Facial Nerve Stimulation in Healthy Human Subjects

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***Abstract*—Stroke affects more than 16 M people worldwide and emergency treatments are available for less than 5% of the patients. Magnetic stimulation of the facial nerve has been tested in pre-clinical studies as a new, non-invasive emergency treatment of ischemic stroke that acts by increasing cerebral blood flow (CBF). The objective of this study in healthy human subjects is to help understand the safety, tolerability, and effectiveness of a clinical prototype facial nerve stimulator as a first step toward clinical studies in ischemic stroke patients. The geniculate ganglion region of the facial nerve was located bilaterally with neuronavigation and then stimulated in 35 healthy subjects. Safety was assessed with adverse event reports and by medical examination in all 35 subjects. Tolerability was defined as each subjects' self-determined ability to withstand at least 2 minutes of stimulation at escalating power levels. MRI perfusion cerebral blood flow (CBF) measurements were available in 31 of the subjects. Stimulation produced a clear (≥ 25%) increase in CBF in 10 of 31 subjects, and smaller increases in most of the remaining subjects. These results support the development of our device as an emergency ischemic stroke treatment.**

I. Introduction

Stroke is the leading cause of severe disability and the second leading cause of death worldwide. Around 20% of stroke patients die in the first year after the event. Stroke can be classified as ischemic or hemorrhagic [1]. Ischemic stroke – which is the majority of all strokes - is caused by the occlusion of a cerebral artery, typically with a blood clot. The occlusive blood clot causes a critical loss of cerebral blood flow (CBF) to a brain region and eventually death of the ischemic brain tissue [2]. Emergency treatment for ischemic stroke is available in the form of intravenous tissue plasminogen activator (rtPA) and endovascular clot retrieval catheter procedures, which aim to enzymatically dissolve the occlusive blood clot or physically remove it so as to restore the lost blood flow. But these standard-of-care treatments are rarely used because of the need for specialized personnel [2, 3] and the numerous contraindications to treatment [4].

Dilation of the cerebral arteries is a well-known effect of facial nerve stimulation whether by invasive electrical stimulation or non-invasive magnetic stimulation [5-10]. Indeed, one company (BrainsGate) is in late-stage clinical testing of an invasive facial nerve stimulator as a treatment for ischemic stroke in the 8-24 hour post-stroke therapeutic window [11, 12]. In contrast, our research team is developing a non-invasive magnetic facial nerve stimulator for clinical use. Our device – called the VitalFlow™ stimulator – places proprietary magnetic stimulation coils on both sides of the head so that the magnetic field is focused upon the geniculate ganglion region of the facial nerve. The ear canal points at the geniculate ganglion region of the facial nerve, which is also the last portion of the nerve to contain the autonomic fibers, which at that point separate from the nerve trunk as the petrosal branches to the cerebral arteries.

In clinical use at specialized "Stroke Center" hospitals, the VitalFlow stimulator would improve delivery of intravenous rtPA to the site of the occlusive blood clot and allow easier navigation of endovascular catheters to retrieve occlusive blood clots. The VitalFlow would also provide rtPA- and endovascular catheter-ineligible patients an emergency treatment option. At non-Stroke Center hospitals, VitalFlow treatment could be administered to ischemic stroke patients prior to transport to a Stroke Center for definitive treatment, thereby expanding the availability of stroke healthcare services and reducing the time from stroke onset to an initial brain-saving treatment. Thus, the value of the VitalFlow stimulator is that it complements the current standard-of-care treatments for ischemic stroke and that it provides an emergency treatment for ischemic stroke patients who have no other treatment option.

Herein we report the results of the first test of the VitalFlow stimulator in humans: a study demonstrating the safety, tolerability, and effectiveness of increasing CBF of the VitalFlow stimulator in healthy subjects.

II. Procedure

The Medica Sur Ethics Committee and the Metropolitan University Ethics Committee approved the research protocols. This study was conducted under Good Clinical Practices (GCP) with auditing. The study was carried out in two parts: Part 1 assessed a full panel of safety measures including audiological and ophthalmologic tests in addition to tolerability and CBF responses; Part 2 discontinued audiological and ophthalmologic testing based on the results of Part 1, and continued to assess other measures of safety, tolerability, and CBF responses.

A. Subjects Selection and Exclusions

In Part 1, a total of 24 subjects (13 males and 11 females) were enrolled. To be eligible for the study, subjects had to have no medical conditions, either active or in the past. As a condition of enrollment, subjects also had to have normal audiological, otologic, and ophthalmic examinations as determined by a contracted clinical audiologist and ophthalmologist. Similarly, prior to stimulation, subjects had to have normal brain MRI, MR angiography, and neurological examinations as determined by a neurosurgeon (F. Castro-Prado). All subjects were between 20-40 years-of-age and the average age of the group was 23.6 years.

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In Part 2, an additional 13 subjects were enrolled, bringing the total group size to 37 subjects (30 males and 17 females). To be eligible for Part 2 of the study, subjects had to be free of renal, neurological, or cardiovascular disease, and had to have normal brain MRI, MR angiography, and neurological examination as determined by the neurosurgeon. All subjects were between 20-40 years-of-age, and the additional subjects changed the overall average of the group to 23.9 years.

After enrollment, two subjects from Part 1, both males, had to be removed from the study on the day of stimulation when they revealed that they had preexisting medical conditions. One subject had previously experienced syncope and another subject had a history of migraines. This left 35 subjects (28 males and 17 females) in the study.

B. *Magnetic Stimulation*

For all subjects, neuronavigation was performed based on T1 and T2 MRI reconstructions and the geniculate ganglion was identified bilaterally as previously described [14]. After the adequate placement of the stimulation coils in a fixed position made possible by a headrest with lockable arms (Figure 1), stimulation was delivered in biphasic pulses of 280 μs at 10 Hz [15, 16].

The power of the magnetic stimulation was adjusted to each subject's individual level of toleration in a stepwise fashion. Stimulation started at 40% power of maximum stimulator output for 10 seconds, and only after the subject indicated 'thumbs up' approval was the power increased by 10% for another 10-second period. Then, the subject could decide in favor of another increase in stimulation power with a 'thumbs up' signal or disapprove of the last increase with a 'thumbs down' signal, which led to a 10% reduction in stimulation power. When the subject decided to maintain stimulation at a certain power level, he or she shook the hand side-to-side, at which point the stimulation was continued at that power for a period of 3 minutes. Subjects were gently encouraged by the study investigator (A. Garcia) to maximize the stimulation power received.

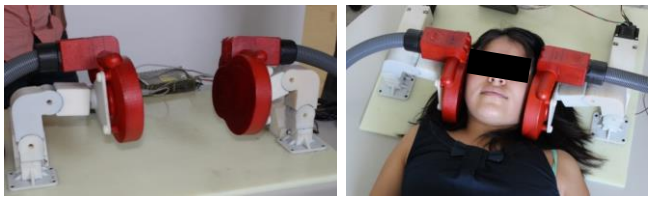

Figure 1. The clinical prototype VitalFlow used in the healthy subject study. Stimulus generator and cooling system components not shown.

B. *Safety and Tolerability*

The study procedures are shown in Table 1. The subjects enrolled in Part 1 of the study had ophthalmologic (intraocular pressure) audiological (audiometric graph, stapedial reflex, and Frenzel maneuvers) evaluations before and after stimulation. All subjects had a neurological examination (cranial nerves, sensation, reflexes, motor strength) prior to and 24 hours after stimulation. Adverse events were spontaneously reported by all subjects throughout the study. Adverse events of interest were also queried immediately after stimulation by the study investigator according to Table 2; the adverse events of interest were expected as a results of stimulation based on the neuroanatomy of the facial nerve and nearby inner ear structures.

Tolerability was defined as the stimulation power a subject could receive continuously for at least 2 minutes. The target duration for stimulation was 3 minutes.

TABLE 1. Table of procedures per visit

Procedure	Visit 1: Subject Eligibility	Visit 2: Stimulation	Visit 3: 24 hours after stimulation
Informed Consent	X		
Eligibility Criteria Review	X		
Medical Evaluation	X		X
MRI baseline		X	
MRI post-stimulation		X	
Intraocular pressure	X		X
Audiological evaluation	X		X
Neurological evaluation pre- and post-stimulation		X	
Stimulation		X	
Adverse Event Reporting	X	X	X
Adverse Event Query		X	
Concomitant medications	X	X	X
Device Events	X	X	X

TABLE 2: Adverse events query after stimulation

Did you feel vertigo or the sensation of movement?
Did you sense visual flashes?
Did you feel pain in stimulation area?
Did you feel pain in another area?
Did you have ringing in the ears?
Did you feel nauseated?
Did you have an abnormal taste sensation?

C. *Efficacy*

Efficacy of stimulation was evaluated as the change in perfusion index measures of CBF by contrast-enhanced MRI. The change in perfusion index between pre-stimulation baseline and post-stimulation was measured for each subject. Post-stimulation MRI was initiated approximately 10 minutes after stimulation ended because of the time required to position the subjects in the MR scanner.

Previously, we determined that the intra-individual variability of the perfusion index measure of CBF in our MR scanner is ± 25%. Therefore, any change in perfusion index between baseline and post-stimulation that was less than 25% was considered as a "non-responder" in this study.

Four subjects did not provide usable CBF data. Technical issues with the MRI scanner rendered the data unusable in the first four subjects and a fifth subject who did not receive a complete stimulation due to overheating of the VitalFlow due to an incomplete cooling line purge.

D. *Image Acquisition*

MRI was performed on a 3T MRI scanner (Achieva; Philips Healthcare), using an 8 channel brain coil. We used T1W_3D_TFE (TR/TE =7.5/3.4 ms, flip angle= 8°, FOV= 250 mm), a T2W (TR/TE =2500/390 ms, flip angle= 90°, FOV= 250 mm), a PRESTO (TR/TE =17/25 ms, flip angle=

7°, FOV= 230 mm, Nr of Dynamics = 50, Dummy 5), MIP 3D_PCA (TR/TE =25.6/3.5 ms, flip angle= 18°, FOV= 220 mm),ASL (TR/TE =4000/10 ms, flip angle= 90°, FOV= 240 mm, Nr of Dynamics = 50), 3D_PCA (TR/TE =16.2/4/4 ms, flip angle= 7°, FOV= 150 mm).

E. Image Processing

The perfusion index maps were generated with the Philips software, using the INDEX maps we selected. Specifically, from 30 slices, we made our selection from the 12th through 23rd slices. The brain was identified in these slices and for each slice we drew an oval-shaped ROI. Then, within each ROI we obtained the mean and the standard deviation of the perfusion index. The ROI was propagated in all the selected slices taking care that only brain tissue was processed.

Perfusion analysis per group was done with ImageJ 1.45s developed by the National Institutes of Health, USA. Dicom Image was loaded and a ROI with a 153355 area applied to each slice using Multi-measure plug-in.

F. Data Analysis

Safety data were analyzed on an individual basis and according to the distribution across stimulation powers. CBF responses were analyzed as the change in perfusion index between pre-stimulation baseline and post-stimulation measures. Individual subject data (the average ± SEM of measures across the slices) were analyzed by linear regression against the stimulation power received by the subjects.

III. RESULTS

A. Safety and Tolerability

Other than the VitalFlow overheating during one stimulation trial and shutting down automatically, no other device events were encountered. No change in audiometric, ophthalmologic, or neurological examination was noted in any of the 24 subjects in Part 1 of the study.

Table 3 shows adverse events reported by all 35 subjects. None of the adverse events experienced by subjects persisted after the stimulation was completed, nor was any adverse event judged as serious. No adverse event limited or caused premature termination of the stimulation; all subjects completed 3 minutes of stimulation at their selected level of stimulation power.

B. Efficacy

Figure 2 shows the perfusion images of CBF before and after stimulation in a representative subject from the responder group. The gray oval shows the ROI used in order to restrict the perfusion index CBF measure for each slice to the brain.

Figure 3 shows perfusion index CBF measures from individual subjects based on a response ≥ 25% over baseline ("responder") and a response < 25% ("non-responder"). Overall, 10 subjects were classified as responders and 21 subjects were classified as non-responders. No subject exhibited a decrease in perfusion index CBF measures after stimulation.

TABLE 3. Adverse events and tolerability.

		Maximum stimulation power achieved (number of subjects)					
		< 50% (2)	50% (1)	60% (4)	70% (8)	80% (17)	90% (3)
Expected adverse events during stimulation	Metallic taste sensation	0	0	**1**	**1**	**1**	0
	Vertigo/ sensation of movement	0	0	0	**1**	**2**	**1**
	Tinnitus/ Ringing ears	0	0	0	0	0	0
Adverse events during stimulation	Visual flashes	0	0	**1**	**2**	**3**	**1**
	Nausea	0	0	0	0	**2**	**1**
	Sweating	0	0	**2**	0	**7**	**2**
	Jaw pain or soreness	0	0	**2**	**5**	**11**	**2**
	Neck pain or soreness	0	0	**3**	0	**1**	0
Adverse events after stimulation	Any	0	0	0	0	0	0

Table 3. Adverse events spontaneously reported by the subjects and reported in response to the query of the study investigator. Tolerability is shown by the number of subjects achieving each level of stimulation power.

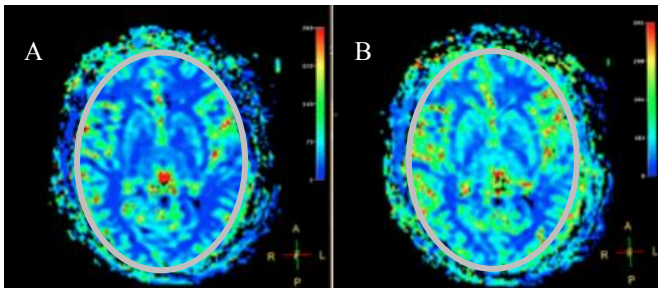

Figure 2. Perfusion image pre-stimulation (A) and post-stimulation (B). Grey oval shows the used ROI. Subject #10, stimulation power = 90%.

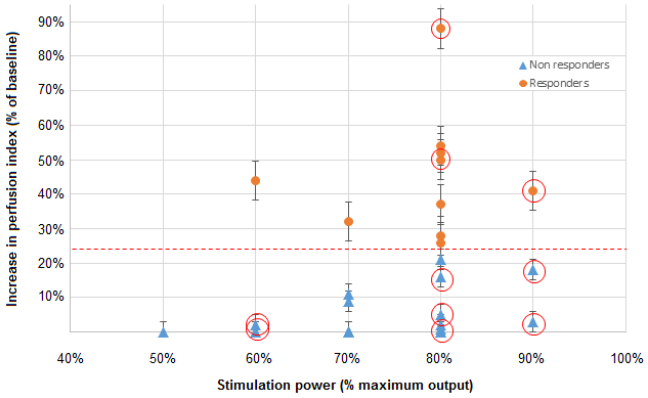

Figure 3. Graph of the responders group (≥25% change in CBF) and the non-responder group (< 25% change in CBF). 10 subjects were classified as responders and 21 subjects were classified as non-responders. 10 subjects exhibited sweating as an adverse event (red circles). Correlation factor is .0311±.0067.

IV. DISCUSION

The clinical prototype VitalFlow demonstrated a better-than-expected adverse event profile, with few adverse events of interest being reported. Common minor adverse events included jaw pain or soreness (20 subjects), sweating on the neck and face (11 subjects), visual flashes (7 subjects), neck pain or soreness (4 subjects), and nausea (3 subjects). None of these adverse events were limiting of stimulation, persisted after stimulation, or posed a risk to patient safety.

Tolerability was found to be improved with gentle encouragement from the study investigator: 20 of the subjects could tolerate stimulation power at 80% or greater with encouragement.

Responders to stimulation (i.e., a CBF increase of ≥ 25%) represents about a third of the total of the group, and in that group the response to stimulation could be quite sizable. No clear dose response relationship could be observed in the available dataset, but such evaluations (currently underway) will include other factors that influence the effective stimulation power at the target, e.g., the distance from the stimulation coil to the target, or else head size as a surrogate.

Early studies in normal animals also reported inconsistent response to electrical facial nerve stimulation [17], with some animals not responding to stimulation and apparently individual animals exhibiting variability in their responses to repeated stimulation. In part, this may reflect opposing neural mechanisms and/or arterial autoregulation that serves to maintain a steady level of CBF in normal animals. Indeed, we unexpectedly observed a high rate of sweating in the head and neck as an adverse event, and sweating reflects activation of the sympathetic nervous system that may independently counteract a CBF response through vasoconstrictive innervation of the cerebral arteries [18]. Further investigation is needed to understand this inter-subject (and potentially intra-subject) variability in healthy human subjects, and whether or not it occurs in conditions where an increase in CBF is clearly needed by the subject, e.g., as in ischemic stroke.

V. CONCLUSION

The VitalFlow stimulator appears to be safe, tolerable, and effective at increasing CBF in an initial normal subject study.

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