PROTOCOL TITLE:
TRAGUS STIMULATION TO PREVENT ATRIAL FIBRILLATION AFTER CARDIAC SURGERY: THE TRAP-AF STUDY

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INTERVENTION: TRANSCUTANEOUS LOW-LEVEL TRAGUS STIMULATION (LLTS)

MANUFACTURER OF INTERVENTION: NOT APPLICABLE

IND OR IDE # NOT APPLICABLE

STUDY SUMMARY

TITLE	**Tragus Stimulation to Prevent Atrial Fibrillation after Cardiac Surgery**
SHORT TITLE	**The TraP-AF Study**
PROTOCOL NUMBER	IRB17-1365
METHODOLOGY	Single-blind clinical trial
STUDY DURATION	1 year
STUDY CENTER(S)	Single-center
OBJECTIVES	To compare the effectiveness of transcutaneous low-level tragus stimulation (LLTS) of the auricular branch of the vagus nerve versus sham in the prevention of postoperative atrial fibrillation (POAF) after cardiac surgery.
NUMBER OF SUBJECTS	80 patients
DIAGNOSIS AND MAIN INCLUSION CRITERIA	Patients undergoing coronary artery bypass graft (CABG) surgery and/or valve surgery who are 18 years of age or older at the University of Chicago will be eligible for evaluation for inclusion into this study. Exclusion criteria include: 1) Prior history of persistent or permanent atrial fibrillation (AF) as determined by detailed chart review 2) Emergency cases 3) Pregnant patients 4) Patients undergoing the following procedures: heart transplant, pulmonary thromboendarterctomy, isolated aortic arch procedures, ventricular assist device insertion, extracorporeal membrane oxygenation insertion, and surgical AF ablation
STUDY PRODUCT	Transcutaneous low-level tragus stimulation (LLTS) is a completely noninvasive technique which utilizes an FDA approved transcutaneous electrical nerve stimulation (TENS) device (Parasym, Parasym Health). This device consists of a battery-powered, programmable transcutaneous electrical nerve stimulation (TENS) unit and a pair of stimulation electrodes that can be clipped to the tragus of the externl ear in order to stimulate the auricular branch of the vagus nerve.
DURATION OF ADMINISTRATION	LLTS will be administered continuously for 48 hours, beginning immediately after surgery. The stimulator will be shifted from one ear to the other every 4 hours.

REFERENCE THERAPY	The reference therapy will be a sham control group; i.e., patients on whom an LLTS device with a non-functioning electrode will be applied and in whom therapy will not be delivered.
STATISTICAL METHODOLOGY	Traditional statistical methods will be employed. The student's T-test will be used for continuous comparisons. Fisher's exact or the Chi-square test will be applied for dichotomous variables. Time to endpoint analysis will be performed using the Kaplan-Meier method.

List of Abbreviations

AAD	Antiarrhythmic Drug Therapy
ACE-I	Angiotensin-Converting Enzyme Inhibitor
AF	Atrial Fibrillation
ARB	Angiotensin Receptor Blocker
BB	Beta-Blocker
CABG	Coronary Artery Bypass Graft
CRT	Cardiac Resynchronization Therapy
FDA	Food and Drug Administration
GDMT	Goal-directed Medical Therapy
HF	Heart Failure
ICD	Implantable cardioverter-defibrillator
IRB	Institutional Review Board
LBBB	Left Bundle-Branch Block
LV	Left Ventricular
LLTS	Low-Level Tragus Stimulation
LVEF	Left Ventricular Ejection Fraction
NYHA	New York Heart Association
POAF	Postoperative Atrial Fibrillation
POD	Postoperative Day
RA	Right atrium
RV	Right Ventricle
SR	Sinus Rhythm
TTE	Transthoracic Echocardiogram
UCMC	University of Chicago Medical Center
UofC	University of Chicago
VT	Ventricular Tachycardia
VF	Ventricular Fibrillation

1. INTRODUCTION

A. BACKGROUND AND RATIONALE

New-onset postoperative atrial fibrillation (POAF) commonly complicates cardiac surgery, affecting between 20 and 50% of patients,[1] with an even higher risk for patients undergoing combined coronary artery bypass graft (CABG) and/or valve replacement procedures.[2,3] The spectrum of POAF varies from self-limited episodes to persistent AF requiring antiarrhythmic drug therapy (AAD) and cardioversion.

Overall, POAF portends significantly worse clinical outcomes, including an up to four-fold increased risk of stroke and doubling of both all-cause 30-day and 6 month mortality.[4] In addition, POAF is independently associated with prolonged intensive care unit (ICU) stays, longer overall duration of hospitalization (extending length-of-stay by 2 to 5 days), and significantly increased costs by $10,000-20,000, even during the index hospitalization.[4,5] POAF usually occurs between 2 and 4 days after surgery, with a peak incidence on postoperative day 2.[6] The pathogenesis of POAF in the cardiac surgical setting remains poorly understood, although there is data to suggest that autonomic imbalance during the post-operative period may play a key role for some patients.[1]

Peripheral vagal nerve stimulation can alter central parasympathetic cardiac inputs, leading to reduced heart rate along with reduced dispersion of atrial effective refractory periods (AERPs), lowering the risk of AF.[7,8] While direct vagal nerve stimulation has an established role in the treatment of intractable epilepsy and treatment-resistant depression,[9,10] its application for POAF has been limited due to its invasive nature and increased risks.

Transcutaneous low-level tragus stimulation (LLTS), however, has recently emerged as a novel, entirely noninvasive means to achieve vagal nerve stimulation, which achieves anticholinergic and antiadrenergic effects.[11] The auricular branch of the vagus nerve localizes to the skin near the anterior protuberance of the outer ear, called the tragus. LLTS has been shown to significantly suppress AF inducibility, reduce overall AF duration, and reduce the production of inflammatory cytokines (i.e., TNF-alpha and C-reactive protein) in acute studies.[12-15] Furthermore, it may have additional benefits in inducing autonomic remodeling, as well as reducing ventricular arrhythmia.[16] The Parasym devicedelivers LLTS through the skin via the outer ear (see Appendix A, Figures 1-2). It has been used in a variety of medical treatments, including tinnitus, depression, anxiety, and rheumatoid arthritis. We seek to evaluate the role of LLTS in preventing POAF, reducing AF duration, reducing average length of stay, and reducing overall arrhythmia incidence after cardiac surgery.

B. OBJECTIVES

<u>We hypothesize that</u>:

a. In patients undergoing cardiac surgery (i.e., CABG and/or valve surgery), new-onset POAF is common
b. LLTS is a simple, noninvasive and effective means to reduce the incidence of POAF, reduce overall AF duration, and reduce incidence of significant ventricular arrhythmias (i.e., nonsustained or sustained VT/VF)
c. Use of LLTS in the inpatient setting leads to reduced overall AF and reduced AF duration in the 30-day period after cardiac surgery

Specific aims:

Aim 1: To determine the overall rate of successful LLTS in the inpatient setting. Patients randomized to LLTS will undergo continuous stimulation for two inpatient days. Tolerance of LLTS versus sham will be assessed.

Aim 2: To assess the impact of LLTS on acute and short-term outcomes. Acute outcomes include the incidence of inpatient POAF during the index hospitalization, length of hospital stay, overall AF duration, and incidence of nonsustained or sustained VT/VF. Short-term outcomes include incidence of AF as assessed by 14-day monitor (i.e. Zio patch or CardioNet event monitor) upon discharge.

2. STUDY DESIGN

Study design: Single-blind study. Patients will be randomized, to LLTS versus sham procedure, and remain blinded to their treatment allocation. Both treatment options will utilize similar equipment, namely the use of alligator clips which will be placed on the tragus and earlobe of the right ear for patients (see Appendix A, Figure 2). The distinction is only that in patients assigned to LLTS, they will be initiated on therapy at the time of device placement.

Prior to cardiac surgery, the discomfort threshold of both left and righ tragus stimulation will be determined for all participating patients. Intermittent electrode signals, or microcurrents, are delivered at 20 Hz with 200 μsec pulse width with variable microampere (mA) output. The discomfort threshold is defined as the stimulation intensity in mA at which point patients experience discomort. The stimulation intensity used in the study will be set just below the discomfort threshold, as established from prior work.[15] The clip will then be placed on the patient's ear at the end of surgery. After surgery is completed, the clip will then be removed and replaced on the contralateral ear. Stimulation will then continue, one ear alternating with the other, every 4 hours for a total of 48 hours. It is possible that the threshold can change during the post-operative period. If the patient shows any sign of discomfort from stimulation, the intensity of stimulation will be reduced to a level at which signs of discomfort disappears.

Follow-up will be performed with 14-day event monitor (i.e. Zio patch or CardioNet event monitor) at the time of discharge.

Electrocardiography (i.e. ECG) will be performed pre-procedure and prior to hospital discharge. Echocardiography will be assessed prior to study initiation and when clinically available in follow-up.

Duration of study: 1 month

Primary endpoints: A combination of clinical and electrocardiographic endpoints will be prospectively studied. These include:

- **Clinical**: Primary clinical endpoint is time to inpatient AF (length of stay >5 days). Secondary endpoint is any occurance of AF during 14 day post procedure monitoring. .
- **Electrocardiographic**: Arrhythmia occurrence (i.e., AF, nonsustained VT, VT or VF requiring device therapy) will be documented throughout the study period

Primary safety endpoint: Procedure-related complications will be assessed prospectively both acutely and throughout the study period, including:

- **Procedure related**: pain, tragus site abrasion or bruising

Randomization scheme: Patients will be allocated to LLTS or sham in a 1:1 ratio at time of implant based on random number generator.

3. Subject Selection and Withdrawal

Sites:
Subjects selected for study will be recruited from the University of Chicago Medical Center (Chicago, IL).

Eligibility:
Eligible patients will be all patients undergoing CABG and/or valve surgery.

Inclusion Criteria:

1. Patients ≥18 years of age, <90 years of age
2. Estimated life expectancy of at least 1 year at the time of enrollment
3. History of sinus rhythm or paroxysmal atrial fibrillation

Exclusion Criteria:

1. Patients ≥90 years of age, <18 years
2. Patients with known prior history of persistent or permanent AF
3. Atrial Fibrillation occurance within the last 24 hours of procedure
4. Urgent or Emergency cases
5. Pregnant patients
6. Patients undergoing the following cardiac procedures: heart transplant, pulmonary thromboendarterctomy, isolated aortic arch procedures, congenital hear disease, ventricular assist device insertion, extracorporeal membrane oxygenation insertion, and surgical AF ablation
7. Antiarrhythmics prior to surgery (Class I and Class III)
8. High degree AV block requiring temporary pacing
9. MAZE procedure

4. Study Device

LLTS will be performed using a transcutaneous electrical nerve stimulation (TENS) device (Parasym, Parasym Health). This device consists of a battery-powered, programmable TENS unit and a pair of stimulation electrodes that can be clipped to the tragus of the externl ear in order to stimulate the auricular branch of the vagus nerve (see Appendix A, Figures 1-2). There is no known interaction with other cardiac devices (e.g., pacemakers and defibrillators)

The device was cleared by the FDA as a Class II device based on Section 882.5890 (see https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfrl/ldetails.cfm?lid=157705). This is a non-significant risk device. It has not been subject to any advisories or recalls.

5. Study Procedures

Pre-Stimulation:

- Patients will be screened for study
- Discomfort threshold bilaterally will be measured (20 Hz) for 5 minutes
- Pre-implant ECG reviewed (to be performed on day of screening)
- Baseline transthoracic echocardiogram (TTE) reviewed (does *not* need to be performed during inpatient hospitalization; outpatient or outside-hospital TTE report may also be performed)
- NYHA functional class to be determined by treating physician
- Operating physician will be informed of patient randomization allocation to facilitate planning of procedure

Randomization, Implant, and Periprocedure Care:

- LLTS or sham will instituted upon arrival in PACU/recovery after surgery with right sided LLTS. The site of stimulation will alternate every 4 hours between right and left tragusfor total stimulation duration of 48 hours.
- Postoperative care for the cardiac surgical patient will be performed as per routine standard of care by the treating primary team
- The patient will be maintained on telemetry during the entire inpatient hospitalization
- Telemetry will be checked daily to evaluate for any new-onset AF
- Predischarge ECG will be performed at the time of hospital discharge
- The patient will be fitted with a 14-day event monitor (i.e. Zio patch or Cardionet monitor) at the time of discharge or to be mailed to the patient/picked-up by patient immediately after discharge on a weekend discharge day
- Blood will be collected for C-reactive protein measurement to assess inflammation per routine lab assessments

Follow-Up Visit (can be performed between 2 weeks and 1 month after discharge):

- The patient will return the 14-day monitor, if not already mailed back
- Routine clinical check as per primary team

Future contact:

- Patients will be asked to participate in an extended registry (protocol IRB16-0272) to evaluate longer-term clinical outcome after study completion. Patients will be asked to sign a separate consent form for participation in this study.

6. Statistical Plan and Considerations

Primary Outcome:

1. Time to the first episode of AF >30 seconds during inpatient admission or within 14-day monitoring period

    a. In hospital: full-disclosure telemetry
    b. Time to AF will be assessed by physicians blinded to randomization
2. Extended hospitalization of >5 days

Secondary Outcomes:

1. Overall AF burden, as assessed by 2 week monitor (CardioNet or Zio Patch) upon discharge
2. Inflammatory markers: C-reactive protein (ordered if clinically indicated)
3. Actionable AF: antiarrhythmic use (including rate-control meds), CDV, anticoagulation, use of inotropes for BP support during AF
4. Stroke or transient ischemic attack (TIA)
5. All cause of mortality

Sample size estimation:

Assuming a two-armed study with composite endpoint of occurrence of AF or >5 days hospitalization, whereby the treatment group will have 50% likelihood of the event occurring and a control group will have 20% likelihood of the event occurring, as well as a 10% dropout rate, we will be able to detect differences in 80 patients (40 in each arm). Under these assumptions and using two-sided Z-Test with unpooled variance to compare the changes between these two groups, we will have 80% power (α=0.05) to detect a difference between the group proportions of 0.30. PASS software Version 15 (NCSS, LLC, Kaysville, UT) was used to calculate the statistical power.

Statistical methods:

Patients will be studied based on the randomization allocation. Patients who refuse to continue with study treatment (i.e. they refuse to wear ear clip) during time of therapy will be analyzed as intention-to-treat per allocation group. Fisher's exact or the Chi-Square test will be used for categorical variables, and continuous parameters will be compared by the two-tailed unpaired Student's t test and the F test for analysis of variance (ANOVA), as needed. Kaplan-Meier method will be used for computing the event free survival curves. Each strategy will be compared within this cohort of patients for its impact on percent incidence of POAF and length of stay. Multiple logistic regression and multiple regressions using the Cox proportional hazards model will be performed to determine the independent association of each of the demographic variables with clinical outcome.

7. RISKS AND BENEFITS

Risks:

LLTS is a novel, entirely noninvasive means to stimulate the auricular branch of the vagus nerve. There are risks associated with alligator clip application which will be similar in the two groups; these risks include discomfort to the tragus or skin abrasion. There is discomfort with high level stimulation, and at the time of neuromodulation, strict attention to patient comfort will be maintained.

Benefits:

There are significant possible benefits to this treatment. Should LLTS be effective at reducing postoperative AF, this would be associated with significant benefit to the patient as well as potentially lead to a significant improvement in overall postoperative management of patients.

8. Safety and Adverse Events

Safety:
As noted above, periprocedural complications will be logged with respect to procedure, system-related, and lead-related events. All complications will be independently reviewed at the midpoint by the primary investigator (PI). Should there be a trend towards increased complication risk, the study will be halted.

Adverse Events:
As noted above, all adverse events associated with devices will be monitored periprocedurally and continuously through the study. The PI will independently review all events after randomization of 20 subjects in order to make a determination for continuance.

Adverse Effect Documentation:

1. Sinus bradycardia or AVB after sitmulation
2. Discomfort or possible skin abrasion due to tragus stimulation
3. Major organ-system failure
4. Death

9. Data handling and Record Keeping

Data will be collected on paper by study coordinators and transcribed into a RedCap database, which will be maintained at the Uof C. Data will be managed by the PI and study coordinators, and only the study team will have access to the data. All patient-specific identifiers will be kept separate from the primary research database. The research database will be organized by a unique patient code.

10. Study Monitoring, Auditing and Inspecting

All periprocedural complications and adverse events will be reviewed by the PI at study midpoint to ensure there is no significant difference in event rate between the study groups. Should there be significant differences, or if there should be a high overall event-rate out-of-line with the procedural norm for AF, the study will be halted.

11. Financial Considerations

No renumeration will be provided to subjects.

12. Ethical Considerations

No specific ethical considerations are identified in relation to this study.

13. Conflict of Interest

This is an internally funded study with no external support.

14. REFERENCES

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15. APPENDIXES

A. FIGURES

Figure 1: Parasym Device

Figure 2: Electrode attached to tragus

B. J AM COLL CARDIOL 2015;65:867–75

Low-level
transcutaneous stimu

C. SCHEDULE OF EVENTS (SCHEMA)

	Screening	Surgery (Day 0)	Post-Op Days 1-2	Day of Discharge	Follow-Up Visit (2 weeks to 1 month after discharge)
Medical Records Review	X				X
Clinical Evaluation (Physical Exam, Vital Signs, Medication Review)	X	X	X	X	X
Electrocardiogram	X			X	
Echocardiogram	X[a]				X[a]
Urine Pregnancy Test	X[b]				
NYHA Functional Class Determination	X				
Randomization	X[c]				
LLTS or Sham Application		X[d]	X[e]		
C-Reactive Protein Blood Test		X[f]	X[f]		
Event Monitor (i.e. Zio Patch or Cardionet Monitor)				X[g]	X
Adverse Events		X	X	X	X

[a] Results from records review, if available
[b] Only for women of childbearing potential
[c] Pre-procedure to facilitate planning of procedure
[d] Immediately after surgery
[e] Continuous for 48 hours
[f] If clinically indicated
[g] Pre-discharge if discharged on a weekday; arrangement for mailing or pick-up for patients discharged on a weekend day