

**Study protocol:**

**Low-Level Transcutaneous Electrical Vagus Nerve  
Stimulation to Suppress Atrial Fibrillation**

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## **Abbreviations**

AF	Atrial Fibrillation
CABG	Coronary Artery Bypass Grafting
CI	Claudicatio Intermittens
PAOD	Peripheral Artery Occlusive Disease

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## 1 Scientific Background

Nearly 30% of patients undergoing coronary artery bypass grafting (CABG), 40% of patients undergoing valvular heart surgery and over 50% of patients with combined coronary and valvular procedures develop atrial fibrillation (AF) [1].

Postoperative AF occurs mostly due to conditions like chronic kidney diseases, emergency surgery, age >75 years, cardiopulmonary bypass time >180 min and due to lacking postoperative application of aldosterone- and beta-blockers [2].

An overview of pre- intra- and postoperative risks for AF is listed in Table 1: Pre-, intra-, postoperative risks for AF [1].

Preoperative	Intraoperative	Postoperative
High age	Endotracheal tube insertion	Return to intensive care unit
Male gender	Intraoperative IABP	Ventilation longer than 24 hours
Previous cardiac surgery	Left ventricular venting	Volume overload
Valvular heart disease	Aortic cross-clamp time	Pneumonia
Chronic lung disease	Extracorporeal circulation	Electrolyte imbalances
Chronic renal failure	Myocardial ischemia	Imbalance of auton. nervous system
Left atrium enlargement	Venous cannulation	Atrial extrasystole
Left ventricular hypertrophy	Damage to the atrium	Increased postop adrenergic status
Withdrawal of beta-blocker medication	Excess inotropic requirements	Increased afterload
History of AF Hypertension	Acute volume change	Inflammation
Obesity		Hypotension
Diabetes		
Metabolic syndrome		

**Table 1: Pre-, intra-, postoperative risks for AF [1]**

Several theories describe the emergence of AF like “multiple-wavelet re-entry”, “focal mechanism” and “mother rotor” but the exact underlying mechanisms are still not well understood [1].

Prevention and treatment of postoperative AF are managed with conservative medication therapies including e.g. beta-blockers and other clinical interventions include radio frequency catheter ablation, cardioversion and occlusion of the left atrial appendage [3].

A novel approach for suppression of AF utilizing low-level transcutaneous electrical vagus nerve stimulation has been described recently in the Journal of the American College of Cardiology [4]. The newly developed “DUCEST Neurostimulator V” device (manufactured by Biegler Medizinelektronik GmbH Mauerbach, Austria) offers similar action as in [4]. This Neurostimulator device is designed to emit small direct current electrical pulses (0-1,2mA) to stimulate the R.auricularis of the vagus nerve located at the Fossa triangularis. The target population are patients with de-novo postoperative AF. The stimulation is achieved with the attachment of two needle-electrodes and connection of the electrodes to the Neurostimulator.

Following the stimulation of the vagus nerve positive effects were already achieved in chronical wound healing, peripheral artery occlusive disease (PAOD), Claudicatio intermittens (CI) and chronic pain patients [5][6][7][8].

## **2 Aim of the project**

The current study will evaluate the potential of stimulating the R.auricularis of the vagus nerve located at the Fossa triangularis to ameliorate or suppress AF in the study population.

## **3 Study population**

The target population are patients with de-novo postoperative AF who underwent bypass operation and/or aortic valve replacement.

### **3.1 Inclusion Criteria**

- De-novo postoperative AF
- CABG or aortic valve replacement
- Age of 18-80 years
- Willing and able to understand, sign and date the informed consent form that has been approved by the institutional review board

### **3.2 Exclusion Criteria**

- Pacemaker or ICD
- Impaired EF < 30%
- Patients with acute myocardial infarction within the past 14 days
- Pregnant or lactating patients
- Any condition that, in the judgement of the investigator, would place the patient at undue risk
- Any concurrent disease or condition that, in the opinion of the investigator, would make the subject unsuitable for participation in the study
- Treatment and/or an uncompleted follow-up treatment of any investigational therapy within 6 months before procedure and intent to participate in any other investigational drug or cell therapy study during the follow-up period of this study
- Active participation in other research therapy for cardiovascular repair/regeneration

## **4 Methods**

Patients are randomized to a treatment or a sham group. The corresponding device is prepared by a third person according to the double-blind setting for the surgeon. The DUCEST Neurostimulator V needle-electrodes are applied post-operatively to stimulate the R.auricularis of the vagus nerve located at the Fossa triangularis. Connecting the needle-electrode cables to the Neurostimulator V activates the device. (The stimulation intensity can be adjusted from 0,05mA to 1,2mA, default value is 0,4mA). The starting stimulation intensity will be adjusted to 1mA and takes place at 1Hz continuously for 40 minutes, followed by a 20 minute break. The built-in 3V battery lasts for approx. 14 days. After 7 days the electrodes are replaced and applied to the other ear of the patient. A plaster with a plastic mounting clip is attached on the shoulder of the patient. The Neurostimulator is connected to the mounting clip. After 14 days or at hospital discharge of the patient, the device is unmounted and the needle-electrodes are removed.

## **5 Benefit of study**

Postoperative AF is a significant morbidity in cardiac surgery which is associated with decreased survival in the long term. Even a slight decrease in postoperative AF is highly desirable. Our goal is to evaluate if the DUCEST Neurostimulator V is a safe and effective alternative to current treatment options for AF.

## **6 Risk of study**

Possible local inflammation at needle-electrodes during prolonged use (>7d)

## **7 Investigational Procedure**

Patients will be randomized double-blind into a treatment and sham group. Each group will consist of 20 Patients (please see "9 Statistical Analysis"). The follow-up covers the post-op hospital stay (approx 7-14 days). Inflammation markers will be assessed at day 0 (at device attachment), +2 and +7 days post device attachment. CRP, TNF-alpha, IL-6, and IL-10 will be assessed. Safety measures will include screening for and treatment of any occurring adverse events, vital signs, physical examination, ECG, 24-hour continuous ambulatory ECG, heart rate variability, laboratory safety tests, infection assessment, inflammation screen. In the event of procedure-related cardiac arrhythmias, ACC/AHA/ESC 2006 Practice Guidelines for management of subjects with ventricular arrhythmias and the prevention of sudden cardiac death will be implemented.

## 8 Documentation

Patients participating in the study will be monitored for:

Atrial Fibrillation, Mortality, Life threatening events, Physical impairment, Prolonged and additional hospitalisation.

Safety measures will include the following examinations:

Adverse Events, Vital Signs, Physical examination, ECG, Laboratory safety tests, Infection assessment, Inflammation screening.

In the event of procedure-related cardiac arrhythmias, ACC/AHA/ESC 2006 Practice Guidelines for management of subjects with ventricular arrhythmias and the prevention of sudden cardiac death will be implemented.

## 9 Statistical Analysis

### Power and sample size calculation

Two-sample test to determine whether the mean in group A,  $\mu_A$ , is different from the mean in group B,  $\mu_B$ . The hypotheses are

$$H_0: \mu_A - \mu_B = 0$$

$$H_1: \mu_A - \mu_B \neq 0.$$

Where the ratio between the sample sizes of the two groups is  $\kappa = n_A/n_B$

Formulas to compute sample size and power, respectively:

$$n_A = \kappa n_B \text{ and } n_B = (1 + 1/\kappa) * (\sigma^2 (z_{1-\alpha/2} + z_{1-\beta}) / (\mu_A - \mu_B))^2$$

$$1 - \beta = \Phi(z - z_{1-\alpha/2}) + \Phi(-z - z_{1-\alpha/2}), \quad z = (\mu_A - \mu_B) / (\sigma \sqrt{1/n_A + 1/n_B})$$

where

$\kappa = n_A/n_B$  is the matching ratio

$\sigma$  is standard deviation

$\Phi$  is the standard Normal distribution function

$\Phi^{-1}$  is the standard Normal quantile function

$\alpha$  is Type I error

$\beta$  is Type II error, meaning  $1 - \beta$  is power

utilizing the values:

Group 'A' mean,  $\mu_A = 20$  (estimates for mean TNF- $\alpha$  in pg/ml in treatment group)

Group 'B' mean,  $\mu_B = 30$  (estimates for mean TNF- $\alpha$  in pg/ml in sham group)

Standard Deviation,  $\sigma = 10$  (estimates for TNF- $\alpha$  standard deviation)

Sampling Size  $n_A = 20$  (treatment group size)

Sampling Size  $n_B = 20$  (sham group size)

Sampling Ratio,  $\kappa = n_A/n_B = 1$

Type I error,  $\alpha = 0,05$

calculates the Power,  $1-\beta = 0,8859$  which is an acceptable value.

For the statistical evaluation of the study data the software Graphpad Prism will be used. The evaluation of the double-blind data will be performed by a competent person utilizing appropriate statistical measures.

#### Primary Endpoint

Incidence of Atrial Fibrillation events in routine ECG following SOPs of clinical department of cardiac surgery.

#### Secondary Endpoint

Markers for IL-6, IL-10, CRP, TNF-alpha.

Utilizing paired t-Tests.

## **10 Randomization**

The randomization procedure will be conducted utilizing the MUW randomizer (<https://www.meduniwien.ac.at/randomizer>) to achieve a 50% / 50% assignment of patients to the treatment and the sham group.

## **11 Data Protection**

Participating patients are pseudonymized using an alphanumeric combination. Collected data are stored on a password-protected work PC in the room 20.E5.02.4. Access to personal data is only available to the sponsor / investigator Prof. Alfred Kocher and by the sponsor authorized persons.



## 12 References

- [1] G. Tokmaji, R. S. McClure, T. Kaneko, and S. F. Aranki, "Management strategies in cardiac surgery for postoperative atrial fibrillation: Contemporary prophylaxis and futuristic anticoagulant possibilities," *Cardiol. Res. Pract.*, vol. 1, no. 1, 2013.
- [2] A. Sezai, K.-I. Nakata, M. Iida, I. Yoshitake, S. Wakui, S. Osaka, H. Kimura, K. Takahashi, Y. Ishi, H. Yaoita, M. Arimoto, H. Hata, M. Shiono, T. Takayama, and A. Hirayama, "A Study on the Occurrence and Prevention of Perioperative Stroke after Coronary Artery Bypass Grafting," *Ann. Thorac. Cardiovasc. Surg.*, pp. 1–7, 2015.
- [3] "Treatment Guidelines of Atrial Fibrillation (AFib or AF)." [Online]. Available: [http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/Treatment-Guidelines-of-Atrial-Fibrillation-AFib-or-AF\\_UCM\\_423779\\_Article.jsp](http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/Treatment-Guidelines-of-Atrial-Fibrillation-AFib-or-AF_UCM_423779_Article.jsp). [Accessed: 12-Jun-2015].
- [4] S. Stavrakis, M. B. Humphrey, B. J. Scherlag, Y. Hu, W. M. Jackman, H. Nakagawa, D. Lockwood, R. Lazzara, and S. S. Po, "Low-Level Transcutaneous Electrical Vagus Nerve Stimulation Suppresses Atrial Fibrillation," *J. Am. Coll. Cardiol.*, vol. 65, no. 9, pp. 867–875, 2015.
- [5] K. Nocon, C. Moosmann, F. Margenfeld, and C. Trummer, "Erste klinische Erfahrungen von vagaler Nervenstimulation über das Ohr bei Patienten mit chronischem Schmerzsyndrom und Wunden der unteren Extremität bei pAVk Stadium IV," Universitätsklinikum Freiburg.
- [6] T. Payrits, "Vagale Stimulation - eine neue Möglichkeit zur konservativen Therapie der Claudication intermittens," in *28. Jahrestagung der Deutschen Gesellschaft für Gefäßschirurgie und Gefäßmedizin*, 2012.
- [7] R.-U. Kuehnel, "Neurovagale Stimulation und Vakuumtherapie bei der Behandlung von chronischen Wunden der unteren Extremitäten," *Wund Manag. Sonderh.*, vol. 2, 2013.
- [8] T. Payrits, "Veränderungen des TcPO<sub>2</sub> durch die vagale Stimulation bei Patienten mit PAVK."