through the study. The PEA signal amplitude values were independent from the position of the lead ($P = 0.821$).

Performance of the algorithm to adjust AV and VV delays

The analysis was conducted on 90 patients with weekly optimization function activated: (i) four patients were in permanent atrial fibrillation (no AV delay optimization possible; the signal can also be collected during atrial fibrillation, and the algorithm can still optimize VV delays during in-clinic follow-up); (ii) the algorithm was not activated in five patients (one patient without an LV lead, therefore VV delay optimization was not possible; three patients not programmed with weekly optimization; one patient lost at PHD). Over 1 year, the system was able to adjust AV and VV delays in 87 (97%) patients over more than 75% of the weeks. Reasons for non-adjustment of delays included unstable atrial rhythm or other rhythm abnormalities such as ventricular premature beats or pacemaker mediated tachycardia. Therefore, failure to optimize was never related to the system performance. The lead position was found to have no impact on the ability of the system to optimize CRT (appendage vs. other positions: $P = 1.000$).

Adverse events

There were five deaths in the study due to heart failure or cancer; none of them were found to be device-related. Adverse events and device issues were reported in 16 patients. During follow-up, one other atrial lead dislodgement was observed. The concerned patient experienced RV lead dislodgement. During revision of the RV lead, the RA lead dislodged accidentally and had to be repositioned. This event was rated as related to the RV revision procedure. In one patient, the helix of the RA lead tip was damaged during a repositioning procedure consecutive to an RV lead revision, 2 months after implant. A new RA lead was implanted without further problems. Since this event was due to the RV lead revision, this event was classified as procedure-related by the Investigator. One patient experienced pocket infection 3 weeks after implantation, which evolved towards a system (device and leads) infection; as a consequence, the device was explanted. A total of eight patients experienced pocket haematoma after implant. None of them necessitated re-intervention and they were classified as procedure-related. Five phrenic nerve stimulation (PNS) episodes were experienced

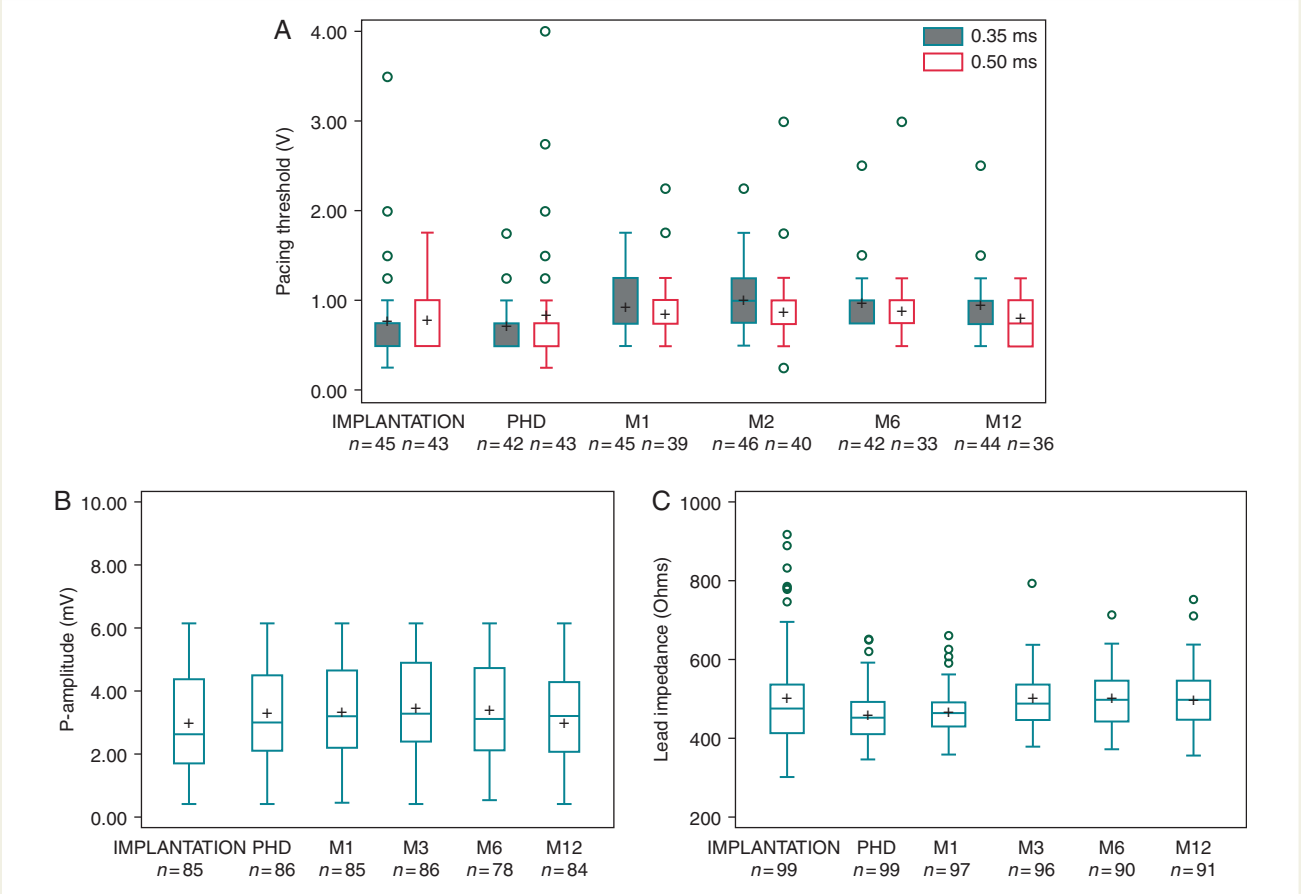

Figure 2 Boxplots showing electrical performance of the SonRtip atrial lead from implantation until 12-months follow-up. The bar inside the box area of the plot is the median (50th percentile), the box area is the interquartile range (25th percentile to 75th percentile). The cross corresponds to the mean value. The lines extend out to the data point closest to but not exceeding 1.5 times the interquartile range. The bullet points are data points that lie outside of 1.5 times the interquartile range. (*A*) Pacing threshold at 0.35 and 0.5 ms, respectively. (*B*) P-amplitude. (*C*) Lead impedance. PHD, pre-hospital discharge; M1, 1-month follow-up; M3, 3-months follow-up; M6, 6-months follow-up; M12, 12-months follow-up.

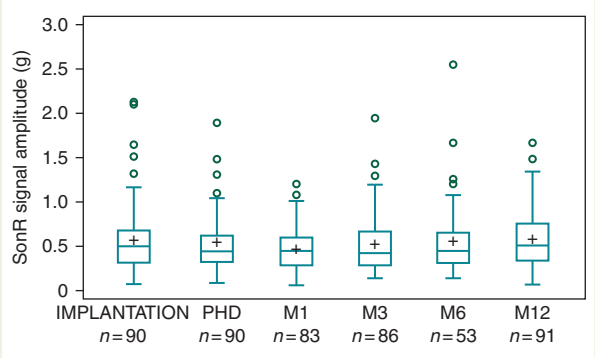

Figure 3 Boxplots showing PEA signal amplitude from implantation to 12-months follow-up. PHD, pre-hospital discharge; M1, 1-month follow-up; M3, 3-months follow-up; M6, 6-months follow-up; M12, 12-months follow-up.

by four patients. While PNS episodes were resolved by device reprogramming in three patients, a new LV lead implantation was necessary in one patient.

Discussion

This was a prospective, multi-centre non-randomized, longitudinal study assessing the safety and 1 year performance of a novel atrial lead embedding a haemodynamic sensor for CRT optimization.

Previously, the PEA principle was shown to be a promising technique to measure haemodynamic condition and capacity and to adapt AV and VV delay in pacemaker patients.[14,16,17,20,21] Originally, the PEA method was implemented into RV pacemaker leads. Delnoy *et al.*[18] reported the PEA technology to be a promising tool for CRT optimization. However, in order to benefit from this promising technology in CRT-D systems, the sensor technology had to be located in an atrial lead to give way to the implantation of defibrillation leads for the RV. This new location necessitated the safety and efficacy of this novel atrial lead to be verified.

With a complication free rate of 99.0% at 3 months, the primary endpoint was achieved ($P < 0.001$). We observed one atrial lead dislodgement that occurred the day after implant and was resolved through lead repositioning. Another atrial lead dislodgement occurred accidentally during a revision of the RV lead and was therefore not considered for the primary endpoint. Lead dislodgements are a

known and constant complication after implantation of cardiac devices and are therefore expectable. However, since the investigational lead implies a special implant technique due to its non-retractable screw, it is important to emphasize on the 4 (max. 6) turns to the whole lead needed for fixation. During the subsequent follow-up beyond 3 months up to 1 year, we did not observe device-related complications.

This new lead is exceptional with the presence of a haemodynamic sensor and other structural features such as a non-retractable screw, a non-flexible long tip, and a PEG coating necessitating 4 min to dissolve. These particularities have previously caused concerns over lead handling and possible fixation problems, especially given the fact that the lead needs to be rotated in whole for screwing and thereby might lose the torque needed for special lead locations. However, these concerns were not confirmed by our study results, as the implanting physicians predominantly rated lead handling as easy or acceptable. Still, most of the atrial leads were positioned in the appendage or the lateral wall (90.9%) and therefore some atrial target positions like Bachmann's bundle might be underrepresented in this study. Still, especially for inexperienced implanters, the unusual structure of the tip might represent a handicap as it is widely known that the final lead localization depends not only on the patient's anatomy and previous operation, but also on the implanter's skills. There were some initial concerns about the implant procedure due to the fixed screw on the lead. However, procedure duration was not prolonged in comparison to standard leads with active or passive fixation and successful implantation was observed at first attempt in 98% of the patients. Our data show that the lead can be implanted in variable RA locations, without impacting the PEA signal. The electrical performance of the lead showed stable values for impedance, pacing threshold, and sensing amplitude over time.

Several automatic algorithms for optimization of CRT have been proposed in recent years. However, these methods are all IEGM-based and therefore error-prone in terms of newly acquired conduction disturbances, e.g. supraventricular tachycardia or myocardial infarction. The CRT optimization algorithm using PEA provides real-time measurements of haemodynamic response allowing ambulatory adaption and optimization. In our study, it was shown to be able to provide optimized timings at follow-ups in more than 75% of the weeks in which this function was activated for 97% of the patients.

Limitations

Even if this study was able to show stable electrical performances of the investigated lead over 1 year, some of the well-known lead complications only occur several years after implantation. The presented follow-up of this study therefore is insufficient for assessment of long-term safety. Moreover, the optimized timings for AV and VV delays calculated by the device were not applied to the patient, as specified in the protocol. Since this was primarily a safety and efficacy study, collecting data on clinical outcomes was not part of the protocol. Data on the clinical benefit of automatic optimization using the PEA principle will be provided by the ongoing randomized RESPOND CRT trial[22] having recently completed enrolment.

Conclusion

In conclusion, the implantation of the SonRtip atrial lead is easy and safe. Electrical performances are adequate and remain stable when implanted in different atrial target positions. The AV/VV optimization algorithm shows good performances for the majority of patients and therefore could offer a promising automatic tool to further improve response rates to CRT.

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