Scientific Research Publishing

World Journal of Cardiovascular Diseases, 2017, 7, 323-331
http://www.scirp.org/journal/wjcd
ISSN Online: 2164-5337
ISSN Print: 2164-5329

# Bipolar Leads for Prevention of Phrenic Nerve Stimulation: Results from the ORPHEE Observational Study

**Henri Benkemoun[1], Maxime Pons[2], Luc Kubler[3], Hugues Bader[4], Antoine Dompnier[5], Cyrus Moini[6], Bérangère Leroy-Salaun[7], Nicolas Lellouche[8]**

[1]Clinique Saint Pierre, Perpignan, France
[2]Clinique du Millénaire, Montpellier, France
[3]Clinique Ambroise Paré, Nancy, France
[4]Public Hospital, Pau, France
[5]Public Hospital, Annecy, France
[6]Private Hospital, Antony, France
[7]LivaNova, Clamart, France
[8]Hôpital Henri Mondor, Créteil, France
Email: henri.benkemoun@wanadoo.fr

**How to cite this paper:** Benkemoun, H., Pons, M., Kubler, L., Bader, H., Dompnier, A., Moini, C., Leroy-Salaun, B. and Lellouche, N. (2017) Bipolar Leads for Prevention of Phrenic Nerve Stimulation: Results from the ORPHEE Observational Study. *World Journal of Cardiovascular Diseases*, **7**, 323-331.
https://doi.org/10.4236/wjcd.2017.710030

**Received:** July 11, 2017
**Accepted:** October 15, 2017
**Published:** October 19, 2017



## Abstract

**Background:** Up to one in three patients implanted with a cardiac resynchronization therapy-defibrillator (CRT-D) device experience phrenic nerve stimulation (PNS). Quadripolar leads are effective at reducing PNS, but compared to standard bipolar leads they have limitations related to maneuverability and high pacing thresholds. The ability of standard bipolar leads to overcome PNS is explored here. **Methods:** The French multicenter, observational study ORPHEE enrolled 90 CRT-D-eligible patients. Detection of PNS took place after satisfactory positioning of the LV bipolar lead (stable pacing threshold < 2.5 V). The aim of the primary analysis was to show that, at implant, three programmable pacing vectors (LV tip - LV ring, LV tip - RV ring and LV ring - RV coil) could prevent PNS from occurring in at least 90% of patients. **Results:** In 80 evaluable patients, PNS was reported in 12 patients (15%). Reprogramming overcame PNS in 10 patients: LV ring - RV coil in 8 patients; LV tip - LV ring in 1; and LV tip - RV ring in 1. As PNS was avoided in 78 of 80 patients (97.5%), the primary endpoint was significant (97.5% *vs.* 90%, p = 0.01). **Conclusion:** During CRT-D implantation, PNS occurred in 15% of patients. In most (97.5%) implanted patients, PNS could be avoided by vector reprogramming using a bipolar LV lead. For patients whose coronary sinus anatomy precludes the implantation of multi-electrode leads, bipolar leads are a suitable, reliable alternative.

**Keywords**

Phrenic Nerve Stimulation, Pacing Vectors, Left Ventricular Lead, Bipolar Lead, Quadripolar Lead

## 1. Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for heart failure (HF) patients presenting with left ventricular (LV) systolic dysfunction, a low ejection fraction and a wide QRS, despite optimal drug therapy [1]. To ensure the effectiveness of the CRT therapy, both ventricles have to be synchronously paced. Major issues that limit the continuous delivery of CRT are high LV pacing thresholds and phrenic nerve stimulation (PNS) [2].

PNS occurs in up to one third of patients at implant [3]. With the exception of LV repositioning, which prolongs implantation time and is possible only if anatomy is suitable, an alternative for bypassing PNS is to reprogram LV polarity. The introduction of quadripolar LV leads allows greater programmability with 10 - 17 vectors available [4] [5] [6]. These leads give the implanting physicians more choice compared to traditional LV bipolar leads. However, in certain patients, difficulty in passing multiple electrodes into coronary sinus tributaries with acute angulations and multiple bends is observed [7]. In these patients, a bipolar lead may offer a reliable alternative.

In the ORPHEE study, we investigated the ability of standard LV bipolar leads to overcome PNS. Three ventricular pacing vectors were assessed: LV tip - LV ring, LV tip - RV ring and LV ring - RV coil.

## 2. Methods

### 2.1. Study Design and Device Implantation

ORPHEE was a French multicenter, observational, prospective study. Patients were enrolled if eligible for an implantation of a CRT-D (defibrillator) device (de novo or replacement, PARADYM or INTENSIA, LivaNova) according to current guidelines at the time of inclusion [8]. The choice of right atrial, right ventricular and bipolar LV leads was left to investigators' discretion. Once the position of the LV lead was judged satisfactory (stability and LV pacing threshold < 2.5 V) by the clinician and ascertained using a venogram, the presence of PNS was tested using a program system analyzer. Three different vectors, LV tip - LV ring, LV tip - RV ring, and LV ring - RV coil (**Figure 1**) were tested to overcome PNS.

Follow-up visits were scheduled at 1 to 3 months and 6 and 9 months post-implant. Follow-up data collection included assessments of adverse events, collection of sensing, and thresholds using the programmer (Orchestra or Orchestra +, LivaNova). In the case of PNS detection, vector reprogramming was attempted.

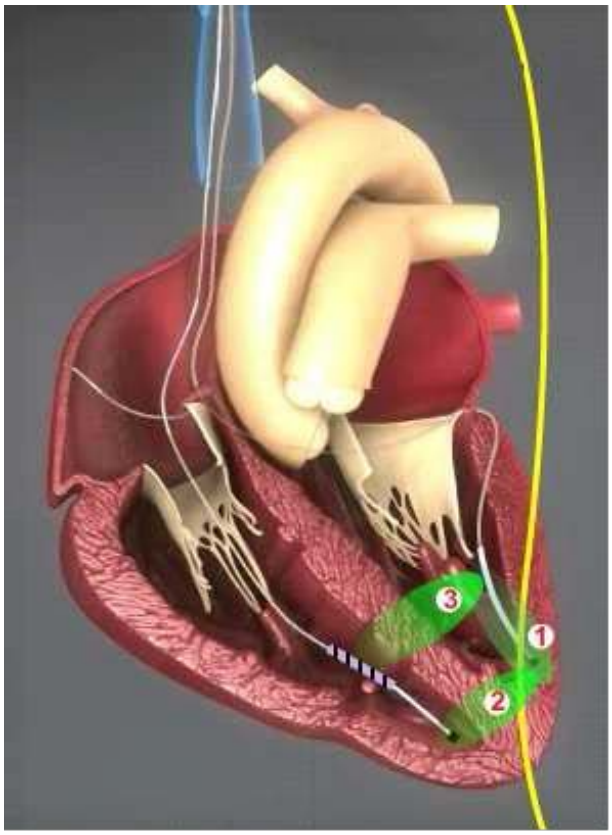


**Figure 1.** Available pacing vectors. 1. LV tip - LV ring; 2. LV tip - RV ring; 3. LV ring - RV coil. LV—left ventricular, RV—right ventricular.

The study was declared to all competent authorities in France. Enrolled patients gave their informed consent and the study conduct complied with Good Clinical Practice and the Helsinki Declaration.

## 2.2. Primary Study Objectives

The primary endpoint of the study was to demonstrate that three different programmable LV vectors could overcome PNS in at least 90% of implants. Success was defined as either an absence of PNS (detected at 7 V) or resolution of PNS by vector reprogramming using one of the three LV pacing vectors (LV tip - LV ring, LV tip - RV ring, and LV ring - RV coil—**Figure 1**). A failure to overcome PNS by reprogramming was not counted as a success for the primary objective.

## 2.3. Statistical Analysis

The intention-to-treat population included all patients successfully implanted with an evaluable primary endpoint (LV pacing threshold < 2.5 V and PNS tested). The primary endpoint was compared with 90% pre-specified value using one-sided test for binomial proportion at an alpha level of 0.05. The safety population included all patients successfully implanted. Categorical variables are

reported as frequencies and percentages, and continuous variables as mean ± standard deviation. Analyses were performed using SAS software version 9.4.

## 3. Results

### 3.1. Study Population and Implant

A total of 90 patients were implanted at 17 French centers, from September 28, 2012, to January 29, 2015. At enrollment, the patient population had a mean age of 70.2 ± 8.9 years old and a mean left ventricular ejection fraction (LVEF) of 28.0% ± 5.5%. A summary of patient demographics is provided in Table 1.

The implant success rate was 100%, 91% of patients with primary indication and 9% with secondary indication (83.3% of de novo implants, 16.7% upgrades). The LV leads implanted were from different manufacturers: Medtronic (48%), Saint Jude (21%), Sorin (16%), Boston Scientific (8%) and Biotronik (7%). The LV lead positions are presented in Table 1.

Table 1. Demographic and implant parameters in ORPHEE participants (n = 90).

| Demographic and implant parameters | |
|---|---|
| *Characteristics* | |
| Male gender | 74 (82.2%) |
| Age (years) | 70.1 ± 8.9 [46; 86] |
| Ischemic cardiomyopathy | 42 (48.8%) |
| NYHA class II/III | 32 (37.7%)/46 (54.1%) |
| *ECG characteristics* | |
| QRS duration (ms) | 153.9 ±25.3 [80; 208] |
| LBBB | 65 (73.9%) |
| *Conduction disorder* | |
| Sinus node disease | 4 (4.5%) |
| Chronic AF | 13 (14.4%) |
| Paroxysmal AF | 8 (8.9%) |
| *Medications* | |
| Beta-blockers | 60 (66.7%) |
| Diuretics | 50 (55.6%) |
| ACE inhibitor | 37 (41.1%) |
| Amiodarone | 17 (18.9%) |
| *Comorbidities* | |
| Atrial hypertension | 36 (40.0%) |
| Diabetes mellitus | 20 (22.2%) |
| Coronary angioplasty | 16 (17.8%) |
| Sleep apnea | 9 (10.0%) |
| *LV lead position (final vein)* | |
| Lateral | 66 (75.9%) |
| Posterolateral | 9 (10.3%) |
| Anterior | 4 (4.6%) |
| Posterior | 2 (2.3%) |
| Great cardiac vein | 1 (1.2%) |
| *Position in the vein* | |
| Proximal | 18 (23.1%) |
| Mid | 39 (50.0%) |
| Distal | 21 (26.9%) |

Data are presented as mean ± standard deviation [minimum; maximum] or numbers and percentages. ACE—angiotensin-converting enzyme, AF—atrial fibrillation, ECG—electrocardiogram, LBBB—left bundle branch block, LV—left ventricular, NYHA—New York Heart Association.

Out of the 90 patients implanted, 84.4% attended the first follow-up visit (M1-M3) and 71.1% attended the second follow-up visit (M6-M9). Reasons for discontinuation were: death (7.8%), patient withdrawal (4.4%), patients lost to follow-up (8.9%), explantation (1.1%), and other reasons (6.7%).

### 3.2. Primary Study Objective

Of the 90 patients implanted, 9 patients had an LV threshold > 2.5 V and in one patient, the PNS threshold was not tested; therefore 80 patients were eligible for the primary endpoint. Out of the 80 evaluable patients, 68 patients did not experience any PNS, while 12 patients experienced PNS.

The presence of PNS was successfully overcome in 10 out of 12 patients (Figure 2); therefore success for the primary analysis was met in 78 patients (78 patients out of 80, 97.5%) and the primary objective was reached (p = 0.01). The vector programming that overcame PNS is presented in Table 2.

The successful vectors were LV ring - RV coil in 8 patients (8/10, 80%), LV tip - LV ring in 1 patient (1/10, 10%), and LV tip - RV ring in 1 patient (1/10, 10%). In two patients, PNS couldn't be resolved at implant. Device programmed output was adjusted to a lower value and PNS was no longer reported at the follow-up 6 months later.

In the total population (n = 90), the final programmed LV vectors were LV tip - LV ring (37.1%), LV tip - RV ring (32.6%) and LV ring - RV coil (30.3%).

### 3.3. Deaths and Device- or Procedure-Related Adverse Events

During a mean follow-up duration of 226.3 ± 98.7 days, 7 cardiovascular deaths (7.8%) were reported with the following causes: septic shock, HF, cardiac arrest,

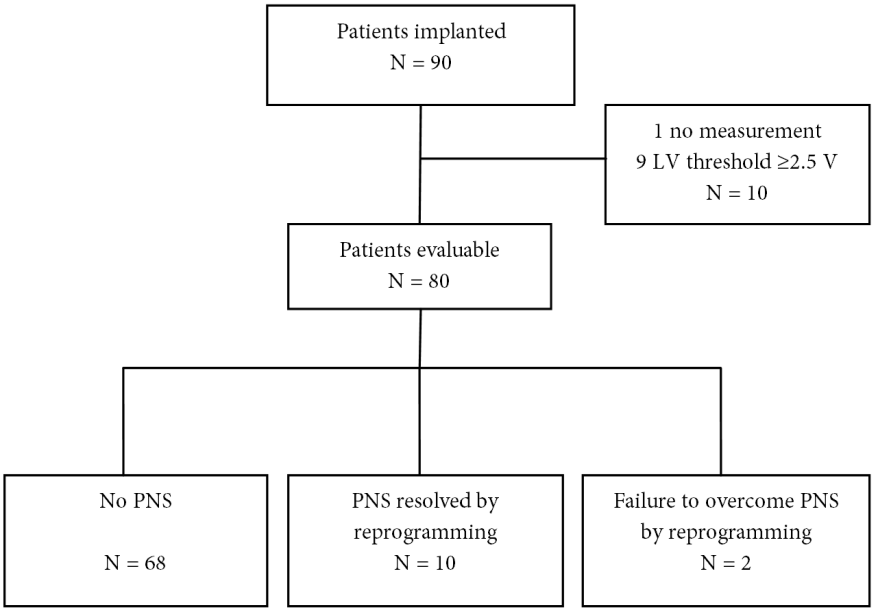


Figure 2. Flow diagram of patients for the primary objective of ORPHEE. LV—left ventricular, PNS—phrenic nerve stimulation.

**Table 2.** Reprogramming in patients with PNS at 7 V—primary objective (n = 80).

| Reprogramming in patients with PNS at 7V—Primary objective (n = 80) | | |
|---|---|---|
| Patient code | PNS threshold | Reprogramming success/failure |
| Center ANN4, #1 | 6.5 V | Success with vector LV ring - RV coil |
| Center ANT2, #2 | 1.0 V | Success with vector LV ring - RV coil |
| Center CRT1, #5 | 1.0 V | Success with vector LV ring - RV coil |
| Center CRT1, #10 | 1.0 V | Success with vector LV ring - RV coil |
| Center CRT1, #24 | 9.0 V | Success with vector LV ring - RV coil |
| **Center LRI1, #2** | **1.0 V** | **Failure** |
| Center MA12, #3 | 1.0 V | Success with vector LV ring - RV coil |
| **Center MPL9, #2** | **2.0 V** | **Failure** |
| Center NCY6, #7 | 3.0 V | Success with vector LV tip - LV ring |
| Center PRP2, #1 | 6.0 V | Success with vector LV ring - RV coil |
| Center PRP2, #3 | 3.0 V | Success with vector LV tip - RV ring |
| Center PRP2, #7 | 3.0 V | Success with vector LV ring - RV coil |

LV—left ventricular, PNS—phrenic nerve stimulation, RV—right ventricular.

intracerebral hemorrhage, cardiogenic shock, and two deaths of unknown cause. In addition, an inappropriate shock due to an atrial flutter conducting to the ventricles was reported 3 weeks after implant. Two dislodgements of an LV lead occurred, one resolved by repositioning and one reprogrammed in VVI.

## 4. Discussion

In this French, multicenter, observational study, PNS occurred in 15% of patients during CRT-D implant. In this observational setting, a bipolar lead with 3 pacing vector configurations avoided PNS in 97.5% of the patients.

PNS turns out to be a relevant issue for LV stimulation delivery as it has been reported in up to one third of CRT-D implant patients and may lead to inaccurate lead placement, lead repositioning, safety margin reprogramming, and ultimately CRT discontinuation in cases where no solutions can prevent the symptoms of PNS [9] [10] [11]. Due to the path of the left phrenic nerve, it is likely that phrenic stimulation is elicited through case by case adjustment of the pacing vector [12]. In this context, quadripolar leads, through multiple pacing vector possibilities, have been shown to efficiently deliver CRT-D therapy, while overcoming PNS. In different studies, almost all PNS was managed (99.7% to 100%) [13] [14]. Nevertheless, more electrodes might result in excessive lead stiffness, leading to reduced maneuverability [15]. In certain patients, difficulty in passing all 4 electrodes into coronary sinus tributaries with acute angulations and multiple bends was reported [7]. Moreover, in reality, quadripolar leads are most of the time programmed to pace using a bipolar configuration between the second and the third electrode. The proximal and the distal electrodes are not commonly used because of high pacing thresholds and PNS, respectively. A bipolar lead may have advantages in this situation.

In ORPHEE, bipolar leads avoided PNS in 97.5% of the patients at implant. This result is in the range of previously reported rates of PNS with bipolar leads, ranging from 1% [16] to 13% [17]. Therefore, bipolar leads remain a reliable and

suitable alternative in patients whose anatomy prevents multiple electrode implantation. It can also be noted that, among the 3 available pacing vectors, PNS was successfully addressed with the same programming (LV ring - RV coil) in 80% of patients, thus questioning the need to increase the number of pacing vectors in bipolar leads.

It is also noteworthy that not all PNS detected at implant with quadripolar leads can be resolved by reprogramming, with a need for repositioning during the implant. The systematic use of quadripolar leads should not obviate the need for proper PNS assessment during implant [18]. In addition, the multiplicity of electrodes leads to increased lead stiffness, which may impact lead longevity [15]. Finally, high left pacing thresholds were reported with quadripolar leads in a nonconventional configuration, which could significantly impact device longevity [18].

### Study Limitations

Our study included a relatively small number of patients, and reports data at implant only as all data were not readily available after implant.

## 5. Conclusion

Our study reveals a high rate of successful management of PNS with bipolar leads, at implant. These results advocate the pertinence of bipolar leads as a reliable and suitable alternative in patients whose coronary sinus anatomy prevents easy implantation of leads with multiple electrodes.

## Acknowledgements

We would like to thank the trial participants and investigators who made the study possible; Aline Chundydyal for her support in study management; Frédérique Maneval and Anne Rousseau-Plasse, PhD, for editorial assistance; and Françoise Tondu, for statistical support.

## Disclosures

The OPRHEE study was sponsored by LivaNova (Clamart, France). All authors received fees from LivaNova. Dr Lellouche has received consulting fees from Medtronic, Boston Scientific, St Jude, and LivaNova.

## References

[1] Brignole, M., Auricchio, A., Baron-Esquivias, G., Bordachar, P., Boriani, G., Breithardt, O.A., *et al.* (2013) 2013 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy. The Task Force on Cardiac Pacing and Resynchronization Therapy of the European Society of Cardiology (ESC). Developed in Collaboration with the European Heart Rhythm Association (EHRA). *European Heart Journal*, **29**, 2281-2329. https://doi.org/10.1093/eurheartj/eht150

[2] Biffi, M., Exner, D.V., Crossley, G.H., Ramza, B., Coutu, B., Tomassoni, G., *et al.* (2013) Occurrence of Phrenic Nerve Stimulation in Cardiac Resynchronization

Therapy Patients: The Role of Left Ventricular Lead Type and Placement Site. *Europace*, **15**, 77-82. https://doi.org/10.1093/europace/eus237

[3] Biffi, M., Bertini, M., Ziacchi, M., Gardini, B., Mazzotti, A., Massaro, G., *et al.* (2011) Management of Phrenic Stimulation in CRT Patients over the Long Term: Still an Unmet Need? *Pacing and Clinical Electrophysiology*, **34**, 1201-1208. https://doi.org/10.1111/j.1540-8159.2011.03147.x

[4] Biffi, M., Zanon, F., Bertaglia, E., Padeletti, L., Varbaro, A., De Santo, T., *et al.*, PING-EP Study Group (2013) Short-Spaced Dipole for Managing Phrenic Nerve Stimulation in Patients with CRT: The "Phrenic Nerve Mapping and Stimulation EP" Catheter Study. *Heart Rhythm*, **10**, 39-45. https://doi.org/10.1016/j.hrthm.2012.08.045

[5] Shetty, A.K., Duckett, S.G., Bostock, J., Rosenthal, E. and Rinaldi, C.A. (2011) Use of a Quadripolar Left Ventricular Lead to Achieve Successful Implantation in Patients with Previous Failed Attempts at Cardiac Resynchronization Therapy. *Europace*, **13**, 992-996. https://doi.org/10.1093/europace/eur032

[6] Shetty, A.K., Duckett, S.G., Bostock, J., Roy, D., Ginks, M., Hamid, S., *et al.* (2011) Initial Single-Center Experience of a Quadripolar Pacing Lead for Cardiac Resynchronization Therapy. *Pacing and Clinical Electrophysiology*, **34**, 484-489. https://doi.org/10.1111/j.1540-8159.2010.03003.x

[7] Nair, K. (2013) The Quadripolar Left Ventricular Lead: An Effective Alternative for Phrenic Nerve Stimulation. *Indian Pacing and Electrophysiology Journal*, **13**, 56-57. Editorial. https://doi.org/10.1016/S0972-6292(16)30604-0

[8] Brignole, M., Auricchio, A., Baron-Esquivias, G., Bordachar, P., Boriani, G., Breithardt, O.A., *et al.*, European Society of Cardiology (ESC), European Heart Rhythm Association (EHRA) (2013) 2013 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy: The Task Force on Cardiac Pacing and Resynchronization Therapy of the European Society of Cardiology (ESC). Developed in Collaboration with the European Heart Rhythm Association (EHRA). *Europace*, **15**, 1070-1118. https://doi.org/10.1093/europace/eut206

[9] Biffi, M., Moschini, C., Bertini, M., Saporito, D., Ziacchi, M., Diemberger, I., *et al.* (2009) Phrenic Stimulation: A Challenge for Cardiac Resynchronization Therapy. *Circulation: Arrhythmia and Electrophysiology*, **2**, 402-410. https://doi.org/10.1161/CIRCEP.108.836254

[10] Seifert, M., Schau, T., Moeller, V., Neuss, M., Meyhoefer, J. and Butter, C. (2010) Influence of Pacing Configurations, Body Mass Index, and Position of Coronary Sinus Lead on Frequency of Phrenic Nerve Stimulation and Pacing Thresholds under Cardiac Resynchronization Therapy. *Europace*, **12**, 961-967. https://doi.org/10.1093/europace/euq119

[11] Gurevitz, O., Nof, E., Carasso, S., Luria, D., Bar-Lev, D., Tanami, N., *et al.* (2005) Programmable Multiple Pacing Configurations help to Overcome High Left Ventricular Pacing Thresholds and Avoid Phrenic Nerve Stimulation. *Pacing and Clinical Electrophysiology*, **28**, 1255-1259. https://doi.org/10.1111/j.1540-8159.2005.00265.x

[12] Sanchez-Quintana, D., Cabrera, J.A., Climent, V., Farre, J., Weiglein, A. and Ho, S.Y. (2005) How Close Are the Phrenic Nerves to Cardiac Structures? Implications for Cardiac Interventionalists. *Journal of Cardiovascular Electrophysiology*, **16**, 309-313. https://doi.org/10.1046/j.1540-8167.2005.40759.x

[13] Behar, J.M., Bostock, J., Zhu Li, A.P., Chin, H.M., Jubb, S., Lent, E., *et al.* (2015) Cardiac Resynchronization Therapy Delivered via a Multipolar Left Ventricular

Lead Is Associated with Reduced Mortality and Elimination of Phrenic Nerve Stimulation: Long-Term Follow-Up from a Multicenter Registry. *Journal of Cardiovascular Electrophysiology*, **26**, 540-546. https://doi.org/10.1111/jce.12625

[14] Crossley, G.H., Biffi, M., Johnson, B., Lin, A., Gras, D., Hussin, A., *et al.* (2015) Performance of a Novel Left Ventricular Lead with Short Bipolar Spacing for Cardiac Resynchronization Therapy: Primary Results of the Attain Performa Quadripolar Left Ventricular Lead Study. *Heart Rhythm*, **12**, 751-758. https://doi.org/10.1016/j.hrthm.2014.12.019

[15] Ohlow, M.A., Lauer, B., Brunelli, M., Daralammouri, Y. and Geller, J.C. (2013) The Use of a Quadripolar Left Ventricular Lead Increases Successful Implantation Rates in Patients with Phrenic Nerve Stimulation and/or High Pacing Thresholds Undergoing Cardiac Resynchronisation Therapy with Conventional Bipolar Leads. *Indian Pacing and Electrophysiology Journal*, **13**, 58-65. https://doi.org/10.1016/S0972-6292(16)30605-2

[16] Goetze, S., Defaye, P., Bauer, A., Merkel, M., Bizeau, O., Treusch, S., ERACE Study Investigators, *et al.* (2013) Phrenic Nerve Stimulation in CRT Patients and Benefits of Electronic Lead Repositioning: The ERACE Trial. *Journal of Interventional Cardiac Electrophysiology*, **38**, 1-9. https://doi.org/10.1007/s10840-013-9811-9

[17] Klein, N., Klein, M., Weglage, H., Przibille, O., Fischer, S., Trappe, H.J., *et al.* (2012) Clinical Efficacy of Left Ventricular Pacing Vector Programmability in Cardiac Resynchronization Therapy Defibrillator Patients for Management of Phrenic Nerve Stimulation and/or Elevated Left Ventricular Pacing Thresholds: Insights from the Efface Phrenic Stim Study. *Europace*, **14**, 826-832. https://doi.org/10.1093/europace/eur412

[18] Moubarak, G., Bouzeman, A., Ollitrault, J., Anselme, F. and Cazeau, S. (2014) Phrenic Nerve Stimulation in Cardiac Resynchronization Therapy. *Journal of Interventional Cardiac Electrophysiology*, **41**, 15-21. https://doi.org/10.1007/s10840-014-9917-8