

# Safety and efficacy of His bundle pacing validated by extracardiac vagal nerve stimulation (HIS-STORY)

Krystian Josiak<sup>1,2</sup>, Sebastian Stec<sup>3</sup>, Dorota Zyśko<sup>1</sup>, Bartosz Skonieczny<sup>1</sup>, Jarosław Kosior<sup>4</sup>, Janusz Śledź<sup>4</sup>, Antoni Wileczek<sup>3</sup>, Edyta Stodółkiewicz-Nowarska<sup>5,6</sup>, Bartosz Biel<sup>1</sup>, Paweł Szymkiewicz<sup>1</sup>, Przemysław Skoczyński<sup>1</sup>, Dariusz Karbarz<sup>4</sup>, Bartosz Ludwik<sup>7</sup>, Waldemar Banasiak<sup>1</sup>, Dariusz Jagielski<sup>1</sup>

<sup>1</sup>Cardiology Department, 4<sup>th</sup> Military Hospital, Wrocław, Poland

<sup>2</sup>Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland

<sup>3</sup>Subcarpathian Center for Cardiovascular Intervention, Sanok, Poland

<sup>4</sup>Cardiology Department, Mazovian Speciality Hospital, Radom, Poland

<sup>5</sup>CardioMedicum, Krakow, Poland

<sup>6</sup>Department of Interventional Cardiology, Cardiovascular Center, American Heart of Poland, Chrzanow, Poland

<sup>7</sup>Department of Cardiology, Regional Specialist Hospital Center for Research and Development, Wrocław, Poland

## Background

Growing interest in His bundle pacing (HBP) is being seen worldwide. HBP is an attractive option for permanent cardiac pacing as it maintains a physiological pattern of ventricular activation and thus may prevent the development of right ventricular pacing-induced cardiomyopathy. The permanent HBP procedure has a two-decade track record and has been refined and improved along the way [1]. However, despite general optimism on 'physiological pacing', concerns about the performance, safety, and clinical benefits of HBP still exist. In the 2021 European Society of Cardiology (ESC) guidelines on cardiac pacing an abstaining prevails and there is no first-class recommendation with HBP as first-line therapy [2].

Hypothesized herein, that in a situation of vagal surge some patients with HBP may be endangered by loss of capture due to parasympathetic influence on His-Purkinje system (HPS). For this group of patients a change to left bundle branch pacing, which is usually not selective, thereby assuring direct ventricular myocardium stimulation,

or implantation of the back-up right ventricular electrode may be necessary. Another reasonable approach, based on a relatively novel therapeutic technique — cardioneuroablation (CNA), i.e., percutaneous radiofrequency ablation of the parasympathetic ganglionated plexi of the heart [3]. The implementation of extracardiac vagal nerve stimulation (ECANS) and recently introduced ultrasound-guided ECANS (US-ECANS) enables validation of impact of right and left vagal nerve stimulation on parameters of automaticity and conduction [4]. Although, ECANS is associated with sinus asystole or atrioventricular (AV) block during atrial pacing, the incidence of vagally mediated HBP exit block and changes in pacing threshold have not been investigated.

To test the present hypothesis it was decided to conduct a study on the effects of ECANS on pacing parameters in patients with permanent HBP [5]. The aim of this clinical investigation is to assess efficacy of HBP during strong activation of parasympathetic system. As ECANS is a novel, non-standardized diagnostic method, another aim of the study is an assessment of effects of left-

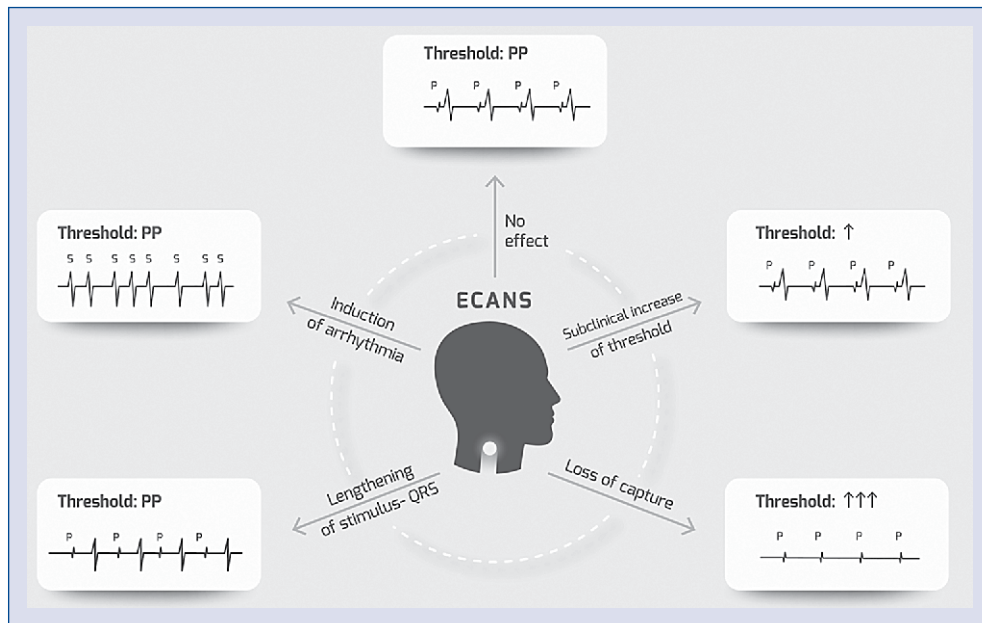
**Address for correspondence:** Krystian Josiak, MD, PhD, Center for Heart Diseases, 4<sup>th</sup> Military Hospital, ul. Rudolfa Weigla 5, 50–981 Wrocław, Poland, tel: +48 261660223, +48 516625985, e-mail: krystian85@hotmail.com

Received: 24.03.2022

Accepted: 27.05.2022

Early publication date: 9.06.2022

This article is available in open access under Creative Commons Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.



**Figure 1.** Possible effects of vagus nerve stimulation on His bundle pacing and underlying heart rhythm; ECANS — extracardiac autonomic (vagal) nerve stimulation; PP — permanently programmed values; ↑ — increase of threshold below PP; ↑↑↑ — increase of threshold above PP.

versus right-sided ECANS on underlying rhythm and/or HBP parameters.

### Methods

HIS-STORY is an investigator-initiated, prospective, multicenter, randomized, interventional clinical study. All the measured parameters, as well as demographic and clinical data will be recorded in the study database. All patients will provide an informed consent form. Patients with indications for permanent pacing, according to the latest ESC guidelines, will be enrolled. All participants will undergo permanent pacemaker implantation for HBP. Subsequently, an invasive electrophysiological study (EPS) and ECANS will be performed under general anesthesia. The study will recruit patients with existing HBP systems and also those in whom a HBP device will be implanted just before the EPS/ECANS procedure. ECANS can be performed from right or left interior jugular vein (IJV) at two levels: at the level of jugular foramen (superior ECANS) or at the level of the angle of mandible (inferior ECANS). Superior ECANS can be fluoroscopy-guided only, however inferior ECANS can be guided by fluoroscopy, ultrasound (US) or both. This study has a factorial design and 2×2 randomization and will be performed thus: patients will be randomized to begin superior ECANS

from the right or left IJV; a second randomization will assess the feasibility of the US-guided inferior ECANS. Patients will be randomized into two groups, blinded to the main operator; to undergo US-guided inferior ECANS or to undergo sham US-guidance. During ECANS, pacing parameters will be tested using a dedicated programmer and will be compared with baseline values. Possible effects of ECANS are depicted in the Figure 1. Patients with an exit block or an increase in a pacing threshold of an HBP electrode will be further managed by electrophysiologists from the research group. The management will be based on clinical relevance and shared decision making with the patient and may involve observation, pacemaker reprogramming, pacemaker upgrade with a backup pacing electrode implantation, or cardioneuroablation. Moreover, additional substrates for supraventricular and ventricular arrhythmias will be managed according to shared decision-making with the patient. Ablations for any arrhythmias will, however, be performed only if they will be clinically justified and indicated by the current ESC guidelines. Study protocol was approved by the Local Bioethical Committee and is registered on clinicaltrials.gov (NCT04816864; <https://clinicaltrials.gov/ct2/show/NCT04816864>). Enrollment began on January 02, 2021, and the study was registered on March 25, 2021.

**Table 1.** Inclusion and exclusion criteria for the HIS-STORY study.

Inclusion criteria	Exclusion criteria
Signed informed consent form	Age below 18 years
Age of 18 years or older	Contraindications to invasive electrophysiology study
Effective and stable His bundle pacing	Contraindications to general anesthesia
Sinus rhythm during the intervention procedure	Contraindications to atropine administration (e.g., glaucoma)
	Persistent atrial fibrillation or atrial flutter
	Pregnancy
	Diseases that may cause autonomic system neuropathy
	Use of medications that may affect the parasympathetic system
	A history of cardiac surgery
	A history of ablation due to arrhythmia

### Study population

The target study population is 60. Inclusion and exclusion criteria are shown in Table 1.

### Intervention

The study intervention will consist of three steps, all of which will be performed under general anesthesia:

- EPS with the measurement of parameters of AV conduction and programmed atrial and/or ventricular pacing;
- ECANS of the right and the left vagus nerve (from the right and left IJV, respectively; patients will be randomized to begin ECANS from either the right or the left side) performed during: 1) the patient’s spontaneous heart rhythm (if present); 2) HBP with permanently programmed impulse parameters; 3) HBP at a pacing threshold of +0.1 V; and 4) 5 min after intravenous injection of atropine (0.02–0.04 mg/kg);
- EPS with the measurement of parameters of AV conduction and programmed atrial and ventricular pacing.

### ECANS

A steerable quadripolar catheter will be inserted through the right femoral vein and advanced under fluoroscopic guidance to the right and left jugular vein at the level of the jugular foramen. The tip of the catheter will be directed medially and 5 s of stimulation with square wave pulsed of 50  $\mu$ s at a frequency of 50 Hz and amplitude of 0.5 to 1.0 V/kg (max: 70 V) will be delivered. Subsequently the catheter will be pulled back under fluoroscopic guidance so that the tip will be at level of the angle of mandible (inferior ECANS). In accordance with prior randomization the US operator will guide the main operator to place

the tip near the vagus nerve or only pretend to do so. Timing of the ECANS will be at the discretion of the US operator, so that the main operator will stay blinded for sham or US-guided ECANS. In patients with subclavian, vena cava superior or IJV thrombosis associated with the lead detailed imaging and clinical management will be performed and ability to cannulate IJV will be recorded.

### Endpoints

- Primary outcome measures:
- Loss of HBP capture or significant increase in pacing threshold, i.e., above the permanently programmed impulse amplitude of HBP electrode induced by ECANS.
- Secondary outcome measures:
- A nonsignificant increase in pacing threshold, that is, below the permanently programmed impulse amplitude of HBP electrode induced by ECANS;
  - Prolongation of the stimulus–QRS interval during HBP induced by ECANS;
  - Any arrhythmia induced within 30 s after ECANS.

### Statistical analysis

For statistical analysis Statistica (Statsoft Polska, Krakow, Poland) software will be used.

The continuous variables will be presented as means and standard deviations or medians and interquartile ranges due to their distribution and compared with the Student t-test or the Mann-Whitney U test. Discrete variables will be presented as numbers and percentages and compared with the  $\chi^2$  test.

The presented outcomes will be assessed as to their presence or absence. The logistic regres-

sion analysis and classification and regression trees analysis will be performed to find factors associated with the outcomes. The models will be constructed using variables which differ in univariate analysis with  $p < 0.15$  or clinically significant.

The multivariable analysis will be performed for the continuous dependent variables.  $P$  less than 0.05 will be considered as significant.

## Discussion

It has been shown that hyperactivity of the parasympathetic system might induce AV conduction disturbances. Zyśko et al. [6] analyzed electrocardiographic characteristics of AV conduction abnormalities induced by neurocardiogenic reflex during tilt-testing and found AV blocks in 3.9% of patients. Taking into account that even 40% of the general population experiences at least one episode of syncope during their life and that about 20% of all syncopes are reflex syncope, vagally mediated functional AV block does not seem to be an uncommon clinical condition [7]. Moreover, excessive vagal tone has been shown to be responsible not only for transient but also for some permanent AV block cases [4]. Therefore, some patients with indications for permanent cardiac pacing who have received the HBP may actually have vagally mediated functional AV conduction abnormalities. Although the impact of ECANS on sinus and AV node electrophysiological properties is well-known, the incidence of functional, vagally mediated reflexes on HPS remain unexplained [8]. In the literature, however, plenty of evidence on vagal innervation and influence on ventricular tissue exists [9, 10]. Similar prospective studies have been performed, however they were assessing the impact of ECANS on the conduction system and electrophysiological properties inferior or superior to HPS [11, 12]. Therefore, the present study might provide new insight into our knowledge of parasympathetic innervation of the conduction tissue. Moreover, some clinically important hypothesis will be tested, as aforementioned remarks raise suspicion that in some patients, vagal surge might be strong enough to hyperpolarize conduction tissue below the AV node level, thereby causing an acute increase in the capture threshold and even exit block. Such patients are in danger of transient loss of ventricular pacing.

## Limitations of the study

Iatrogenic high parasympathetic tone induced by vagal nerve stimulation might never be experienced

by the patient in natural, real-life circumstances, thereby increases in pacing thresholds or loss of capture may not necessarily be clinically important.

**Conflict of interest:** Sebastian Stec: author of several patents and shareholder of Medicine S.A. No specific product of the company will be used in this study. All other authors have no conflict of interest to declare.

## References

1. Deshmukh P, Casavant D, Romanyshyn M, et al. Permanent, direct His-bundle pacing. *Circulation*. 2000; 101(8): 869–877, doi: [10.1161/01.cir.101.8.869](https://doi.org/10.1161/01.cir.101.8.869).
2. Glikson M, Nielsen J, Kronborg M, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2021; 42(35): 3427–3520, doi: [10.1093/eurheartj/ehab364](https://doi.org/10.1093/eurheartj/ehab364).
3. Pachon JC, Pachon EI, Pachon JC, et al. „Cardioneuroablation”-new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. *Europace*. 2005; 7(1): 1–13, doi: [10.1016/j.eupc.2004.10.003](https://doi.org/10.1016/j.eupc.2004.10.003), indexed in Pubmed: [15670960](https://pubmed.ncbi.nlm.nih.gov/15670960/).
4. Wileczek A, Polewczyk A, Kluk M, et al. Ultrasound-guided imaging for vagus nerve stimulation to facilitate cardioneuroablation for the treatment of functional advanced atrioventricular block. *Indian Pacing Electrophysiol J*. 2021; 21(6): 403–406, doi: [10.1016/j.ipej.2021.06.008](https://doi.org/10.1016/j.ipej.2021.06.008), indexed in Pubmed: [34186197](https://pubmed.ncbi.nlm.nih.gov/34186197/).
5. Pachon MJC, Pachon MEI, Santillana P TG, et al. Simplified method for vagal effect evaluation in cardiac ablation and electrophysiological procedures. *JACC Clin Electrophysiol*. 2015; 1(5): 451–460, doi: [10.1016/j.jacep.2015.06.008](https://doi.org/10.1016/j.jacep.2015.06.008), indexed in Pubmed: [29759475](https://pubmed.ncbi.nlm.nih.gov/29759475/).
6. Zyśko D, Gajek J, Koźluk E, et al. Electrocardiographic characteristics of atrioventricular block induced by tilt testing. *Europace*. 2009; 11(2): 225–230, doi: [10.1093/europace/eun299](https://doi.org/10.1093/europace/eun299), indexed in Pubmed: [18987129](https://pubmed.ncbi.nlm.nih.gov/18987129/).
7. Aksu T, Guler TE, Bozyel S, et al. Potential usage of cardioneuroablation in vagally mediated functional atrioventricular block. *SAGE Open Med*. 2019; 7: 2050312119836308, doi: [10.1177/2050312119836308](https://doi.org/10.1177/2050312119836308), indexed in Pubmed: [30906551](https://pubmed.ncbi.nlm.nih.gov/30906551/).
8. Stec S, Dobaj Ł, Śledź A, et al. Cardioneuroablation for management of cardioinhibitory vasovagal syncope and pacemaker complications. *HeartRhythm Case Rep*. 2020; 6(8): 531–534, doi: [10.1016/j.hrcr.2020.04.021](https://doi.org/10.1016/j.hrcr.2020.04.021), indexed in Pubmed: [32817835](https://pubmed.ncbi.nlm.nih.gov/32817835/).
9. Tsun L, Chow LT, Chow SS, et al. Autonomic innervation of the human cardiac conduction system: changes from infancy to senility—an immunohistochemical and histochemical analysis. *Anat Rec*. 2001; 264(2): 169–182, doi: [10.1002/ar.1158](https://doi.org/10.1002/ar.1158), indexed in Pubmed: [11590594](https://pubmed.ncbi.nlm.nih.gov/11590594/).
10. Coote JH. Myths and realities of the cardiac vagus. *J Physiol*. 2013; 591(17): 4073–4085, doi: [10.1113/jphysiol.2013.257758](https://doi.org/10.1113/jphysiol.2013.257758), indexed in Pubmed: [23878363](https://pubmed.ncbi.nlm.nih.gov/23878363/).
11. A Study to Evaluate the Effect of Vagus Nerve Stimulation in Patients Undergoing VT Ablation [ClinicalTrials.gov Identifier: NCT04359004](https://clinicaltrials.gov/ct2/show/study/NCT04359004).
12. Stec S, Jankowska-Polańska B, Jagielski D, et al. Rationale and design of SAN.OK\_1 randomized controlled clinical trial and registry: Comparison of Early vs Late Permanent Pacemaker Implantation and Cardioneuroablation in Sinus Node Dysfunction. [ClinicalTrials.gov Identifier: NCT05196126](https://clinicaltrials.gov/ct2/show/study/NCT05196126).