Potential Benefit for non invasive Vagus Nerve stimulation (nVNS) using GammaCore in the Treatment of Raynaud's Phenomena.

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Abstract

Raynaud's phenomenon (RP) is a common vascular disorder that affects approximately 10% of the general population. RP is associated with significant morbidity that may include loss of the digits due to repeated episodes of vasospasm of the digital arteries in addition to significant impairment of quality of life. It is well known that cold exposure precipitates episodes of RP, but the mechanism for cold sensitivity is not known, and treatment of RP is not satisfactory to the subjects and their physicians.
Our goal in this proposal is to test the possibility that non invasive vagus nerve stimulation (nVNS) with gammaCore may be an effective and well tolerated therapy for RP. We will perform the first proof of concept human study to demonstrate the clinical efficacy and safety of nVNS using gammaCore in RP.
We anticipate at the conclusion of the proposed work that we will have gained fundamental understanding of the role of nVNS as a potential therapy for RP, a truly unmet medical need. If successful in demonstrating measurable local vasodilatory effects, we will proceed in a second phase of the study to evaluate the effects of gammaCore on RP associated with Scleroderma.

RESEARCH PLAN

A. SPECIFIC AIMS

Raynaud's phenomenon (RP) is characterized by repeated episodes of vasospasm that may lead to vascular injury and tissue ischemia. RP is classified as primary (PRP) or secondary (SRP) in the absence or presence of underlying autoimmune connective tissue disease, respectively. The exact cause of RP is undetermined and the current treatment modalities are largely unsatisfactory and frequently associated with significant side effects. In this proposal, we aim to investigate the efficacy of nVNS using gammaCore in PRP subjects. nVNS using gammaCore has recently received clearance from the US FDA for acute cluster headache and migraine treatment in adults. RP is frequently associated with headaches, particularly migraine headaches. Indeed, migraine is a risk factor for development of RP with a pooled OR of 4.02 (95% CI 2.62 to 6.17) in six studies [1], suggesting vasospasm as a common pathogenic process.

The Specific Sequential Aims of this application are as follows:

Aim 1: Evaluate the clinical efficacy of gammaCore (16 subjects) vs sham device (16 subjects) in preventing vasospasm in 32 PRP subjects.

Aim 2: Evaluate the clinical efficacy of gammaCore (16 subjects) vs sham device (16 subjects each) on Raynaud's symptoms and chronic PRP in 32 subjects with chronic PRP for four weeks using Raynaud's condition score.

Aim 3: Observe response rates in an open label fashion after sham subjects are transitioned to gammaCore.

B. BACKGROUND AND SCIENTIFIC SIGNIFICANCE

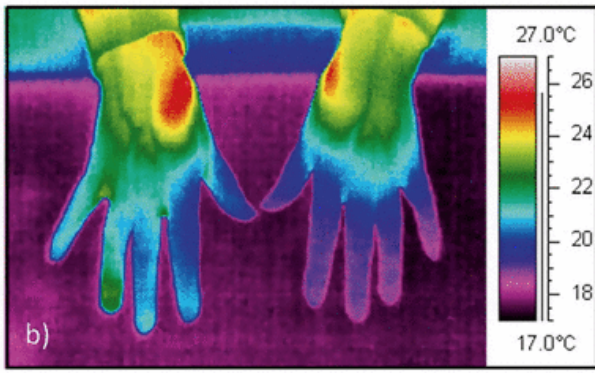
Raynaud's phenomenon is classified as PRP in the absence of other vascular or connective tissue disease, or SRP if it is associated with connective tissue disease, like systemic sclerosis (SSc, Scleroderma). RP is a common disorder that is characterized by reversible vasospasm of the digits induced by cold exposure or emotional stress, which induces episodes of tri-phasic color changes of the digits with blanching, cyanosis, and rubor followed by numbness, pain and often-functional disability with a significant impact on the quality of subject's life. Moreover, RP can be associated with digital ulceration and autoamputation [2]. PRP affects up to 10% of the general population in the United States [2]. The etiology and pathogenesis of RP are incompletely understood.

Treatment of RP is not satisfactory in general, as current therapy employing calcium channel blockers and other vasodilators are frequently ineffective or not well tolerated, due to significant side effects [3].

Noninvasive evaluation of blood flow at the digits in RP. We use **Infrared Thermography (IT),** a technology that relies on evaluating the difference of skin temperature as a tool for dynamic evaluation of digital blood flow by creating temperature maps. IT has been validated as a tool to evaluate RP and assess response to therapeutic interventions [4,5], with a conclusion that IT is a sensitive test with high reproducibility [6-9]. Studies have shown that IT correlate with digital blood flow at baseline and after cold challenge test by using temperature evaluation [9]. IT is considered a cost and time-saving to use for the monitoring of perfusion changes in subjects with RP [9].

Non-invasive assessment of RP often incorporates local cold challenge to allow dynamic vascular assessment under conditions thought to simulate those responsible to for an attack of RP [7].

Figure 1: Captured images of Raynaud's attack by IT, blue color represents lower temperature of the skin compared to red. (From Non-invasive Methods of Assessing Raynaud's phenomenon by Murray and Pauling, Raynaud's phenomenon 2015)



D. APPROACH and METHODOLOGY

1. Assessment of digital blood flow in response to cold challenge test

We used FLIR thermography system (Wilsonville, OR) to evaluate blood flow in the digits in response to cold challenge test. The advantage of IT is that we can obtain dynamic assessment of blood flow in the hands as reflected by change in temperature in response to cold challenge tests, as well as the ability to obtain single point measurements. **Figure 2** shows dynamic changes in surrogate marker of blood flow as detected by thermal images during the three phases of active Raynaud's phenomena that we were able to reproduce by cold challenge test.

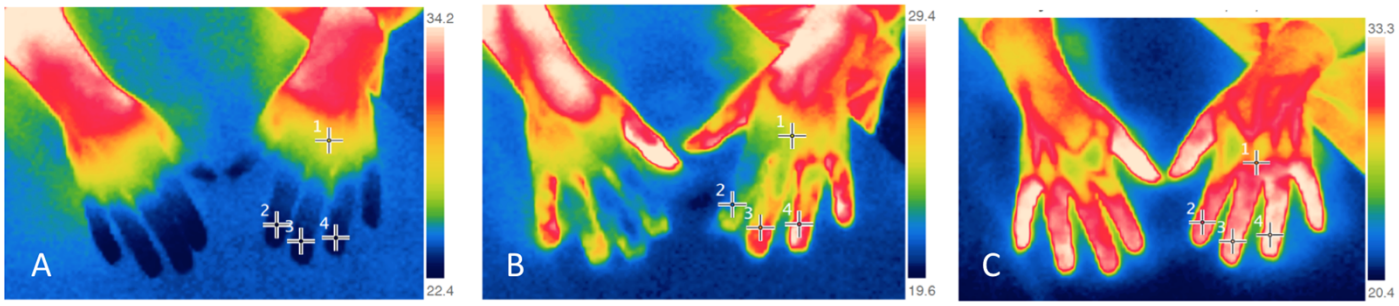


Figure 2: An illustrative example of dynamic changes in vascular perfusion that are detected by infrared thermography. A) Active vasospasm, B) spontaneous improvement in blood flow, C) Hyperemia. Blue-yellow regions indicate areas of lower perfusion compared to red regions.

2. EXPERIMENTAL DESIGN

Study population

We will consent 40 subjects with Raynaud's phenomenon seen previously at the University of Toledo Medical Center (UTMC). After meeting the screening requirements 32 subjects will be randomized 1:1 to sham device (16) or gammaCore device (16). The sample size calculation is based on the minimum recommended number of samples to detect a difference in the outcome of the intervention with a confidence level of 90%, and margin of error of 10%. Each individual will sign an informed consent that is approved by the IRB at UTMC before participating in this study. The research protocol will be explained in detail and in lay language to each subject. We will exclude subjects who currently smoke, subjects with digital ulcers, subjects who are less than 18 years of age, subjects with pulmonary hypertension, and subjects who are receiving vasodilators such PDE-5 inhibitors, prostacyclin, nitroglycerine, or other nitric oxide derivatives. Subjects who are using Calcium Channel Blockers (CCBs) will be allowed to continue their medication, however, should be on stable therapy at least 4

weeks prior to study initiation. We will also exclude pregnant women from these studies, which will be evaluated at screening with a urine dipstick pregnancy test. Subjects who have had neck surgery in the past year (i.e. carotid endarterectomy) or that have a carotid bruit, will be excluded as well. GammaCore device cannot be used in those that have a history of metallic device such as a stent, bone plate, or bone screw implanted at or near their neck. Any history or current evidence of any condition, therapy, or other circumstances which, in the opinion of the investigator, might pose an unacceptable risk to the subject (i.e. unable to comply with requirements of the trial, or likely to interfere with the subjects participation for the full duration of the trial).

Evaluation of reduced blood flow in the hands in response to cold challenge test.

Due to lack of consensus on a standard approach to noninvasive evaluation of blood flow in the hands of subjects with RP, and inadequate data to demonstrate that one modality is superior to another, we decided to take an approach where we evaluate the outcome of treatment using the cold challenge test.

Cold challenge test.
We will standardize the cold challenge procedure as follows: We will ask subjects to refrain from caffeine for at least 4 hours prior to testing. The procedure will be performed at ambient room temperature of 23^{o}C $\pm$ 0.5^{o}C using an air conditioning or heating unit if needed. Subjects will be acclimatized for 20 minutes in the test room and standardized with subjects wearing a single layer of clothing. FLIR camera will be used to obtain thermal images from an 80 cm distance to the table top, measured from the middle of the bottom lens rim, at ambient room temperature. We will mix tap water with ice to produce a basin, with the dimensions of a length 28 cm by 21 cm wide and a depth of 14.5 cm, to create a tap water mixture with a goal temperature of 15^{o}C $\pm$ 0.5^{o}C. The basin will be filled to a measurement of 9 cm of water to allow uniform submersion and cooling around subjects hands. Subjects will then be instructed to submerge hands for one minute, timed, remove immediately once one minute submersion is complete, dry briefly with paper towels, and be instructed to sit, with proper hand placement, for imaging process using FLIR system.

Thermography
We will use FLIR system to measure temperature and blood flow at the digits. After the cold challenge, subjects will place their hands on a setup of a carpet square measuring a length of 42.5 cm by 29.5 cm wide, placed backing side up (to reduce reflection), on a table with a grate resting on the carpet where the subject will be instructed to rest hands on. We will use 2 thresholds for use as screening when subjects do the first cold challenge without neurostimulation:

1. A Distal Dorsal Difference (DDD) >1^{O}C at base line or
2. DDDI should $\geq$ 20% at 5 min after the cold stress.

Subjects who meet the screening threshold of clinically meaningful change from baseline on the initial cold challenge will be enrolled into the study.

Week -4 (Screening). The screening visit where eligibility testing will be performed utilizing the cold challenge test, a baseline image will be taken, and physician verbal history interview performed. Subjects will begin to keep a diary of Raynaud's symptoms and number of attacks. Throughout the study, the diary will be collected at week 0, 4, 8, and 12. A diary will be provided at week -4, 0, 4, and 8. Beginning at week 0, stimulation time and occurrences with gammaCore device will be recorded in the diary along with at week 4. There is no use of gammaCore or sham at this point. Subjects continue their current standard of care treatments, except for medications prohibited while enrolled in the study.

Week 0 (Randomization). The first 32 subjects that meet screening criteria will be enrolled into the study. Diaries from Week -4 to Week 0 will be collected, and a new diary given. The 32 subjects will be randomized 1:1 to either sham device (16) or gammaCore device (16). At week 0 subjects will have a follow up image #1 taken and then be treated with sham or gammaCore -20 minutes prior to cold challenge. The first set of stimulation begins at -20 minutes (2 minutes on each side of the neck for a total of 4 minutes) and then at -4 minutes the second set of stimulation occurs (2 minutes on each side of the neck for a total of 4 minutes)

performed by the subject, monitored by the investigator, or delegated study personnel immediately after cold challenge. Using FLIR thermography to measure absolute temperature, DDD, and DDDI will be calculated from images of both hands taken at baseline, obtained by a video where images are captured at 1 min, 5 min, 10 min, 15 min and 20 minutes after the cold challenge will be measured at the dorsum and digits 2nd-4th. Images measuring the absolute temperature, DDD, and DDDI at specific regions as well as the average of all regions will be generated as a surrogate marker of blood flow.

Prior to cold challenge subjects will be trained on proper usage and administration of sham and gammaCore devices. Subjects will stimulate for 4 minutes (2 minutes each side of neck) twice a day, once in AM and once in the PM, at least 8 hours apart for a total of 8 minutes of stimulation daily. Subjects will begin to log the completion of stimulation and occurrences with the device, and continue recording Raynaud's symptoms and number of attacks in the diary. Subjects will continue on their current treatments with sham or gammaCore device, and continue to refrain from medications prohibited while enrolled in the study.

Week 1. Subjects will return for observation of administration of treatment with any correction if necessary and confirm that subject is documenting RP symptoms and number of attacks as well as the use of the device in the diary.

Week 2. Subjects will be contacted via telephone for a follow up call to address any device stimulation issues, make corrections if necessary, as well as confirm that subject is documenting RP symptoms and number of attacks as well as the use of the device in the diary.

Week 4 (Open Label). Subjects will return for cold challenge test and bring device back with them. Subjects will have follow up image #2 taken and then be treated with their current sham or gammaCore -20 minutes prior to cold challenge (stimulation 2 minutes each side of the neck for a total of 4 minutes) and then at time -4 minutes (stimulation 2 minutes each side of the neck for a total of 4 minutes) performed by the subject and monitored by the investigator, or delegated study personnel) immediately before cold challenge. Using FLIR thermography to measure absolute temperature, DDD, and DDDI will be calculated from images of both hands taken at baseline, obtained by a video where images are captured at 1 min, 5 min, 10 min, 15 min and 20 minutes after cold challenge will be measured at the dorsum and digits 2nd-4th. Images measuring the absolute temperature, DDD, and DDDI at specific regions as well as the average of all regions will be generated as a surrogate marker of blood flow.

Following Week 4 cold challenge sham subjects will be placed on active treatment with gammaCore so that all subjects will be on open label active treatment at Week 4. All subjects will be retrained on proper usage and administration of gammaCore. Subjects will stimulate for 4 minutes (2 minutes each side of neck) twice a day, once in AM and once in the PM at least 8 hours apart, for a total of 8 minutes of stimulation daily. The diary from week 0 to 4 will be collected and subjects will be provided a new diary to continue recording the completion of stimulation and occurrences with the device, and Raynaud's symptoms and attacks. Subjects will continue their treatments with the gammaCore device and continue to refrain from medications prohibited while enrolled in the study.

Week 8. Subjects return for cold challenge test and bring device back with them to be returned. The diary from week 4 to 8 will be collected and subjects will be provided a new diary to record their Raynaud's symptoms and number of attacks in. Subjects will have follow up image #3 taken and then will be treated with gammaCore -20 minutes prior to cold challenge (stimulation 2 minutes each side of the neck for a total of 4 minutes) and then at time -4 (stimulation 2 minutes each side of the neck for a total of 4 minutes, performed by the subject and monitored by the investigator, or delegated study personnel) immediately before cold challenge. Using FLIR thermography absolute temperature, DDD, DDDI will be calculated from images of both hands taken at baseline, obtained by a video where images are captured at 1 min, 5 min, 10 min, 15 min and 20 minutes after cold challenge will be measured at the dorsum and digits 2nd-4th. Images measuring the absolute temperature, DDD, and DDDI at specific regions as well as the average of all regions will be generated as a surrogate

marker of blood flow. Study will end at Week 12 with the possibility of long term open label extension that will be decided later.

Week 12. Subjects will return to turn in completed diary.

Demonstrating the effect of treatment in response to cold challenge.
We will calculate absolute temperature, DDD, and DDDI from images of both hands taken at baseline, 1 min, 5 min, 10 min, 15 min and 20 minutes after cold challenge at the dorsum and digits 2^{nd}-4^{th}. High gradient of DDDI indicates insignificant response of the treatment modality.

Statistical analysis.
Comparisons between absolute temperature, DDD, and DDDI between subjects and visits will be made. Mean values and standard deviations of the measurements IT end points will be determined. Sequentially, the differences in the mean values of temperature after a baseline and in response to cold challenge will be calculated and categorized as greater or less than1.2-fold change from the baseline average. Also, we will measure absolute temperature, DDD, and DDDI across the 2^{nd}-4^{th} digits bilaterally. We will calculate the mean of all absolute temperatures, DDD, and DDDI values and rate of change, and use t-test to calculate P value. P value <0.05 will be considered statistically significant. We will use one-way ANOVA for the means will be used for statistical analysis. Statistical significance will be considered if $P < 0.05$.

Anticipated results and interpretation. We predict that these experiments will provide the first clinical evidence that nVNS with gammaCore may be an effective treatment in PRP, by demonstrating that the stimulation abrogates vasospasm that is classically induced by cold challenge in subjects with PRP.

***Potential pitfalls and contingency plan*.**
Should we be unable to detect significant changes in temperature in the digits after gammaCore vagal stimulation, we will consider using gammaCore vagal stimulation at different time intervals. Also, to eliminate effects of seasonal variability on RP, we will recruit all subjects for this study in the same season. To avoid effect of environment temperature variability on evaluation of blood flow in the digits, we will perform the testing at standard room temperature ($23^{o}C \pm 0.5^{o}C$).

Conclusion:
The work described in this application is novel and it addresses an unmet need for a common condition like PRP that affects up to 10% of the population. There is an unmet need for safe and effective treatment for this condition. The work that we proposed will help in addressing this need.

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