A Feasibility Study to Evaluate the Safety and Effect of the Optimization of Vagus Nerve Stimulation in Epileptic Patients to Induce Cardioprotection

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STUDY TITLE: A FEASIBILITY STUDY TO EVALUATE THE SAFETY AND EFFECT OF THE OPTIMIZATION OF VAGUS NERVE STIMULATION IN EPILEPTIC PATIENTS TO INDUCE CARDIOPROTECTION

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STUDY SUMMARY

TITLE	A Feasibility Study to Evaluate the Safety and Effect of the Optimization of Vagus Nerve Stimulation in Epileptic Patients to Induce Cardioprotection
PRIMARY OBJECTIVES/AIMS	The primary objective is to evaluate in epilepsy patients the effects of adjusting vagus nerve stimulation parameters to engage known cardioprotective aspects.
SECONDARY OBJECTIVES	The secondary objective is to quantify the effects of vagus stimulation on cardiac function by metrics of autonomic testing and a cardiopulmonary exercise testing.
FDA APPROVED DEVICES	LivaNova VNS Therapy (Vagus Nerve Stimulator (VNS)
PROTOCOL NUMBER	UCLA: IRB # 19-002279
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STUDY SITE	University of California Los Angeles (UCLA)
FUNDING SOURCE (S)	NIH-NCATS National Center For Advancing Translational Science
NUMBER OF SUBJECTS	12

1. INTRODUCTION

A. BACKGROUND AND RATIONALE

The autonomic nervous system controls every aspect of cardiac function. This fine control is maintained by a concerted interplay of afferent impulses that reach the central nervous system (CNS) via multiple afferent pathways, and this information results in appropriate efferent sympathetic and parasympathetic responses. Thus, the nerves control cardiac excitation on a beat-by-beat basis. In the setting of myocardial injury, the autonomic nervous system plays an important role in the genesis and maintenance of ventricular tachyarrhythmias (VT). Sympathetic activation and parasympathetic dysfunction accompany cardiomyopathy and predispose to VT and ventricular fibrillation (VF). The neurohormonal response, although acutely beneficial, is chronically damaging. Blockade of the sympathetic nervous system has been the target of multiple successful therapeutic strategies, including beta-blockers and angiotensin converting enzyme inhibitors.

Cardiovascular effects of vagus nerve stimulation (VNS) and delineation of optimal parameters

VNS has shown mixed results in studies of heart failure patients likely due a variety of different stimulation parameters (frequency, pulse-widths, outputs) utilized, without clear human data on which parameters would provide optimal *cardiac* effect. In this study, a range of stimulation parameters will be evaluated in epilepsy patients with structurally normal hearts to delineate the "neural fulcrum" for cardiovascular effects. We will then utilize these "optimal" parameters to assess whether sympathetic responses to autonomic stressors are mitigated and exercise tolerance increased.

Parasympathetic dysfunction accompanies cardiomyopathy and increases the risk of sudden cardiac death. Indirect markers of parasympathetic dysfunction, such as decreased heart rate variability and abnormal baroreceptor reflex sensitivity (BRS), are associated with VT/VF in cardiomyopathy patients. Furthermore, in animals with myocardial infarction (MI), a higher parasympathetic tone portends a greater likelihood of survival in the setting of ischemia. The mechanism behind the cardiomyopathy-induced parasympathetic dysfunction is poorly understood, and could provide new targets for therapies. VNS is an emerging technique that has the potential to impact cardiac function, the neural networks that control cardiac function and higher centers of the central nervous system.

VNS for epilepsy

30-35% of patients with epilepsy do not respond to medical treatment and benefit from surgical intervention. Neurostimualtion is a less invasive alternative to resective surgery and one of the the few successful options for those for whom resection in not an option. Vagus nerve stimulation (VNS) is the oldest neurostimulation technique, FDA approved to treat refractory generalzied and focal epilepsy with outcomes showing over 50% seizure reduction in 70% of patients.

Epilepsy patients are at increased risk for sudden cardiac death. Mechanism behind this predisposition is poorly understood but parasympathetic dysfunction is heavily implicated. VNS protocols as currently set for seizure management are poorly optimized for cardioprotection, therefore this patient population presents a unique opportunity to assess VNS control of cardiac function, when VNS is appropriately titrated for cardiac and seizure benefit.

This proposed study leverages recent advances in VNS stimulation protocols that were developed primarily for treatment of heart failure. From these studies we have defined what is referred to as the neural fulcrum hypothesis for VNS. When VNS is delivered at the neural fulcrum, both ascending (afferent) and decending (parasympathetic efferent) nerves are functionally engaged such that homogeneous control is restored to cardiac reflex control. This applies to both right and left cervical vagal stimulation. VNS as current delivered for epilespy treatment is below that neural fulcrum point. This represents a missed opportunity to improve quality of life and patient outcomes.

B. Summary of Pre-Clinical Studies

The cardiac nervous system, composed of the intracardiac ganglia, intrathoracic extracardiac ganglia, spinal cord, brainstem, and higher centers, coordinates regional cardiac function on a beat-to-beat basis. Globally, the cardiac nervous system is optimized to handle physiological stressors (e.g. orthostatic changes). However, it has not evolved a mechanism to adequately deal with catastrophic events such as myocardial infarction or the central and peripheral consequences of epilepsy.

Progression of cardiac disease reflects maladaptive interactions between the cardiac nervous system and the heart. Epilepsy patients are particularly susceptible to heart attacks with a survival rate ¼ of that of other populations (Stecker, Circ Arrhythm Electrophysiol, 6, 912-916, 2013). Our recent work has demonstrated that targeting select elements within this neural network can lead to efficacious results in select cardiac disease states, including atrial arrhythmias, myocardial infarction, and congestive heart failure. With appropriate neuromodulation therapy, myocytes are rendered stress resistance, autonomic responsiveness for control of the heart is preserved, and the potential for fatal arrhythmias is reduced (Hanna, Card Fail Rev 4, 92-98, 2018). Cervical VNS is at the forefront of such neuromodulation.

C. Objectives

The primary objective is to evaluate in epilepsy patients the effects of adjusting vagus nerve stimulation parameters to engage known cardioprotective aspects.

The secondary objective is to quantify the effects of vagus stimulation on cardiac function by metrics of autonomic testing and a cardiopulmonary exercise test (CPX).

2. Study Design

This is a single-center feasibility study. We plan to enroll 12 subjects (6 female, 6 male). Screening data will be reviewed to determine subject eligibility. All subjects will undergo baseline autonomic testing and cardiopulmonary exercise testing. Patients that agree to continue in the study will have VNS titration over a 2 - 4 week period to achieve the neural fulcrum for control of cardiac function (heart rate and heart rate variability index. The neural fulcrum will be defined by less than 2% change (+/-) in heart rate, and a 5% shift (+/-) in variability in the SD1-SD2 (RR interval beat N=1 vs beat N). The Poincaré plot analysis is a geometrical and nonlinear method to assess the dynamics of HRV. It is a diagram in which each R-R interval is plotted as a function of the previous R-R interval where the values of each pair of successive R-R interval define a point in the plot. SD refers to interval between beats. Once individual neural fulcrum is achieved, the patient will return after 4 weeks for the final

visit in which autonomic testing and cardiopulmonary exercise testing will be repeated. Subjects will be monitored for changes in seizure frequency or duration at each clinic visit as well as any adverse events during the study by having continuous 24 hours per day/7 days per week access to the study team with the neurologist on call.

3. Subject Selection

A. Study Sites
The study will be performed at the University California Los Angeles (UCLA).

B. Recruitment
Subjects with a diagnosis of epilepsy with scheduled or implanted VNS devices will be recruited. The investigators of this study will identify patients. Along with being told about the study, it will also be made clear to the subjects that they have the right to refuse to be in the study and that refusal will not affect their healthcare in anyway.

C. Eligibility Criteria
Eligible patients will be enrolled in the study by the principal investigator after meeting inclusion and exclusion criteria and informed consent is obtained.

D. Inclusion
1. Clinical diagnosis of refractory epilepsy and implanted with a VNS device or are scheduled to be implanted with a VNS device.
2. 18 years of age or older
3. Subjects must demonstrate willingness and ability to comply with study requirements

E. Exclusion
1. Other implantable neuromodulatory device (e.g., brain stimulator)
2. Treatment with cholinergic or anticholinergic medication in the past month
3. Pre-existing cardiac arrhythmia or presence of cardiac pacemaker/defibrillator
4. History of dysautonomias
5. History of vasovagal syncope
6. Progressive neurological diseases other than epilepsy
7. Women that are pregnant
8. Cognitive or psychiatric deficit that in the investigator's judgment would interfere with the subject's ability to accurately complete study assessments

4. Study Methods

A. Screening and Enrollment
All patients who are being considered for enrollment into the clinical trial will be screened by the site investigator or a member of the designated study staff for study eligibility. Subjects who meet the inclusion criteria based on routine care and agree to participate in the study will be asked to sign a written informed consent that has been approved by the Institutional Review Board (IRB). No study related testing or procedures will take place until the informed consent is signed. The patient will be

assigned a study number after the consent is signed and the patient is enrolled. Study data will be stored using the study code.

B. Patient Selection

- Twelve (12) subjects with a clinical diagnosis of refractory epilepsy and implanted with a VNS device or are scheduled to be implanted with a VNS device will be enrolled.

C. Patient Consent

- Patient consent will be conducted in a private setting.
- Member(s) of the study staff will meet with the prospective subjects/families to review the consent document(s) and/or provide an oral explanation of the study. Individuals will be given a chance to ask questions before making a considered decision about whether or not to participate in the study.
- Prospective subjects/families will have the opportunity to review the consent form and/or take the consent form(s) home and to discuss the documents with others prior to deciding whether or not to participate in the study.
- The consent form and other study documents will be available in the subjects' primary language. Study staff or qualified translators will discuss the study in the subjects' language.
- Subjects will be given as much time as they need to consider enrollment. If they are not sure and believe they need more time they will not be enrolled.

5. Study Procedures

A. Data Collection

The following data will be collected from the patient's medical record. Study data will be stored using the patient's study code.

After written informed consent is obtained, the following screening procedures will be performed:

- Demographics (date of birth, gender, race)
- Medical History
- Concomitant medication review
- Assessment for presence of VNS or patient is scheduled to have a VNS implant
- Seizure history over the last 3 months (semiology, frequency, duration of seizures). These parameters will be assessed at every study visit.

B. Study Protocol

The study protocol involves changing the output current/frequency of the default device settings in a FDA approved device for VNS therapy systems manufactured by LivaNova. The LivaNova VNS Therapy Systems include the following models: Model 103, Model 105, Model 106, Model 1000, Model 302, Model 303, and Model 304. LivaNova's Programming Wand Model 2000 version 1.1 will be used to change the device settings. The proposed frequency changes in this study are within the FDA approved output current/frequency levels.

The VNS programmer device as used in current clinical practice comes with pre-set options, but no set standards exist given a physician freedom to decide how to change these parameters within the safety zone (duty cycle) as defined by the manufacturer. Changing the parameters is done on a regular basis with hopes of improving seizure control. However, there are times when parameter changes lead to worsening seizures; patients are routinely warned about this risk and are able to turn off the VNS themselves by a simple magnet (provided to them by the manufacturer or provider)

The following are the available parameter ranges which could be modified during this study:

Output current (miliamps, mA) - range: 0-3.5 [typical: 1-2]

Signal frequency (Hz) – range: 1-30 [typical: 20-30]

Pulse Width (microseconds) - range: 130-1000 [typical: 250 or 500]

Signal on-time (seconds) – range: 7-60 [typical: 30]

Signal off-time (minutes) – range: 0.2-180 [typical: 5]

Duty cycle is proportional to the time device is on

Our objective for the parameter optimization is to define the neural fulcrum, i.e parameters which should be cardioprotective, for the individual patient based on the base frequency that have been titrated to (Ardell et al., 2017). Based on our prior experience with the ANTHEM studies, we anticipate that we will be able to define the neural fulcrum in 90% of patients. This protocol that has been validated in humans with quantitative beat-to-beat analysis (Libbus et al., 2016; Nearing et al., 2016) and with efficacy for HFpEF (DiCarlo et al., 2018) and HFrEF (Premchand et al., 2016).

Defining the neural fulcrum will be achieved in 1-5 sessions over a 2 – 4 week period. Each of the sessions may take up to one hour. Autonomic studies and/or cardiopulmonary exercise stress tests are expected to take a maximum of 2 hours with the VNS turned off or on. The study neurologist will work with the patient to decide if they can do all of the testing or some of the testing. Our prior studies have indicated the VNS has a memory function for up to 30 min after termination of VNS. We allow time between stresses to control for that memory function and for the hemodynamic status to return to baseline. Stimulation protocols as outlined above are within design for treatment of epilepsy and for cardiac disease – no IDE is required.

The following protocol will be used:

Consent and Baseline Testing: Autonomic testing and/or cardiopulmonary exercise testing will be performed on all subjects. The study neurologist will work with the patient to decide if they can do all of the testing or some of the testing. The VNS will be turned off or on during autonomic and cardiopulmonary exercise testing. The baseline visit will take up to 4 hours. Subjects that agree to baseline only will have completed the study.

VNS Titration Visits: Subjects that agree to participate in titration visits will continue in the study. There will be up to 5 titration visits over 2 – 4 weeks. The number of sessions will depend on how many parameters will need to be changed to achieve neural fulcrum and on the subject's tolerability of change in parameters. Titration visits will take up to one hour. Subjects will be instructed to contact the study's neurologist and/or study team with any issues in the interim.

Final Visit: Subjects that participated in titration visits will return to the clinic for the final visit 4 weeks after the neural fulcrum was achieved. Autonomic testing and/or cardiopulmonary exercise testing will be performed. The study neurologist will work with the patient to decide if they can do all of the testing or some of the testing. The final visit will take up to 3 hours.

Subjects will be monitored for changes in seizure frequency or duration at each clinic visit as well as any adverse events during the study by having continuous 24 hours per day/7 days per week access to the study team with the neurologist on call.

C. **STUDY DURATION**

Subjects will be in the study up to 9 weeks. All subjects will undergo baseline autonomic testing and/or cardiopulmonary exercise. Subjects that complete the baseline only testing will complete the study in one visit. Subjects that participate in titration visits will have VNS titration over a 2-4 week period. After titration is complete, the IPG's will be programmed to the neural fulcrum stimulation protocol and left there for 4 weeks. Following the 4 week phase, the autonomic testing and/or cardiopulmonary exercise test will be repeated.

D. Procedures to assess efficacy

Autonomic Testing

- **Valsalva Maneuver:** Improvements in late phase II and in phase IV of the Valsalva maneuver, and a normalized pressure recovery time (PRT) after up-titrated VNS. Poor adrenergic response is indexed by a prolonged PRT, absent or blunted phase IV or late phase II. A 10% improvement in these parameters in response to up-titrated VNS will be considered a significant clinical benefit.
- **Tilt Test**: (orthostatic stress) A 10% decrease in tilt-induced hypotension or a 10% decrease in the heart rate response to a 70 degree heads up tilt after up-titration of VNS will be considered a significant clinical benefit.
- **Oximetry**
- **Electrocardiogram**: The ECG will be used to assess Tp-Te (a measure of repolarization heterogeneity in the heart).

- **Cold Pressor Test**: A 10% reduction in evoked heart rate (HR) and blood pressure (BP) response to cold stimulus is considered a significant response of clinical benefit.

Cardiopulmonary Testing
This is a progressive dynamic exercise test. A 10% improvement in exercise duration and/or a 10% improvement heart rate recovery after exercise will be considered a significant clinical benefit. Heart rate and blood pressure will also be plotted against time. At 85% of the maximum exercise achieved before up-titration of VNS a 5% decrease in heart rate at the same intensity point will be considered a significant clinical benefit with VNS.

E. Procedures to assess safety

- Incidence of adverse events

F. Schedule of study visits

- Please see Schedule of Events in Appendix 1

6. Statistical Plan

This is primarily an exploratory study. Descriptive statistics will be used including paired Student's T test to detect difference in cardiac physiology parameters at baseline vs. during stimulation, for the sample size of n=12. The sample size 'n' will consist of 6 females and 6 males. Each subject will be their own control.

7. Risks and Benefits

Risks associated with stimulation are addressed in the standard consent form and are considered acceptable in the opinion of the investigator.

A. Risks

- The subject can experience coughing and hoarseness during VNS changes. If this occurs the parameters will be immediately reversed to previously tolerated parameters.
- A risk to VNS changes is a change in seizure frequency. The subject will be asked his/her seizure history at each visit and have access to the neurologist. The study neurologist will adjust the VNS parameters per routine seizure management guidelines..

- Additional risk of VNS modulation can include a decrease in heart rate and blood pressure. The parameters can be adjusted or set back to those before the study initiation and if deemed necessary, the subject will exit the study.

- Risks related to monitor pads and electrodes: Some people can have minor skin irritation or an allergic reaction from the sticky patches that are placed on the chest and limbs. The irritation should go away once the patches are removed.
- Risks related to tilt table test, valsalva maneuver or deep breathing: Some people may report feeling dizzy or lightheaded from these tests. The technician can stop the test at any time if this is reported.
- Risk related to cold pressor test: Some people may be uncomfortable with having their arm cooled for 15 minutes. The technician can adjust the temperature or stop the test if this is reported.
- Risks related to Cardiopulmonary Exercise Test (CPX): Some people may report feeling short of breath, fatigue, dizzy, or have an arrhythmia. The technician can stop the test at any time if this is reported.
- As with any use of electronic means to store data, there is a risk of breach of data security. A special code (number combination) and the patient initials will be used to identify personal health information. No personal health information about the patient, their illness, or their treatment will be made public.

B. Benefits

This study is not being done to immediately improve the patient's condition or health. It is aimed at acquiring scientific information regarding the heart's electrical behavior. Information obtained in this study does not have any immediate application for planning treatments for any heart condition. Patients have the right to refuse to participate in this study. There will be no personal benefit for participating in this study. However, information gained from this study helps us better understand the mechanisms of sudden cardiac death, which effects >400,000 people each year in the U.S.

8. Adverse Events

A. Definition of Adverse event

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

All Adverse Events (AE) will have the following assessed by the study team, as defined below:

- Diagnosis
- Event description
- Dates of onset and resolution
- Causality: assessment of relatedness to procedure
- Severity
- Outcome

B. ADVERSE EVENTS MONITORING
The patient's status will be closely monitored by the study team to assess adverse events. The study team that includes neurosurgery, neurology, and electrophysiology, will be conducting the study protocol and are the primary care team for the patient.

C. ADVERSE EVENTS
All reported AEs will be monitored by the study team until they are adequately resolved or explained.

Potential Adverse Events
Most common adverse events seen in long-term treatment with VNS (12mo and 5yrs) as reported in the literature. These symptoms were rated as mild-moderate and did not require adjustment of parameters:

- Voice alternation 55/18.7%
- Headache 16%
- Cough 15/1.5%
- Pain 15/4.7%
- Paresthesia (abnormal skin sensation) 15/1.5%
- Dyspnea 13/12.3%
- Pharyngitis 10%
- Depression 5%
- Infection 6%

Increase in seizure frequency is also a potential adverse event and will be discussed with patients during screening.

D. SERIOUS ADVERSE EVENTS

- An event that is fatal, resulting in death
- An event that is life threatening. In the opinion of the study center physician, the patient was at immediate risk of death due to the event as it occurred;
- An event that results in persistent or significant disability/incapacity;
- An event that requires inpatient hospitalization or prolongs hospitalization;
- An important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: Prolonged hospitalizations for a pre-existing condition is not considered a serious adverse event.

E. REPORTING SERIOUS ADVERSE EVENTS
The site investigator is responsible for ensuring that all SAEs are fully recorded and reported to the IRB per IRB reporting requirements.

9. Data Safety Monitoring Plan (DSMP)

The Principal Investigator and co-investigators will be the primary data safety monitors for this clinical trial. They will provide "real time" adverse event review and actively monitor the trial for adverse event reporting, regulatory and protocol compliance, and data accuracy. A physician group that is separate from the study will also provide Data Safety Monitoring. The group will review the protocol, study data, and safety information, such as any adverse events, twice per year. This group will include a cardiologist, a neurologist that specializes in autonomics and epilepsy, and a statistician.

The following may be reviewed:

- Annual accrual numbers and study drop-out rates. A description of any problems with recruitment or enrollment, study enrollment, and a determination as to whether the current accrual rate is sufficient to meet the intended accrual goal.
- A summary of any problems with study implementation.
- A list of all adverse events and each one's frequency from the study population.

They may determine at any time, that the study should be modified or terminated due to patient harm and/or futility considerations.

10. Data Handling

The patient will be assigned a study number after the consent is signed and the patient is enrolled. Study data will be collected and stored using the study code. Personally, identifiable data will not be collected, transmitted, or stored via the internet. A secure network server will be used to store data. A study code will link the data to the study subject. A key to the code exists. Only the study team members listed in the IRB will have access to the code.

This is a safety and feasibility study, therefore the data will be maintained for future research in the case that:

- The study team wants to use the data set to investigate any additional research questions.
- The study team uses the data set as part of a larger study in the future.

11. Financial Considerations

- Subjects will be not billed for any research procedures.
- Subjects will be provided a parking voucher for each research visit.
- Patients will receive a gift card for each visit completed, up to $200 for the entire study:
    - Screening and Baseline: $100
    - VNS Titration Visits (up to 5 visits): $50
    - Final Visit: $50

APPENDIX 1. SCHEDULE OF STUDY VISITS

	Screening and Baseline Visit[a]	VNS Titration Visits (up to 5 visits at UCLA)	Final Visit	Early Study Withdraw Visit
Informed Consent	**X**			
Medical History	**X**			
Seizure History	**X**	**X**	**X**	**X**
VNS Titration		**X**		
Autonomics Test: Tilt Table Test Deep Breathing Valsalva Maneuver Cold Pressor Test	**X**		**X**	
Cardiopulmonary Exercise Test	**X**		**X**	
Medication Review	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**

[a] ±2 days

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