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# Methods of preventing phrenic nerve stimulation in patients with cardiac resynchronisation therapy

## Metody zapobiegania stymulacji nerwu przeponowego u chorych z wszczepionym układem resynchronizującym

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### Abstract

Cardiac resynchronisation therapy is an established therapy for patients with advanced heart failure, decreased left ventricular ejection fraction, a wide QRS syndrome, and the presence of left ventricular dyssynchrony despite optimal pharmacotherapy. The key feature for applied treatment is proper qualification and the optimal placing of left ventricular electrode implantation. The major issues that limit resynchronisation therapy are high left ventricle pacing threshold and phrenic nerve stimulation (PNS). PNS occurs in 30% of patients at implantation. In this paper, we present alternative methods of avoiding PNS based on the latest clinical trials and our own experience.

Key words: cardiac resynchronisation therapy, heart failure, phrenic nerve stimulation (PNS)

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## Introduction

Heart failure (HF) is one of the most common cardiovascular diseases in Europe and the United States. Despite significant advances in the diagnosis and treatment of the diseases that cause it, such as coronary artery disease and hypertension, the number of patients with HF is on the rise.

In Poland, its symptoms are estimated to occur in 700,000 to 1,000,000 patients, which is 2.5% of the general population: 2% of those aged 40–59 and more than 10% of people aged over 70 [1]. Despite the introduction of new pharmacological treatments, it is estimated that more than one million patients with HR require hospitalisation, of whom about 20% will need re-admission to hospital within one month of discharge, and up to 50% within six months. These patients are burdened with nearly 12% 30-day mortality, and up to 33% during 12 months follow-up. Sudden cardiac death (SCD) among patients with HR occurs 6–9 times more often than in the general population. Cardiac resynchronisation therapy (CRT) has an important place as a valuable supplement in the treatment of these patients in addition to optimal pharmacotherapy.

In 1994, researchers from two independent teams (Cazeau et al. from France and Bakker et al. from the Netherlands) described the beneficial effect of simultaneous biventricular stimulation in patients with left ventricular systolic dysfunction and prolonged QRS syndromes. Since then, there has been an unusually rapid development of cardiac electrotherapy as a treatment for HR in patients without indications for pacemaker implantation due to conduction abnormalities.

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## Resynchronisation therapy

According to the latest guidelines of the European Society of Cardiology (ESC), this form of therapy is indicated for patients with symptomatic HR in New York Heart Association (NYHA) functional classes II–IV despite optimal pharmacotherapy, with significant impairment of left ventricular systolic function [ejection fraction (EF) < 35%] and prolonged QRS syndrome (> 130 ms) against a background of intraventricular conduction abnormalities, while maintaining sinus rhythm [2]. In this group of patients, the beneficial effect of CRT on prognosis, improvement of quality of life, as well as reduction of HR symptoms expressed as a reduction in the frequency of hospitalisation due to HR, have been proved based on many randomised clinical trials [*e.g.* COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure), CARE-HF (Cardiac Resynchronization-Heart Failure)] [3, 4]. Disturbances in electrical activation in the heart with impaired systolic function may cause dyssynchronisation:

- atrioventricular — ineffective filling of the left ventricle and its delayed contraction in relation to the atrial contraction;
- interventricular — no simultaneous contraction of the right and left ventricles;
- intraventricular — desynchronous contraction of individual segments of the left ventricle muscle.

CRT works by restoring synchronous two-chamber stimulation through electrodes introduced into the heart through the venous system. The right ventricular pacing electrode with cardioversion/defibrillation function (CRT-D) is placed in the right ventricle apex or ventricular septum, depending on the sensing/pacing parameters. However, the key role in response to CRT is the introduction of the left ventricular electrode through the coronary sinus to the place with the greatest delay in electrical activation of the left ventricular muscle. This is usually the epicardial vein located on the posterior or lateral wall. This site can be located non-invasively by modern methods of echocardiography (Doppler tissue technique or speckle tracking imaging) or by nuclear magnetic resonance [5, 6]. The condition for successful stimulation of the left ventricular electrode in this area is the absence of a scar to ensure propagation of proper simulation parameters and pulse. Despite this, the successful implantation of the left ventricular electrode is additionally determined by several aspects such as [7]:

- operator experience;
- availability of different sets for coronary sinus intubation (various shapes and curves);
- availability of catheters for selective intubation of heart veins;
- possibility of widening the vein with angioplasty;
- ability to stabilise the electrode in the vein with a stent.

If the left ventricular electrode cannot be implanted through the coronary sinus, as an alternative an epicardial suture electrode may be used during cardiac surgery by lateral microthoracotomy or thoracoscopy [7]. This procedure is very rare in Poland. It is mainly caused by the occurrence of serious thromboembolic complications and a high risk of peri-electrodal bacterial endocarditis.

The percentage of resynchronisation stimulation is very important from a clinical point of view. Based on many multicentre studies, it has been proven that the higher the percentage of resynchronisation stimulation, the greater the benefit of the therapy. According to current recommendations, it is believed that the percentage of two-chamber stimulation should be as close as possible to 100%.

However, despite a large number of implantable resynchronisation systems and progressive experience, 20–30% of patients still do not respond to the therapy (non-responders). The success of the therapy depends on the proper selection of patients (clinical symptoms, low ejection fraction, duration of QRS syndrome with left bundle branch block (LBBB) morphology (class I recommendations according to ESC) and the features of dyssynchronisation of left ventricular contraction, but also on the presence of viable left ventricular myocardium with the latest electrical activation. In experienced centres, the effectiveness of this treatment is estimated at 93–95% [8]. The success of the procedure depends mainly on the variability of an individual's venous system anatomy and possible phrenic nerve stimulation (PNS). Perioperative complications are rare, but must be taken into consideration. Such possible complications include:

- coronary sinus dissection (2.1–3.3%);
- left-chamber electrode dislocation (4–13.6%);
- PNS (1.5–12%);
- infections (1.3–3.4%).

## Methods of preventing phrenic nerve stimulation

In patients after CRT implantation, the main problem limiting permanent two-chamber stimulation is the high threshold for left-ventricular electrode stimulation and phrenic nerve stimulation. In this paper, we are focusing on different methods of phrenic nerve stimulation avoidance. Sensing, pacing threshold (*i.e.* the lowest voltage causing effective left ventricular contraction), and PNS threshold are assessed in patients after left ventricular electrode placement [9]. After successful CRT implantation, it has been noted that approximately one third of patients have PNS [10].

The first way to avoid this is to reposition the left ventricular electrode, which extends the duration of the procedure, and is possible only with appropriate epicardial vein anatomy.

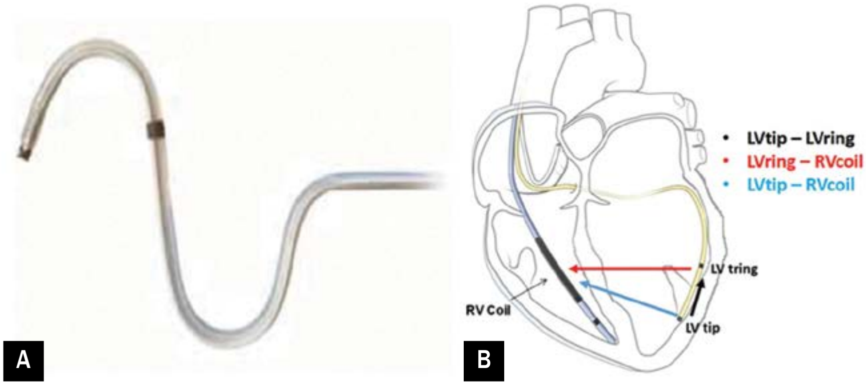


**Figure 1A**, **B.** Left ventricular bipolar electrode — available stimulation vectors (1. LVtip–LVring; 2. LVring–RVcoil; 3. LVtip–RVcoil); LV — left ventricle; RV — right ventricle)

The second alternative method for bipolar electrodes is electrode polarisation reprogramming — stimulation vectors (Figure 1). Thanks to this, we have the option to programme different ventricular muscle stimulation vectors in these electrodes. We are always looking for a suitable vector that causes effective resynchronisation stimulation in the absence of PNS. The basic stimulation vector is the one in which an electrical impulse is delivered from the tip to the left ventricular electrode ring (LVtip–LVring). Thanks to this, we get bipolar stimulation at the very tip of the electrode which minimises the risk of PNS. The second vector is stimulation between the left ventricular electrode tip (LVtip) and the right ventricular electrode ring (RVring). The third and last available stimulation vector to check is the stimulation between the left-cell electrode ring (LVring) and the right-cell electrode coil (RVcoil). Changing the polarity of the left ventricular electrode to avoid PNS was the purpose of the **ORPHEE (Bipolar Leads for Prevention of Phrenic Nerve Stimulation)** study [11]. This multicentre observational study was conducted in France in 2012–2015. It included 90 patients who met the criteria for CRT-D implantation [91% — primary prevention of SCD; 9% secondary prevention of SCD (83.3% *de novo* implantation, 16.7% — systemic extension)]. The mean age of patients was: 70.2 ± 8.9 years, mean EF 28.0% ± 5.5%, mean follow-up 226.3 ± 98.7 days. After placing the left ventricular electrode in the epicardial vein (stable stimulation threshold < 2.5 V), the occurrence of phrenic nerve stimulation was assessed. No PNS stimulation was defined as no PNS at a threshold > 7 V, or no PNS after changing the polarity of the LV electrode. The aim of the study was to show that changing the polarisation of the LV electrode (LVtip–LVring, LVtip–RVring, LVring–RVcoil) prevents the occurrence of PNS in at least 90% of patients. Of all patients included in the study, 10 patients were withdrawn from the study: nine due to the high threshold of LV electrode stimulation > 2.5 V, and one due to the lack of a PNS test. Eventually, 80 patients were enrolled in the study, of whom 12 (15%) had phrenic nerve stimulation. In only 10 out of 12 patients was a change in electrode polarity associated with a lack of PNS [LVring–RVcoil: eight patients (8/10, 80%); LVtip–LVring: one patient (1/10, 10%); LVtip–RVring one patient (1/10, 10%)]. In the entire study population (n = 90), the finally programmed LV electrode stimulation vectors were as follows: LV vectors were LVtip–LVring (37.1%), LVtip–RVring (32.6%), and LVring–RVcoil (30.3%). The authors of the study emphasised that after implantation of CRT-D, PNS occurred in 15% of patients. In nearly all of the patients (78/80, 97.5%) PNS could be avoided by changing the left ventricular electrode stimulation vector alone. In patients whose heart vein anatomy prevents four-pole electrode implantation, bipolar electrode implantation is a suitable and reliable alternative.

The third and final way to avoid PNS during CRT implantation is to use a quadripolar electrode during the procedure. This solution was evaluated in a multicentre study with the acronym **EffaceQ (Effectiveness and Reliability of Selected Site Pacing for Avoidance of Phrenic Nerve Stimulation in CRT Patients with Quadripolar LV Leads)** [12], in which 344 patients were enrolled. The aim of the study was to demonstrate that in at least 90% of patients with an implanted quadripolar electrode, changes in electrical pulse polarity in the absence of phrenic pacing (LV ≤ 2.5 V/0.5 ms) are effective in lowering the left ventricular pacing threshold. The results showed that PNS stimulation was present in 65.0% of patients during CRT implantation. Reprogramming of the left ventricle electrode polarity was performed in 49.8% of patients. PNS was assessed to decrease from distal to proximal ring stimulation, while LV stimulation thresholds increased from distal to proximal ring. The conclusions emphasised that the change in polarity of the quadripolar left ventricular

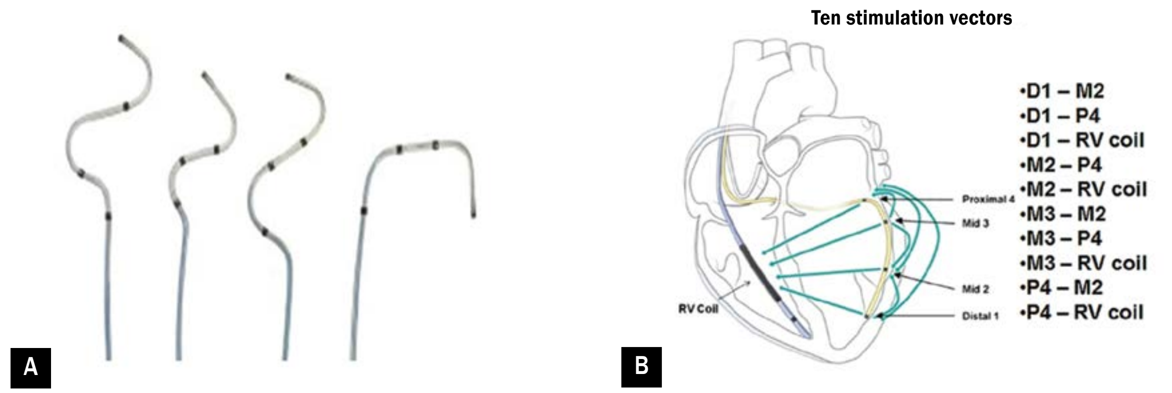


**Figure 2A, B.** Quadripolar left ventricular electrode — available stimulation vectors (1. D1–M2; 2. D1–P4; 3. D1–RVcoil; 4. M2–P4; 5. M2–RVcoil; 6. M3–M2; 7. M3–P4; 8. M3–RVcoil; 9. P4–M2; 10. P4–RVcoil); D — distal; M — mid; P — proximal; RV — right ventricle

electrode is an alternative to non-invasive repositioning of LV stimulation to avoid PNS.

Currently, each of the CRT manufacturers offers such electrodes. They differ in diameter, shape, length, arrangement of stimulation rings, and the place of steroid release in order to prevent the phenomenon of increasing stimulation's threshold. These electrodes increase the chance of successful stimulation of the left ventricular muscle even in a case of slight dislocation. This requires changing the settings of the stimulation vector, which, depending on the manufacturer, can be from 10 (Figure 2B) to as much as 17 [13]. Then, no further treatment to reposition the electrode is required. This extends the time of the procedure, associated with the time to look for the optimal vector for effective left ventricular muscle stimulation and the lack of PNS. Many registries have shown lower mortality in patients with CRT using a quadripolar electrode compared to a bipolar electrode [9]. The use of quadripolar electrodes significantly reduces the percentage of patients in whom left ventricular stimulation causes PNS. In addition, a large area of the stimulation ring, ranging from 16 to 64 mm depending on the manufacturer, causes no difference in response to electrotherapy between patients with ischaemic and non-ischaemic aetiology of chronic HF. This suggests improved response to CRT therapy in patients after myocardial infarction [14]. An additional advantage of quadripolar electrodes is the possibility of using multipoint stimulation with one electrode. This is particularly important in patients with areas of myocardial necrosis that significantly impair the propagation of electrical impulses, thus inhibiting synchronous contraction of the left ventricle. In this case, the use of multipoint stimulation with a quadripolar electrode allows stimulation of the myocardial areas with a sequential/simultaneous pulse that would not be possible with the use of one stimulation pulse. Multipoint stimulation covering a larger area of the left ventricle causes earlier stimulation of the places with the latest electrical activation, which results in improved synchronisation of contraction and increased cardiac output.

In the electrocardiogram, this is manifested by narrowing of the stimulated QRS complexes. Due to such advanced techniques, it is believed that multipoint stimulation in certain groups of patients may cause inverted left ventricular remodelling. In addition, multipoint stimulation gives a chance to improve the haemodynamic response, and hence the prognosis, in patients who did not achieve the expected effects of current dual-chamber stimulation. However, some studies do not explicitly confirm the advantage of this stimulation method over current CRT stimulation [15].

## Summary

Resynchronisation therapy is a well-recognised method of chronic HF treatment, especially in patients who show no clinical improvement despite optimal pharmacological treatment.

The biggest challenge for the operator is implantation of the left ventricular electrode through the heart system. The success of this procedure is hindered by the variability of the anatomy of the heart's venous system and the increasingly more common PNS. Modern technology allows the use of left-ventricular electrodes: bipolar and quadripolar, together with the variable polarity of the stimulation vector to avoid PNS. This has a positive effect on improving the effectiveness of electrotherapy, while minimising the risk of complications and the need for subsequent treatments.

## Streszczenie

Terapia resynchornizująca serca jest uznaną metodą leczenia chorych z zaawansowaną niewydolnością serca, obniżoną frakcją wyrzutową lewej komory, szerokim zespołem QRS i obecnością dyssynchronii skurczu lewej komory mimo optymalnej farmakoterapii. Właściwa kwalifikacja oraz optymalne miejsce implantacji elektrody lewokomorowej mają kluczowe znaczenie w odpowiedzi na zastosowane leczenie. Głównymi problemami, które ograniczają terapię resynchronizującą, są wysoki próg stymulacji elektrody lewokomorowej oraz stymulacja nerwu przeponowego (PNS). Stymulacja nerwu przeponowego występuje nawet u 30% chorych. W niniejszej pracy przedstawiono alternatywne metody unikania PNS na podstawie najnowszych badań klinicznych oraz własnego doświadczenia.

Słowa kluczowe: terapia resynchronizująca serca, niewydolność serca, stymulacja nerwu przeponowego (PNS)

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