2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Cerebral and muscle near-infrared spectroscopy during lower-limb muscle activity – volitional and neuromuscular electrical stimulation

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Abstract*—Chronic venous insufficiency (CVI) can lead to blood clotting in the deep veins of the legs, a disease known as deep vein thrombosis. An estimated 40 percent of people in the United States have venous insufficiency that may be ameliorated with neuromuscular electrical stimulation (NMES). Near-infrared spectroscopy (NIRS) is a non-invasive optical imaging method for monitoring hemodynamics. NIRS, being an optical technique has no stimulation artefact, can be combined with NMES for theranostics application. In this study, we combined muscle NIRS (mNIRS) with electromyogram (EMG) of the calf muscles to detect blood volume changes (based on total hemoglobin concentration) in the muscle during volitional tiptoe movements at different frequencies. Also, blood volume changes were measured during NMES (using the *geko*™ device) at different device settings. In the mNIRS+NMES study, we also measured the cerebral hemodynamics using functional NIRS (fNIRS). The mNIRS was conducted using a frequency domain (FD) method (called FDNIRS) that used a multi-distance method to isolate muscle hemodynamics. FDNIRS-EMG study in ten healthy humans found a statistically significant ($p<0.05$) effect of the tiptoe frequencies on the EMG magnitude (and power) that increased with tiptoe frequency. Also, the muscle blood volume (standing/rest) decreased ($p<0.01$) with increasing tiptoe frequency and increasing NMES intensity that was statistically significantly ($p<0.05$) different between males and females. Moreover, increasing NMES intensity led to a statistically significant ($p<0.01$) increase in the cerebral blood volume – measured with fNIRS. Therefore, combined mNIRS and fNIRS with NMES can provide a theranostics application for brain+muscle in CVI.

I. Introduction

Near-infrared spectroscopy (NIRS) is a non-invasive optical imaging method for monitoring oxygen availability and utilization in the tissues [1]. NIRS allows relative measurements of changes in the hemoglobin oxygenation and deoxygenation in the brain and hemoglobin plus myoglobin oxygenation and deoxygenation changes in the muscle during a functional task. In this paper, we applied multi-distance frequency domain (FD) NIRS to study muscle hemodynamics and continuous-wave (CW) fNIRS to study cerebral hemodynamics during lower-limb tip-toe exercise and neuromuscular electrical stimulation (NMES) of the common peroneal nerve using the *geko*™ device. In FDNIRS, the light intensity is modulated at radio frequencies in the range of several 10 − 100 MHz and then sent through the tissue. The photomultiplier tubes or fast photodiodes collect the scattered light, which shows attenuation as well as a phase shift with respect to the incident signal. The measurement of phase shift allows the calculation of the optical path length and thereby differentiates between scattering and absorption effects. In CW fNIRS, continuous light is used to non-invasively investigate changes in the hemoglobin oxygenation in the human brain tissue [2]. We also combined muscle NIRS with electromyogram (EMG) to better quantify the hemodynamic response during tip-toe exercise in young and healthy humans [3], as shown in Fig. 1.

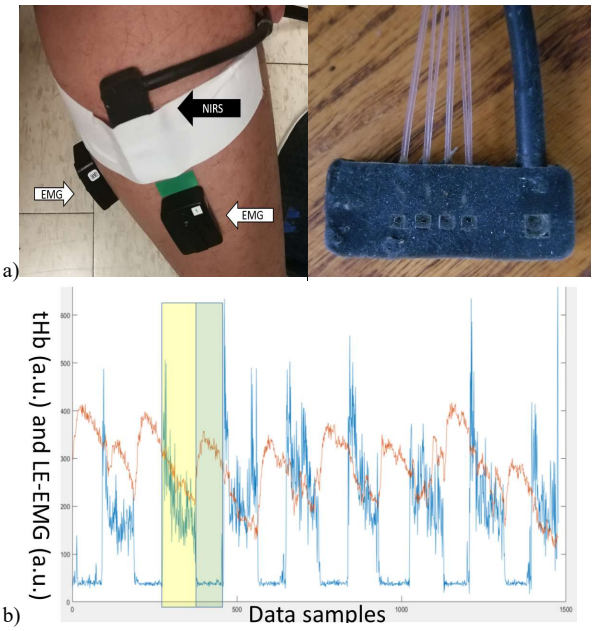

Fig. 1. a) Left panel: electromyogram (EMG) detectors positioned on the lower part of the calf muscle. Multi-distance frequency domain NIRS (FDNIRS) detector (see the right panel for details) positioned on the upper part of the calf muscle. b) Total hemoglobin concentration (tHb, orange line) changes in conjunction with EMG linear envelope (LE-EMG, blue line) during tip-toe movements in healthy people. The region of muscle activation (LE-EMG activity) and recovery (tHb recovery) is highlighted in yellow and green respectively.

II. Methods

A. Muscle NIRS-EMG and human study

The institutional review board and ethics committee of the

*Research supported by University at Buffalo, specifically, the Community for Global Health Equity funding and the Buffalo Blue Sky funding. The *geko*™ devices were provided by the Firstkind Ltd, UK.

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university approved the study. Ten young and healthy subjects (age 21-28 years, six males and 4 females) participated in the study I. In order to capture the effects of muscle contraction on hemodynamics, we combined muscle NIRS (mNIRS) with EMG of the calf muscles to detect blood volume changes in the muscle based on total hemoglobin concentration (HbT) at different frequency of tip-toe movements. The subjects were provided a metronome (beats per minute, BPM: 10, 30, 50) to make the tiptoe movements. Fig. 1 shows the multi-distance FDNIRS-EMG sensor montage. Here, mNIRS was captured at 10Hz using the Imagent™ FDNIRS system (ISS, USA) and the EMG (DC-500 Hz, 160 dB/Dec) was captured at 2000 Hz by the Trigno EMG Systems (Delsys, Inc. USA). Multi-distance FDNIRS flexible sensor (right panel of Fig. 1) was placed on the skin using a flexible bandage without tightening (muscle movement artefact). Two EMG detectors were placed under the FDNIRS to record calf muscle activation during tip-toe movements. Three tip-toe rates, 10, 30, 50 BPM, were presented to the subjects in random order. Each subject was tested twice for 10, 30 and 50 BPM, as listed in the Table I.

In a separate study II on ten young and healthy subjects (age 21-28 years, six males and 4 females), NMES was conducted using a disposal *geko*™ device for transcutaneous common peroneal nerve stimulation at 11 preset stimulation levels at a frequency of 1 Hz – presented in a random order to subjects. The 11 preset stimulation levels included pulse-widths of 35 µs, 50 µs, 70 µs, 100 µs, 140 µs, 200 µs, 280 µs at 27mA pulse current, then 280 µs and 400 µs pulse-widths at 38mA pulse current, and then 400 µs, 560 µs pulse-widths at 54mA 38mA pulse current. After a rest of 5 minutes, the baseline measures were taken for 5 minutes while the subject was seated. Then, NMES was applied at eleven stimulation intensities in random order. In a repeated-measure design, NMES was applied for 2 minutes with a rest of 3 minutes while mNIRS-EMG and fNIRS were recorded for a duration of 55 minutes with the subject seated with the knees bent at 90-degrees.

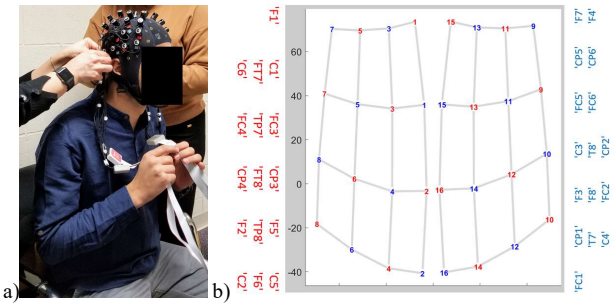

Fig. 2. a) fNIRS cap. b) fNIRS optodes with sources (red) and detectors (blue) placed according to 10/10 electroencephalogram locations.

TABLE I. EXPERIMENTAL PROTOCOL FOR FDNIRS-EMG TEST – SUBJECT-WISE BPM ALLOCATION

Name Mark Gender	Test1	Test2	Test3	Test4	Test5	Test6
Subject1 [M] M	30	50	10	30	10	50
Subject2 [R] F	10	30	50	30	50	10
Subject3 [Z] F	10	30	50	30	50	10
Subject4 [W] M	30	50	10	30	10	50
Subject5 [B] M	10	30	50	30	10	50
Subject6 [Y] F	30	10	50	30	50	10
Subject7 [J] M	30	10	50	10	50	30
Subject8 [C] F	30	10	50	30	50	10
Subject9 [X] M	10	30	50	30	50	10
Subject10 [P] M	10	50	30	50	10	30

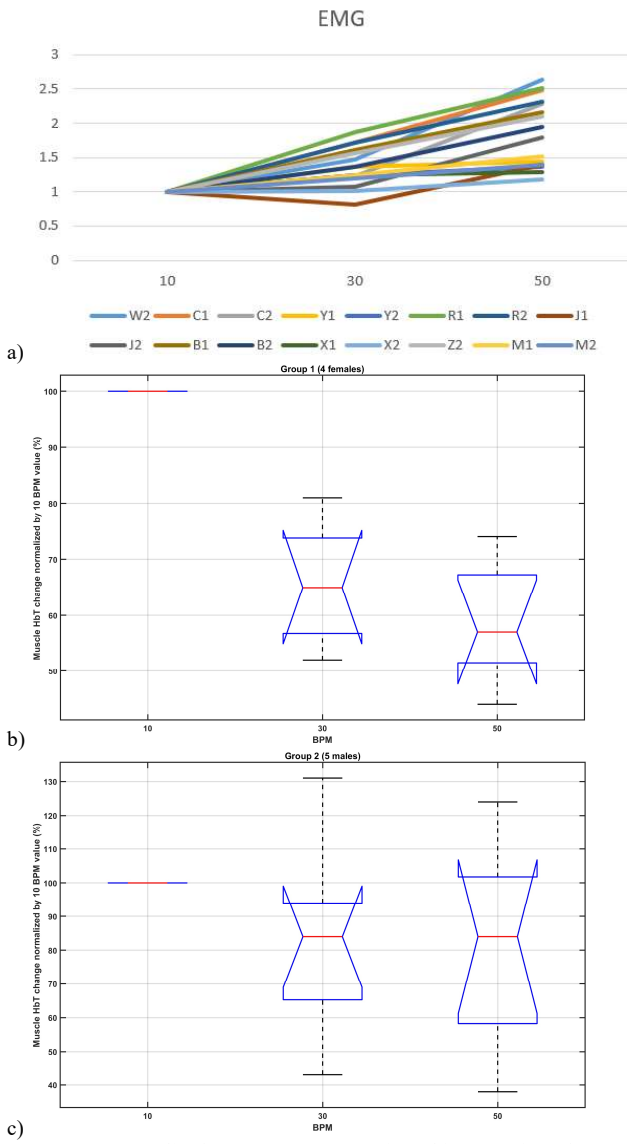

Fig. 3. a) Normalized EMG power (Y-axis, arbitrary units) changes across 10, 30, 50 beats per minute (BPM) (X-axis) volitional tip-toe movements. EMG power at BPM 10 was considered one for normalization purposes. b) Boxplot of the Group 1 (4 female subjects: C Y R Z) data for normalized muscle HbT (Y-axis) changes across BPM (X-axis). c) Boxplot of the Group 2 (5 male subjects: W B X J M) data for normalized muscle HbT (Y-axis) changes across BPM (X-axis).

B. fNIRS and human study

After fNIRS cap setup (see Fig. 2a), fNIRS was conducted at 10Hz using NIRSPORT 2 (NIRx, USA) during eleven repeated blocks of 3 minutes rest and 2 minutes NMES for with different NMES intensity applied in random order. Our fNIRS optode montage consisted of 16 long-separation (~3.5cm) sources and 16 long-separation (~3.5cm) detectors that covered the sensorimotor brain areas as shown in Fig. 2b.

C. EMG pre-processing

EMGworks Analysis (Delsys Inc., USA) was used to compute the root-mean-square EMG envelope, as shown in Fig. 1b. Root-mean-square EMG envelope provided the amplitude of the EMG signal as a measure of the signal power. The volitional EMG envelope was resampled at 10Hz to match

the sampling frequency of FDNIRS. EMG was not

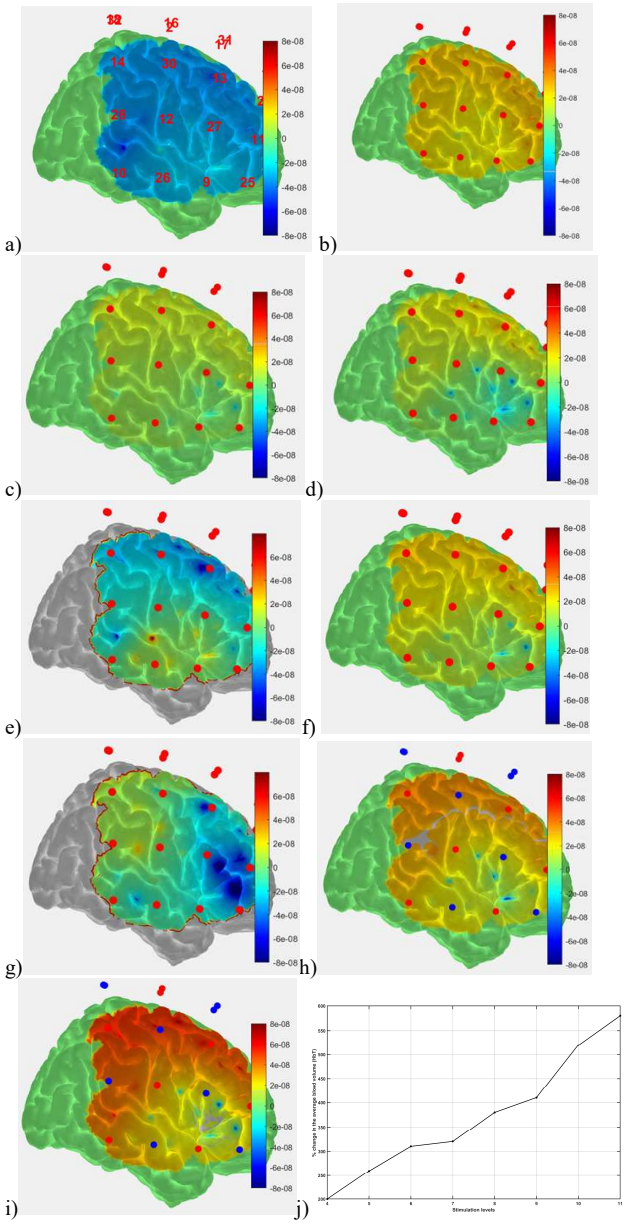

Fig. 4. Group cortical activation from AtlasViewer at baseline (a), and at the NMES stimulation levels 4 (b), 5(c), 6(d), 7(e), 8(f), 9(g), 10(h), and 11(i). (j) Percent change in the average HbT from baseline across all fNIRS channels for the stimulation levels from 4 to 11.

investigated for NMES study due to stimulation artefacts and needs additional processing as discussed earlier [4].

D. Muscle NIRS-EMG joint-processing

ISS Boxy Software package (ISS, USA) was used to process the multi-distance FDNIRS data. We computed total hemoglobin concentration (HbT) by adding the oxyhemoglobin and deoxyhemoglobin concentration to estimate the blood volume [5]. Here, the calf venous blood-filling index (during standing/rest) and calf venous ejection index (after tip-toe movement) are important parameters to be considered during light-intensity exercise for clinical stages of CVI [6]. Therefore, the related regions of muscle activation (tip-toe movement) and recovery (standing/rest) from EMG were epoched in yellow and green respectively as shown in Fig. 1b. At an increased tip-toe rate (10, 30, 50 BPM), the time available for recovery following calf venous ejection was reduced. All subject data was normalized with the measures at 10 BPM in order to compare the changes in the EMG envelope and average HbT at recovery epoch for 30 and 50 BPM. After normalization with 10 BPM, we used two-way ANOVA (analysis of variance) and post-hoc multiple-comparisons ('multcompare' in Matlab) to see if factors - subjects and/or BPM - have an effect.

E. fNIRS processing

Data processing was conducted using the open-source HOMER3 toolbox [7] in Matlab (Mathworks Inc., USA). The raw optical intensity signal was first converted into optical density (function: hmrR_Intensity2OD), then motion artifact detection and correction was conducted using a hybrid method based on a spline interpolation method and Savitzky–Golay filtering (function: hmrR_MotionCorrectSplineSG) [8] using default parameters. Then, bandpass filtering was conducted (function:hmrR_BandpassFilt:Bandpass_Filter_OpticalDensity) within 0.01-0.1Hz followed by conversion to oxy-hemoglobin (HbO) and deoxy-hemoglobin (HHb) concentration with default partial path-length factor (function: hmrR_OD2Conc). Finally, systemic artefacts were removed using the average of all long separation channels before computing the hemodynamic response function (HRF) using General Linear Model (GLM) (function: hmrR_GLM_new). GLM was performed to determine the HRF during the stimulation period from the resting state using ordinary least squares [9] with the consecutive sequence of Gaussian functions (stdev=0.5, step=0.5). Then, we used open-source AtlasViewer [10] in Matlab (Mathworks Inc., USA) to determine cortical activation for the HRF. We used their default "Colin27" digital brain atlas for HRF image reconstruction with regularization scaling parameter = 0.01.

III. Results

A. Muscle mNIRS results

Fig. 3a shows an increase in the EMG power with increase in BPM during volitional tip-toe movements, as expected. The mNIRS (HbT) data showed subject's gender specific effect ($p<0.05$), as shown by the boxplots in the Fig. 3b and 3c where the subjects were divided into two groups – female (Group 1) and male (Group 2) respectively. On each box, the central mark indicates the median, and the bottom and top edges of the box indicate the 25th and 75th percentiles, respectively. The whiskers extend to the most extreme data points not considered outliers. The mNIRS (HbT) decreased with an increase in BPM due to reduced time for recovery; however, a floor effect (i.e., a minimum venous retention index) is postulated for higher BPM which is more prominent in male Group 2 than the female Group 1. Fig. 3b and 3c also show a significant ($p<0.01$) effect of BPM. In the NMES study, the male and female mNIRS (HbT) responded differently ($p<0.05$), as well as there was a significant ($p<0.01$) effect of the NMES stimulation levels that needs further investigation.

B. Brain fNIRS results

Group cortical activation maps from the AtlasViewer [10] are shown in the Fig. 4. There was a significant ($p<0.01$) effect of the NMES stimulation levels where higher stimulation levels led to higher hemodynamic change across most fNIRS channels when compared to the baseline (no NMES) as shown in Fig. 4j as percent change from the baseline. Stimulation levels 7 (Fig. 4e) and 9 (Fig. g) led to regional hypoactivation that are related to 280 μs at 27mA pulse current (level 7) and 400μs pulse-widths at 38mA pulse current (level 9) where somatosensory stimulation needs further investigation [11].

IV. Discussion

Our preliminary study showed the feasibility of mNIRS and fNIRS during volitional lower limb activity and NMES. During volitional lower limb tip-toe movements, a floor effect was observed with an increasing BPM (see Fig. 3) where HbT (blood volume) in the muscle could not decrease at the same rate (i.e., a minimum venous retention index) with increasing BPM (or, muscle activation as seen by EMG power – Fig. 3b,c). From the FDNIRS-EMG data, we found that the change in EMG with increasing BPM was similar across subjects, which indicated similar calf muscle activation across male and female subjects. Here, as BPM increased, the EMG power increased almost linearly with BPM where the slopes were found similar across subjects. However, for mNIRS (HbT), HbT decreased more with an increase in BPM in female Group 1 when compared to the male Group 2, as shown in Fig. 3b and 3c respectively. Prior work [12] have shown that males have a higher peak systolic velocity and higher volume flows due to bigger calf muscles and the vein diameters are greater in males than females. Therefore, difference between the female Group 1 and the male Group 2 can be explained by gender differences in the anatomy, and it is postulated that the changes during increasing BPM are smaller in males than females due to faster hemodynamic recovery (venous blood-filling) rate. Gender differences were found by mNIRS-EMG approach during muscle activation that is proposed to be related to venous sufficiency (venous blood-filling) that can be different according to individual vessel geometry, blood viscosity, etc.

In our prior computational modeling [13], we concluded that in the range of 3.4 - 4.25 N*s/m^2 of viscosity and 6 - 12 Hz stimulation frequency, the first peak of the blood vessel's end velocity decreased with an increase in viscosity and a decrease in pulsatile frequency. This is critical since CVI is a condition that makes it difficult for blood to return to the heart from the legs leading to venous stasis. Here, blood flow from the periphery to the right atrium is referred to as venous return and this flow back to the heart against gravity is facilitated by lower limb muscle contraction that compresses the local intramuscular and deep veins. This increases the intraluminal pressure that drives this venous flow while retrograde flow is prevented through the action of a system of muscular venous pumps and bicuspid valves. Aging and many cardiovascular diseases are related to abnormal cardiac output that may be partly due to inadequate venous return. Also, CVI can lead to blood clotting in the deep veins of the legs, a disease known as deep vein thrombosis, which is also known as post-thrombotic syndrome where NMES may facilitate venous return during walking even in low resource settings [14]. Based on our preliminary results, we postulate that mNIRS in conjunction with EMG can not only be used to screen for CVI but can also improve hemodynamics using NMES. Also, an interesting hypothesis is an increase in cerebral blood flow during the acute phase of cerebrovascular accident, thus reducing the final infarct volume and improving the outcome. Electroacupuncture [15] and external counter pulsation [16] have been shown to increase cerebral blood so could NMES using the *geko*™ device can achieve a similar effect by somatosensory stimulation along with leg muscle contraction?

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