A novel device for non-invasive cerebral perfusion assessment

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Abstract

Currently brain perfusion can be assessed by the means of radio-invasive methods, such as single-photon emission computed tomography and positron emission tomography, or by high-tech methods such as magnetic resonance imaging. These methods are known to be very expensive, with long examination time, and finally, cannot be used for assessing brain oxygen distribution in relation to exercise and/or cognition-tests. The near infrared spectroscopy (NIRS) is a non-invasive diagnostic technique. In real time it is capable of measuring tissue oxygenation using portable instrumentation with a relative low cost. We and other groups previously adopted this instrument for investigation of the oxygen consumption in the muscles at rest and during exercise. NIRS can be now used to assess brain perfusion through the intact skull in human subjects by detecting changes in blood hemoglobin concentrations. Changes in perfusion can be related to both arterial and venous problems. This novel equipment features allow for a wide field of innovative applications where portability, wearability, and a small footprint are essential. The present review shows how to use it in relation to exercise protocols of the upper and lower extremities, measured in healthy people and in conditions of arterial and chronic cerebro-spinal venous insufficiency.

Historical background

The discovery of the infrared region in 1800 is credited to William F. Hershel's famous work, *Experiments on the Refrangibility of the Invisible Rays of the Sun*.[1] Wheeler[2] described the near infrared (NIR) region as extending *from about 2 microns (m) into the visible at about 0.7 m*. Goddu and Delker[3] demonstrated the spectra-structure correlations and average molar absorptivity for a number of functional groups for the NIR region, and the maximum recommended path lengths for twelve solvents over the wavelength region 1.0 to 3.1 *m*. Ellis[4], Kaye[5] and Goddu[6] *et al.* compiled an extensive review of NIR spectrophotometry prior to 1960 and subsequently Schrieve *et al*.[7] discussed applications for the short-wave NIR region, referring to synonyms such as *the far-visible*, the *near, near-infrared* to describe the range of approximately 700 to 1100 nanometers (nm) of the electromagnetic spectrum.[8,9]

The new decade of the 1960s brought about a prolific series if papers related to direct determination and the measurement of light transmittance and reflectance properties of intact biological materials. Early work, most of which used multiple linear regression to identify key calibration wavelengths, used both filter and dispersive scanning instruments to relating NIR spectral response to reference analytical data.[8,9]

Near infrared has been used for analysis of gasoline, fine chemicals, polymers and pharmaceuticals, both with dispersive and Fourier-transform NIR based instruments.[10] More recently, medical applications for near-infrared have proliferated into areas of blood analyze monitoring and imaging of materials including tissue.[11]

Near infrared spectroscopy

The near infrared spectroscopy (NIRS) was recently quoted in *Annals of the New York Academy of Sciences*[12] as one of the most promising technology in the next decade in monitoring finalized to the neuro-protection, being able to measure at regional level parameters such as oxygenation and blood flow within the brain tissue.

The NIRS is a non-invasive diagnostic technique. In real time it is capable of measuring tissue oxygenation using portable instrumentation and a low cost. The NIRS uses a means harmless for studying biological tissues, optical radiation, precisely the spectral band infrared with a wavelength of 700-950 nm.[13,14] The photon NIR launched in biological tissue through it a second path between source and detector. NIR probes have the most used source revealing, that one or more optical fibers which capture the light radiation leaking from the biological tissue after covering a distance of variable depth and shape comparable to a banana shape (Figure 1), by same side of the light source.[13,14]

The maximum distance between the fiber end and the revealing of the fiber, which emits optical radiation, is usually 3-4 cm, allowing the NIR photons penetrate into the biological tissue below up to a maximum depth of 3.5 cm.[15] The NIR photon in biological tissue undergoes two main processes: diffusion and absorption. The diffusion, dominant process in the NIR spectral band, is the basis of the typical zigzag of the photon within the tissue, and is quantized by the scattering coefficient. The absorption by the biological tissue is mainly due to hemoglobin, and quantized by the absorption coefficient, measured by microseconds, with the recent NIRS methods.[16-18] The oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (Hb) have different absorption spectra in the NIR. This feature allows you to measure separately the two forms of Hb and therefore the oxygen saturation of hemoglobin (StO_2) in the tissues studied.[19] The instrumentation for NIRS time-resolved, based on the emission of light of variable intensity over time, allows to obtain data that reproduce the real state of oxygenation of the biological tissues investigated, using the dosage absolute HBO_2 and Hb and then the StO_2.[17-20]

Applications of near infrared spectroscopy for assessment of muscular metabolism in peripheral arterial disease

Peripheral arterial disease (PAD) affecting blood flow in the lower limbs is responsible for altered oxygen delivery to tissues and muscles during walking. Available methods or techniques to assess the presence or severity of PAD are performed mainly in static conditions with the ankle brachial index (ABI).[21-23] Otherwise, dynamic evaluations, such as functional tests, are related to patients symptoms and disease severity.[24]

NIRS measurements have been proposed for PAD patients, whose performance depends on both oxygen availability and its use.[25-30]

Manfredini *et al*.[24] have demonstrated that a dynamic assessment of muscle metabolism and cardiovascular response during exercise are useful for the evaluation of patients with claudication or exertional leg pain in order to

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quantify the degree of metabolic disease and to determine the presence of PAD. This muscular test with NIRS technology is particularly useful in a clinical setting to exclude vascular diseases.[24,31,32]

It is known that the exercise training is an effective treatment for claudication,[33] and walking sessions performed at a moderate level of pain are recommended for patients with PAD.[33,34] For this reasons the rehabilitation of PAD patients is monitored in dynamic conditions and not in static assessment. In literature it has been shown that using NIRS technique guidance we may obtain a significant improvement in dynamic muscle perfusion when the exercise were carried out at a prescribed intensity. These patients exhibited better walking performance, together with a greater capacity to extract oxygen in the calf and improvements in the ABI, especially in the worse limb.[35] The modifications detected through NIRS measurements, when combined with noninvasive parameters including the ABI, may explain how adaptations affect training outcomes and may therefore be useful to evaluate rehabilitation programs in patients with PAD.[35]

Thus, in summary, a parameter that can be easily measured by the means of NIRS is the resting muscle oxygen consumption (rmVO2),[36] which allows a quantification of the muscle's capacity to extract oxygen from blood. We have seen that this parameter was found to be impaired in legs of patients with chronic diseases[31,37-40] and modified following exercise training in PAD.[35]

Finally, NIRS in PAD was used to compare pneumatic pumps for the treatment of PAD in patients who cannot walk, for foot wound or whatever other concomitant problems. For instance, a novel concept for treating PAD patients by a device named gradient pump was found to be more effective as compared to classic pneumatic pump.[41]

Cerebral perfusion

Disturbances in brain perfusion can have immediate, severe and lifelong consequences.[42] Monitoring perfusion of the brain holds considerable significance to a broad range of clinical situations.[43-45] Functional studies have shown that the brain activation produces a spatially distributed and temporally varying response.[46-49]

An imaging modality that is proving to have significant impact in investigative studies is functional magnetic resonance imaging (fMRI). This technique is sensitive to the vascular response resulting from neuroactivation, specifically to the level of deoxyhemoglobin. While the utility of fMRI continues to expand, it is also clear that the technique has a number of limitations that are not encountered using NIRS technique, like the cost effectiveness as well as the impossibility to evaluate a subject under movement.[50,51]

In addition, also radio-invasive methods [single-photon emission computed tomography (SPECT) and positron emission tomography (PET)] or methods with contrast imaging (MRI) are used.[52-54] These methods prove to be very expensive, very difficult and the examination results to be long. But above all these methods are static and not dynamic.

However, all this methods of investigation allowed us to understand that even the venous drainage may lead to cerebral hypoperfusion.[55,56]

As above described, the primary application of NIRS to the human body uses the fact that the transmission and absorption of NIR light in human body tissues contains information about hemoglobin concentration changes. When a specific area of the brain is activated, the localized blood volume in that area changes quickly. Optical imaging can measure the location and activity of specific regions of the brain by continuously monitoring blood hemoglobin levels through the determination of optical absorption coefficients.[16,17]

NIRS can be used for non-invasive assessment of brain perfusion through the intact skull in human subjects by detecting changes in blood hemoglobin concentrations associated with neural activity, for example, in branches of cognitive psychology as a partial replacement for fMRI techniques.[57] However, NIRS cannot fully replace fMRI because it can only be used to scan cortical tissue, where fMRI can be used to measure activation throughout the brain. Special public domain statistical toolboxes for analysis of stand-alone and combined NIRS/MRI measurements have been developed.[58] NIRS provides quantitative data in absolute terms on up to a few specific points. The latter is also used to investigate other tissues such as, for example, muscle,[59] breast and tumors.[60]

NIRS can be used to quantify blood flow, blood volume, oxygen consumption, reoxygenation rates and muscle recovery time in muscle.[59] In perspective, it will be very interesting to measure oxygen consumption contemporaneously in the brain and in the muscle of patients with neurodegenerative disorders.

Malagoni *et al*.[61] have demonstrated that the rmVO2 values measured by NIRS were found to be significantly higher in multiple sclerosis patients compared to healthy control, and in low versus better performing patients. Such parameter might represent a marker of peripheral adaptations occurred to sustain mobility. It might be potentially useful in a clinical setting for assessing the level of skeletal muscle metabolic impairment, and for monitoring the progression of the disease, therapeutic treatments or rehabilitative programs.[61]

The instrumental development of NIRS has proceeded tremendously during the last years and, in particular, in terms of quantification and imaging.[62]

Cerebral near infrared spectroscopy

The idea to measure micro-circulatory parameters in the brain of people with neurodegenerative disorders, or with multiple sclerosis (MS), is not new. However, after the description of an association between extracranial venous flow impairment and MS, Alzheimer' and Parkinson' diseases determined a renewed interest in brain perfusion assessment.[55,56,63,64]

For the reasons above, it is important to assess perfusion also with cheaper and portable instruments. Recently, also photoplethysmography has been proposed to measure at cortical venular level deoxygenated hemoglobin in relation to cerebral perfusion in patients affected by MS. The cerebral blood volume increase was significantly smaller in the MS patients (left frontal cortex: 58%, $P<0.0001$; right frontal cortex: 59%, $P<0.0001$) compared with healthy people, again demonstrating a significant low perfusion linked with venous function.[65] However, photoplethysmography is less reliable and advanced respect to modern cerebral NIRS, which includes also several channel and devoted software for building imaging.

The latter instrument[66] is a lightweight, freely configurable, multi-channel NIRS imaging system that combines LED illumination with active detection technology for a truly wearable brain imaging solution.

These novel product features allow for a wide field of innovative applications where portability, wearability, and a small footprint are essential.

This system allows for non-invasive real-time hemoglobin measurements of the cerebral cortex (Figure 2).

The available NIRS instruments offer more than 8 sources and 8 detectors (16 sources/16 detectors in tandem mode) with a diverse array of available headgear and optical probes.[67]

The device finds application in many diseases, *e.g.* autism, intra operative monitoring, language, learning and attention, motor masks, neonatal-infant monitoring, psychiatric disorders, stroke and rehabilitation, traumatic brain injury and of course, in case of problems of cerebral venous drainage.[66,67]

Ours first experiences in brain perfusion assessment in relation to chronic cerebro-

spinal venous insufficiency (CCSVI) were performed by the means of NIRSport (NIRSport88/2.01, EMS Medical, Bologna). Dimensions 105×170×40 mm, net weight 660 g, illumination type LED, number of illumination sources 8 (16 in tandem mode), number of illumination detector 8 (16 in tandem mode), dual wavelength 760 nm, 850 nm, mode of operation continuous wave.[68]

Software for imaging building starting from hemoglobin signal

NIRS, as above explained, provides information about the level of hemoglobin/deoxygenated hemoglobin level from the different channels in the scalp of the subject under evaluation. To compare NIRS assessment with more complex diagnostic systems such as MRI, SPECT and PET is desirable to transform the biochemical signal into a mapping image. The NIRStar software package provides a user friendly graphical user interface for system control (calibration and probe setup), patient monitoring, real-time cortical 2D and 3D display capabilities and a module for hyper-scanning (Figure 3).

Contemporaneously, the instrument may derive real-time hyper-scanning capability of oxygenated, deoxygenated and total hemoglobin[69] (Figure 4).

Placement and arrangement of near infrared spectroscopy

To position NIRS optical sensors (optode), the NIRScap are used. The NIRScap is a headset that is worn on the head of the subject on which there are holes in which are inserted the optode (source and detector). Once worn NIRScap, the sensors are inserted into the holes inherent in the motor or the cognitive area to be analyzed. Through the NIRS maps we can identify the correct holes in the affected area. Very important for the graft of the sensors on the NIRScap is to remove, through a suitable stick, the hair from the entrance hole (Figure 5).

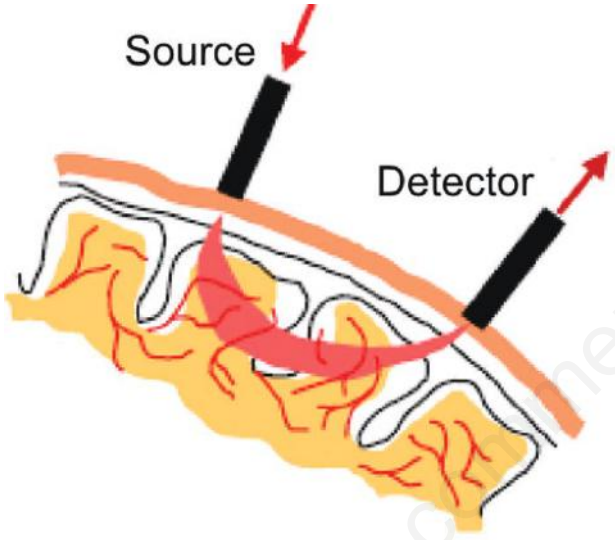

Figure 1. Propagation of the near infrared signal.

Figure 2. The near infrared spectroscopy cup with optode for the non-invasive assessment.

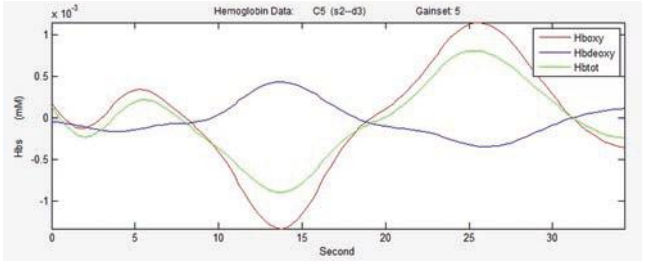

Figure 4. Oxygenated (red line), deoxygenated (blue line) and total hemoglobin (green line) variation during the near infrared spectroscopy measurement.

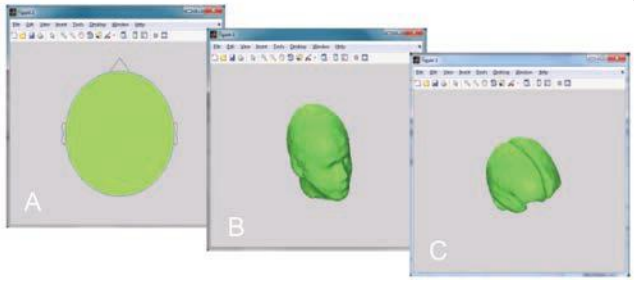

Figure 3. A) 2D graphical interface, B) 3D graphical interface, C) cortical view.

Figure 5. Left image: cap in place; middle image: remove hair; right image: ready for optode insertion.

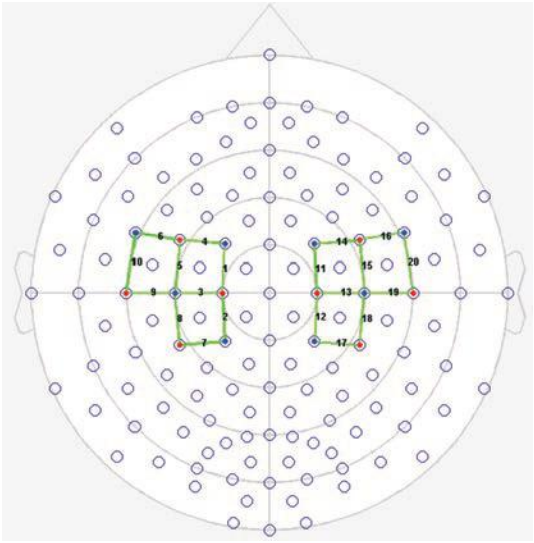

Figure 6. Motor area map to insert the optode.

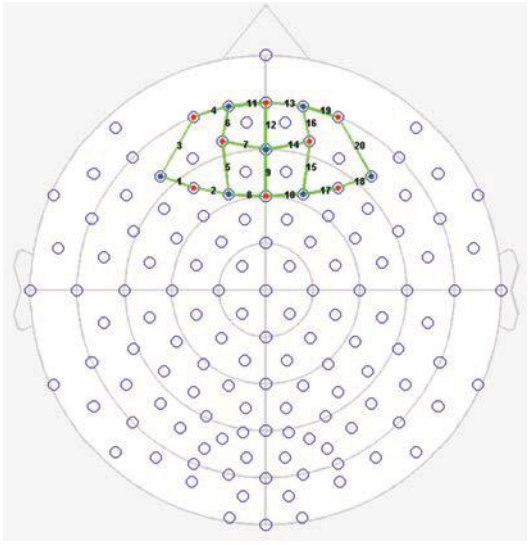

Figure 7. Prefrontal area map to insert the optode.

Cognitive and motor functional assessment by cerebral near infrared spectroscopy

The big advantage of NIRS assessment of brain perfusion is the repeatability of the assessment, as well as the fantastic opportunity to evaluate perfusion in functional conditions. For example we can analyze the cognitive and motor function of the examined subject.

Depending on the cerebral area that we want to analyze we must change the position of the sensors in the NIRScap. To assess motor function we have to analyze the cerebral motor area (Figure 6). Once positioned the sensors we can proceed with testing. Having a dynamic and not static instrumentation, we can afford to run any motor test to the subject and our protocol of investigation.

We can perform the classic finger taping, until the six minute walking tests.[46,70,71]

In this case, if we previously assess CCSVI, NIRS leads us to understand how cerebral venous function may affect brain perfusion in experimental conditions which cannot be assessed by more sophisticated equipment. Actually, it is the only way to derive micro-circulatory information during exercise.

Being the NIRS a portable instrumentation and equipped with tablet for recording data, if the subject is an athlete, we can think to do an athletic simulation or physical activity to assess the relative activity of oxygenation during exercise and then adjust the trainability or monitoring the rehabilitation exercise after trauma to measure the consumption of oxygen. To assess cognitive function, we need to change the positioning of the sensors in the NIRScap and place them in prefrontal area (Figure 7). In this case we can propose cognitive tests, *e.g.* the static paced auditory serial addition task (PASAT test) or dynamic box and block test. [71-73] The advantage of these evaluations with NIRSport is the speed of acquisition of the test; the freedom of performing the test; the opportunity to redo the test without constraints of instrumentation and recalibration, the possibility to perform any dynamic test without time and space limit.[74] NIRS is also so versatile to permit acquisition with finger compression of one carotid and or jugular, so deriving information at bed side of respective value in ensuring the correct perfusion of the organ (Figure 8).

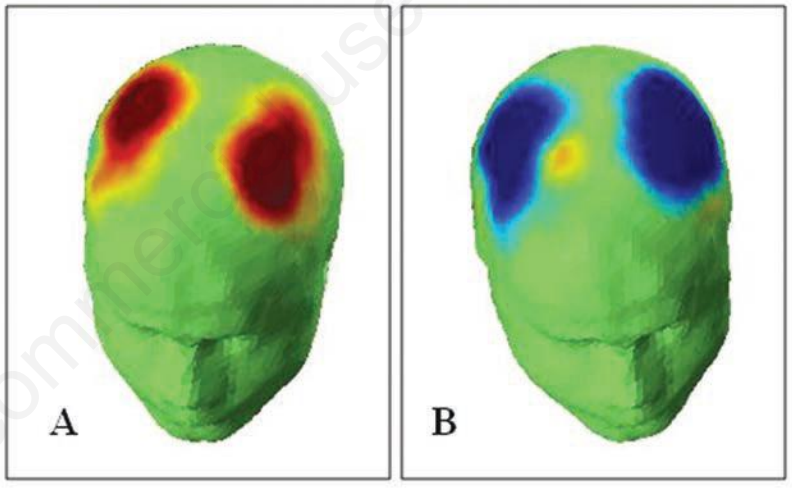

Figure 8. An example of brain perfusion with near infrared spectroscopy: A) the red area corresponds to the oxygenated hemoglobin absorption spectra image. B) the blue area corresponds the deoxygenated hemoglobin absorption spectra image.

Perspectives in neurodegenerative disease

Literature describes the first quantification by NIRS assessment of neurodegenerative diseases. In particular, the focus is based on Alzheimer and Parkinson disease.[75-78]

Given the excellent tolerability of measurement by NIRS[74] and the possibility of repeat

measurements quickly without requiring the patient immobility during the examination as a diagnostic techniques with contrast imaging, we are bringing more and more towards this new method of measuring NIR since it allows to evaluate the oxygenation and deoxygenation brain in real time.

In addition to the part of the imaging NIRS is used to monitor the rehabilitation[78,79] and post-surgical treatment, monitor the surgical procedure[80,81] and the relative perfusion and the ability to constantly monitor the progress of the patient during daily activities. The life is not static and the perfusion parameters in dynamic approaches to the actual daily activities are to be analyzed.

It is known that the CCSVI is a condition leading to cerebral hypoperfusion.[55,82] Currently for this survey are used SPECT and MRI[52,56] to be valued the brain perfusion. These allow us to see deep into the cranial perfusion, but only in a static way. The NIRS could help us to complete the perfusion assessment in patients with CCSVI in dynamic condition and then we have global information given by more accurate functional evaluations to the patients.

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