First interventional exchange of a left transvenous phrenic nerve stimulation lead from the novel remedē system

Klaus-Jürgen Gutleben MD1,2 | Thomas Eitz MD3 | Randy Westlund BS4 | Jan F. Gummert MD3,5 | Philipp Sommer MD, FEHRA1,5 | Henrik Fox MD, FHFA3,5

1Clinic for Electrophysiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany
2Medizinische Klinik III/Kardiologie, Klinikum Herford, Herford, Germany
3Clinic for Thoracic and Cardiovascular Surgery, Herz- und Diabeteszentrum NRW, Ruhr, Universität Bochum, Bad Oeynhausen, Germany
4Respicardia, Inc., Minnetonka, Minnesota, USA
5Heart Failure Department, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

Correspondence
Henrik Fox, MD, FHFA, Clinic for Thoracic and Cardiovascular Surgery, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Georgstr. 11, D-32545 Bad Oeynhausen, Germany.
Email: akleemeyer@hdz-nrw.de

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Abstract
The remedē system is a novel fully implantable transvenous phrenic nerve stimulation (TPNS) device developed to treat central sleep apnea. No information is published on how to explant or replace its leads. An eighty-one-year-old had a fractured lead and we removed it over a wire. However, unbreachable resistances occurred with a new lead deployed over the enclosed wire and interventional endovascular techniques were performed to reimplant a new fully functioning system. This first report demonstrates TPNS lead exchange is possible but can be challenging. Interventional maneuvers and techniques, including balloon angioplasty, can facilitate this procedure.

KEYWORDS
central sleep apnea, heart failure, lead exchange, lead extraction, lead fracture, phrenic nerve stimulation

1 | INTRODUCTION

Central sleep apnea (CSA) is a highly prevalent comorbidity in cardiovascular and heart failure patients and is associated with increased morbidity and mortality. Conventional CSA therapies, such as mask-based ventilation treatment, can alleviate symptoms and lead to positive outcomes, but are also associated with limitations of effectiveness due to restricted patient compliance and mask tolerance. In addition, contraindications exist for specific algorithms, such as adaptive-servoventilation in heart failure patients with reduced ejection fraction.

The novel remedē system® (Respicardia Inc.) was developed as a fully implantable transvenous phrenic nerve stimulation (TPNS) device to specifically treat moderate to severe CSA in adult patients. It consists of an impulse generator (IPG) and a stimulation lead, typically placed into the pericardiophrenic vein (PPV) that adjacently accompanies the left-sided phrenic nerve. From this transvenous position, the phrenic nerve can be stimulated.
Recently, Fox et al. demonstrated long-term efficacy and safety of TPNS 3 years postimplant.

Briefly, the target PPV is accessed from the left brachiocephalic vein via over-the-wire technique after insertion of a guiding catheter. Venography allows visualization of the stimulation lead as it is advanced to its desired position in the PPV. An optional sensing lead can be implanted into the azygos vein that is used to detect respiration via transthoracic impedance as previously described. However, to date, no information is available addressing explantation, replacement, or exchange of TPNS leads.

This is the first report to describe effective transvenous TPNS stimulation lead extraction, followed by reimplantation into the same PPV position, restoring effective continuous CSA treatment.

## 2  |  CASE REPORT

An 81-year-old female patient presented for IPG exchange due to battery depletion, 4 years after initial TPNS device implantation. This patient exhibited severe and highly symptomatic CSA and was diagnosed with heart failure, with high-grade reduced left ventricular ejection fraction (20%, heart failure with reduced ejection fraction [HFrEF]) and broadened QRS width (150 ms), secondary to dilated cardiomyopathy. She was treated with optimal guideline-derived heart failure medication and cardiac resynchronization therapy-defibrillator (CRTD) had been implanted before TPNS device. Despite receiving optimal treatment, this patient remained in symptomatic HFrEF, with shortness of breath and she suffered from severe symptomatic CSA. Moreover, she complained of mask intolerance and adaptive servoventilation was not an option as it is contraindicated in HFrEF with predominant CSA. Initial TPNS device implantation was then performed 4 years ago and pre-procedural sleep lab parameters of polysomnography are depicted in Table 1.

### 2.1  |  Primary implantation procedure and TPNS efficacy

A Biotronik Lumax 340 CRTD device was implanted 32 months before the TPNS device in the left pectoral region with transvenously placed right atrial, right ventricular dual shock coil, and bipolar coronary sinus leads. The initial TPNS device implantation was performed in the right pectoral area as previously described. TPNS stimulation lead (respistim LQS, Model 4055; Respiciardia Inc.) was positioned within the left PPV (Figure 1) and electrical testing revealed desired and effective phrenic nerve stimulation. An optional lead was not implanted in this case to avoid potential complications given this patient already had multiple leads implanted in both the left brachiocephalic vein and superior vena cava. The procedure lasted 120 min, required 28 min fluoroscopy time and 45 ml of contrast. The patient was discharged 2 days following the procedure and routine follow-up visits in our outpatient clinic were regularly scheduled. The patient had the TPNS device for more than 4 years and reported improved sleep, but also enhanced quality of life with TPNS treatment and clinical benefit represented in better daily activity and increased physical capacity.

### 2.2  |  IPG and stimulation lead exchange

Approximately 4 years following the initial implant and immediately before her biannual checkup the patient noticed a loss of therapy. The present remedi® system does not have an audible indicator of battery status, why battery depletion was assumed, and the patient was scheduled for device interrogation. During her follow-up, battery status beyond the end of life was detected, consequently no further diagnostics were possible. Promptly, the patient was scheduled for device replacement and intraoperatively the stimulation lead was tested and showed unanticipated high impedance suggesting lead fracture. Thus, now, this patient required an IPG exchange for battery exhaustion as well as TPNS lead revision.

Local anesthesia was applied and the IPG pocket was carefully reopened. After removal of the old IPG, the stimulation lead became immediately visible, and visual inspection disclosed apparent fracture of the lead (Figure 2). The lead was trimmed and a 0.014 Sion Blue ES wire (Asahi Intecc Co.) was introduced into the LQS lead. The wire passed through all the lead and distal portion of the PPV, through the inferior phrenic vein into the inferior vena cava (Figures 3A,B). Next, following subclavian vein puncture, a Lasso Snare (Amplatz Goose Neck, 30 mm; Medtronic) was inserted after subclavian vein puncture to catch the distal end of the Sion Blue wire and externalize it (Figure 3A). With control of both ends of the wire, the lead was extracted over the wire through the application of traction to the...
lead body. Deployment of a new quadripolar LQS lead (respistim 4065; Respicardia Inc.) was attempted by delivery over the enclosed wire (Figures 3A and 3E). However, unbreachable resistance occurred within the left brachiocephalic vein and the location was documented using fluoroscopy. Presumably fibrous scar tissue in combination with the previously implanted CRT-D leads, in particular the SVC coil of the shock lead, added to the constriction. Because the new lead could not be advanced, it was pulled back and removed from the guidewire. Additional maneuvers were necessary to prepare a path to reimplant a new lead. We utilized balloon angioplasty using conventional angioplasty balloons (2 mm × 20 mm, Solaric; Medtronic and 2.5 mm × 20 mm Pantera Pro; Biotronik) was employed and they were placed into the implied brachiocephalic vein position. The balloon was inflated to 16 bar pressure for 30 s in five nearby locations (Figure 3C). This resulted in opening access to the brachiocephalic vein, but a second constriction became apparent when reaching the PPV ostium. Balloon angioplasty was performed again, inflations were employed in this second position using a semicompliant balloon (2.5 mm × 20 mm Pantera Pro; Biotronik). The balloon was inflated inside the PPV ostium with 16 bar pressure for 30 s in three close-by locations to reopen the PPV ostium (Figure 3C). Subsequently, the new LQS lead passed all constrictions and was delivered into the targeted left PPV (Figure 3E). Stimulation testing demonstrated adequate phrenic nerve capture resulting in sufficiently strong diaphragmatic response, with no uncomfortable side effects or extra respiratory sensations. Concomitant device testing was performed with no interactions observed between the CRT-D and the TPNS devices. Also, the CRT-D device did not require any parametric changes following the TPNS device implant. Moreover, visual analysis of fluoroscopic images and a chest X-ray revealed no change to the CRT-D leads. The new IPG was connected to the new lead, placing the fully revised functioning system back into its device pocket.

The patient was discharged 2 days after the procedure, and she returned to her regular daily life. During recent follow-up visits, the patient reported complete restoration of therapeutic effectiveness as she had experienced during the initial period with the TPNS device. Clinical aspects and quality of life improved again, and the patient reported enriched sleep quality.

Overall procedural parameters are summarized as follows: Total procedure time: 124 min, fluoroscopy time: 13.9 min, and total use of contrast dye: 0 ml.

3 | DISCUSSION

This is the first report to describe the lead exchange of novel fully implantable TPNS therapy, using the remed® system (Respicardia Inc.). During the procedure, we demonstrate the need to use interventional techniques, as inaprocedural unanticipated vessel constrictions may otherwise have resulted in the termination of the procedure. Because experience with this new emerging therapeutic device in CSA treatment...
is scarce, providing information on solutions using surgical and interventional techniques will be helpful to other implanters.

TPNS is a promising and emerging new therapeutic approach to treat CSA and recently published 3-year data showed sustained safety and effectiveness of continuous TPNS therapy. However, implantable device-based therapies to treat sleep-disordered breathing are a new approach with limited experience in lead extractions and revisions. Reports documenting the challenges and difficulties of implantation as well as device maintenance from experienced centers are of particular value. Gutleben et al. recently reported on 29 TPNS procedures describing the practicalities and feasibility of using established intravascular intervention tools to enhance TPNS implantation success. In their study, angioplasty balloons and other vascular intervention, utensils helped to facilitate TPNS implantation in difficult cases when otherwise no placement would have been possible.

Regarding lead extractions, additional risks such as vessel injury, infection, and bleeding complications are feared that may result in immediate surgery. Vascular obstacles and constrictions are to be taken seriously but still may be resolvable. The main challenges include procedural hindrances that are not foreseen and the interventionalist suddenly has to deal with them during the running procedure. While there are some experience and learning objectives derived from CRT implantation procedures, phrenic nerve stimulation lead explantation and lead reimplantation in a previously implanted TPNS system have not been previously reported. The discriminating features of this case include lead exchange in small extracardiac veins that usually are not approached in the interventional world. Worley et al. describe technical details comprising wire stabilization to manage transvenous stimulation lead implantation into coronary sinus branches in CRT cases, not resulting in major complications. However, in contrast to coronary sinus anatomy, the left PPV typically is isodiametric, it branches from the brachiocephalic vein and accompanies the left heart silhouette. At the level of the diaphragm, it connects to the inferior phrenic vein that intraabdominally runs along with the diaphragm, draining into the inferior vena cava. Herein, vein diameters are larger compared to

![Fluoroscopic documentations from revision procedure with the guidewire captured by the snare (A), TPNS lead retraction, which also moves CRT-D leads towards the right brachiocephalic vein (B), balloon angioplasty within brachiocephalic (C), and pericardiophrenic (D) veins and final lead position of the new TPNS lead (E). CRT-D, cardiac resynchronization therapy-defibrillator; TPNS, transvenous phrenic nerve stimulation.](image-url)
coronary sinus branches. When snare techniques are used in TPNS lead placement, the distance to capture the through-the-lead wire is longer.

In addition, in our case, fibrous adhesions from the previously implanted TPNS lead as well as enclosed CRT lead associated scar tissue hampered prompt lead exchange. The practice of balloon angioplasty has been described to overcome fibrous adhesions during lead implantations in CRT, and we demonstrate adaption of these techniques for TPNS lead exchange.

An alternative, in this case, could have been to implant a right-sided TPNS stimulation lead. However, in this case, the patient already had three leads implanted for CRT, and then leaving in place the fractured left-sided TPNS lead, an additional right-sided TPNS stimulation lead would have numbered a total of five transvenous leads, bearing high complication risks, in particular infections. Such approaches should be avoided. In addition, an alternative right-sided stimulation lead has a helical shape and is placed in the upper portion of the superior vena cava. This location may interfere with the previously implanted CRT-D leads, resulting in possible loss of TPNS therapy and stimulation instability. Second, a right-sided lead requires more electrical energy, is associated with shorter battery longevity, and is less stable compared to the LQS lead due to its anatomical location. For these reasons, it may be profitable to pursue advanced techniques as reported in this unique case to primarily achieve PPV lead positioning.

Although technically more challenging, PPV stimulation lead exchange is feasible through wire stabilization using snare catheters, intravenous angioplasty maneuvers, or even stent implantations in selected cases in the context of transvenous lead implantations. As TPNS therapy for moderate to severe CSA becomes more prevalent, it will be important to document and share different interventional techniques to provide optimal and safe therapy.

4 CONCLUSION

TPNS lead exchange in the preferred left PPV position is possible but can be challenging. Interventional maneuvers and techniques, including balloon angioplasty as well as wire-based stabilization together with snare techniques, can facilitate this procedure, avoiding larger surgery and potential complications. Further data are needed to investigate other singularities of novel TPNS lead handling, including safety and therapy effectiveness.

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ORCID

Henrik Fox http://orcid.org/0000-0002-2187-8715

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