

Muscle studies

Investigators: Angelo Sassaroli, Matthew Hoimes*, Shalini Nadgir*, Vo Van Toi, and Sergio Fantini (Department of Biomedical Engineering, Tufts University); Renato Palumbo, Gaetano Vaudo (University of Perugia, Italy); Valentina Quaresima, Marco Ferrari (University of l’Aquila, Italy). (*Past Investigators)

Optical study of muscle hemodynamic and oxygenation

The optical measurement of the near-infrared absorption coefficient at multiple wavelengths can be translated into measurements of the concentrations of oxy-hemoglobin ($[HbO_2]$) and deoxy-hemoglobin ($[Hb]$) in tissue. In turn, these concentrations can be combined to provide the total hemoglobin concentration ($THC = [HbO_2] + [Hb]$) and the oxygen saturation of hemoglobin ($StO_2 = [HbO_2]/THC$). The quantitative measurement of the absorption coefficient, leading to absolute measurements of hemoglobin concentration and saturation, requires a model for light propagation in tissue. A common model for tissue studies in a reflectance geometry is diffusion theory for macroscopically homogeneous media, with semi-infinite boundary conditions. While the assumption of homogeneity is not strictly fulfilled in the case of most biological tissues, the case of large skeletal muscles (for example, muscles in the human limbs) justifies using this assumption, and allows for absolute measurements of hemoglobin-related parameters.

Venous and arterial occlusions: Blood flow and oxygen consumption

Figure 1 shows typical traces of hemoglobin concentration and saturation measured in the brachioradialis muscle (forearm) of a human subject during venous occlusion (left panel) and arterial occlusion (right panel). These measurements were taken with a frequency-domain tissue oximeter (Model OxiplexTS, ISS, Inc., Champaign, IL). The two wavelengths employed in this particular case are 690 and 830 nm, and the acquisition time per point is 1.28 s. The traces appear in real time on the computer screen during the examination. Note that the y-axes for hemoglobin concentration and saturation are quantitative and absolute.

The main effect of the venous occlusion is to increase the hemoglobin concentration, as a result of blood accumulation. In fact, while the arterial inflow is unaffected by the venous occlusion, the venous outflow is blocked. The initial rate of increase of THC during venous saturation can be used to measure the muscle blood flow (BF) according to the following equation (De Blasi *et al.*, 1994; Homma *et al.*, 1996; van Beekvelt *et al.*, 1998; Casavola *et al.*, 2000):

$$BF = \frac{1}{C} \left. \frac{d[THC]}{dt} \right|_{\max}, \quad (1)$$

where C is the concentration of hemoglobin in the blood (typically ~2.3 mM, or 15g/dL), and “max” refer to the maximum value (some authors use the initial value) of the time derivative after the onset of venous occlusion.

The tissue desaturation during arterial occlusion results from a rate of decrease of $[HbO_2]$ that is equal to the rate of increase of $[Hb]$ because the total hemoglobin concentration THC remains constant during arterial occlusion. The rate of conversion of HbO_2 to Hb can be used to quantify the muscle oxygen consumption (OC) as follows (Chatle *et al.*, 1991; de Blasi *et al.*, 1992):

$$OC = 4 \frac{d}{dt} \left(\frac{[Hb] - [HbO_2]}{2} \right), \quad (2)$$

where the factor 4 accounts for the fact that each hemoglobin molecule has four binding sites for oxygen.

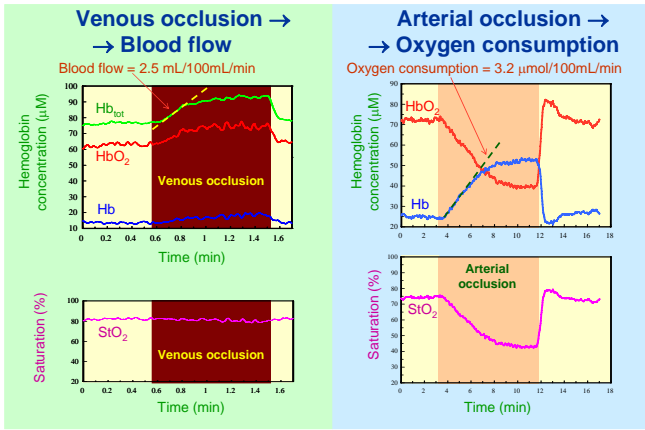


Fig. 1. Changes in forearm hemoglobin concentration and saturation induced by venous occlusion (left) and arterial occlusion (right) in the upper arm. The initial rate of increase of total hemoglobin concentration (Hb_{tot}) during venous occlusion can be translated into a measurement of blood flow. The initial rate of increase of deoxy-hemoglobin concentration (Hb) during arterial occlusion can be translated into a measurement of the oxygen consumption.

Electrical model for the hemodynamic response to venous occlusion

The proposed electrical model for the hemodynamic response to venous occlusion is shown in Fig. 2 (right panel). The constant voltage sources V_a and V_v represent arterial and venous pressures, respectively, while the time-dependent voltage source v_{ext} represents the pressure externally applied by the pneumatic cuff. The resistors R_a and R_v represent the arterial/capillary and venous resistances, respectively, and the ideal diode D guarantees the unidirectional flow of currents i_a and i_v , which in turn represent blood flow. By preventing the change in direction of i_v , the ideal diode D is the circuit element that confines the effect of v_{ext} to limiting the amplitude of i_v without possibly changing its sign. The key element of the model is the capacitor C , which represents the overall ability of blood vessels to increase the local blood volume as a result of vascular compliance and capillary recruitment. The charge stored in the capacitor C is specifically used to model the local blood volume.

The left panel of Fig. 2 shows a typical response of the total hemoglobin concentration (THC) measured with near-infrared spectroscopy on the human forearm during venous occlusion in the upper arm achieved by inflating a pneumatic cuff to a pressure of 60 mmHg. The THC increases during the time that the cuff is inflated because of the accumulation of blood in the forearm induced by the venous occlusion in the upper arm. The experimental data of $\langle THC \rangle$ (average across six subjects) is compared with the predictions of the model for the cases of “small” V_{ext} (which never reverse-biases the diode in the circuit model of Fig. 2) and “large” V_{ext} (which initially reverse-biases the diode). The capacitor voltage v_C is proportional to the

capacitor charge, which describes the blood volume (or THC) in this model.

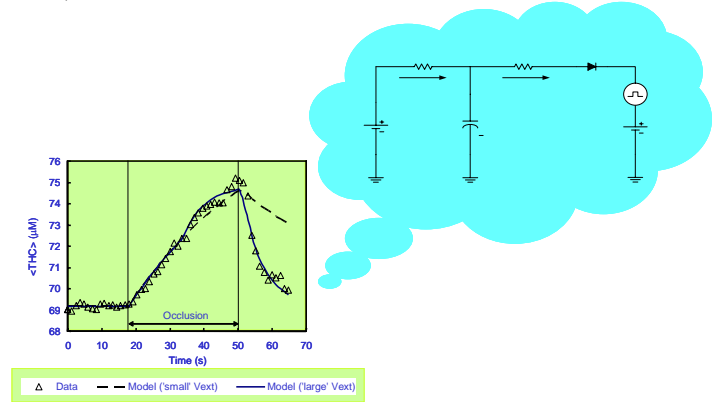


Fig. 2. Typical response of total hemoglobin concentration during venous occlusion as measured in the human forearm (left), and electrical model for the hemodynamic response to venous occlusion (right).

Diagnosis of peripheral vascular disease

Peripheral vascular disease (PVD) is a progressive arterial narrowing or obstruction mainly caused by an atherosclerotic process which reduces blood flow to the lower limbs during exercise or also at rest. Iliac arteries (lower abdomen leading to the legs) and femoral arteries (legs) are among the peripheral vessels most commonly affected by the disease. The reduced oxygen supply (from the oxy-hemoglobin in the blood) to the muscle tissue results in a cramping pain in the thigh or calf muscles, and can limit walking capabilities. Current non-invasive diagnostic modalities for PVD include the ankle-arm blood pressure index (AAI) (McKenna *et al.*, 1991), plethysmography (Payne 1992), ultrasonic duplex scanning, and transcutaneous oxymetry (Rooke and Osmundson, 1989; Mannarino *et al.*, 1987). Because of the sensitivity of near-infrared spectroscopy (NIRS) to the tissue hemoglobin content and to the hemoglobin oxygenation state, it has been proposed that NIRS may be a useful tool in the diagnosis of PVD and/or in the follow up of the patients after therapy (Cheatle *et al.*, 1991; McCully *et al.*, 1994; Franceschini *et al.*, 1998; Wolf *et al.*, 2003).

Fig. 3 reports the results of an experiment to measure the desaturation in the legs of PVD patients during stationary bicycle exercise. The comparison of the typical hemoglobin saturation traces recorded on healthy controls (blue line) and PVD patients (red line) in Fig. 3 shows the difference in the response of healthy and diseased legs. In the control subjects, the hemoglobin saturation decreases slightly during the exercise, whereas the PVD patients showed a consistent decrease in hemoglobin saturation ($\Delta StO_2 = -21 \pm 3\%$). The recovery time after exercise was also significantly shorter in the controls than in the PVD patients. These results are consistent with an insufficient

blood flow adjustment in the PVD patients to compensate for the increased oxygen demands during muscle exercise.

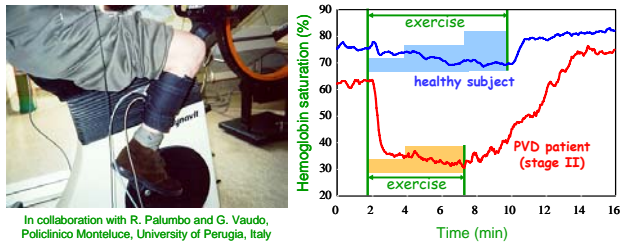


Fig. 3. (Right) Picture of the optical probe attached to the leg of a patient during a stationary-bicycle exercise protocol. (Left) Typical traces of hemoglobin saturation for a healthy control (blue line), and for a stage-II PVD patient (red line) during the stationary-bicycle routine.

Acknowledgements:

This project is supported by the National Science Foundation, Award No. BES-93840.

References:

- Casavola, C., L. A. Paunescu, S. Fantini, and E. Gratton, "Blood Flow and Oxygen Consumption with Near-Infrared Spectroscopy and Venous Occlusion: Spatial Maps and the Effect of Time and Pressure of Inflation," *J. Biomed. Opt.* **5**, 269-276 (2000).
- Cheatle, T. R., L. A. Potter, M. Cope, D. T. Delpy, P. D. Coleridge Smith, and J. H. Scurr, "Near-Infrared Spectroscopy in Peripheral Vascular Disease," *Br. J. Surg.* **78**, 405-408 (1991).
- de Blasi, R. A., M. Cope, and M. Ferrari, "Oxygen Consumption of Human Skeletal Muscle by Near-Infrared Spectroscopy During Tourniquet-Induced Ischemia in Maximal Voluntary Contraction," *Adv. Exp. Med. Biol.* **317**, 771-777 (1992).
- de Blasi, R. A., M. Ferrari, A. Natali, G. Conti, A. Mega, and A. Gasparotto, "NonInvasive Measurement of Forearm Blood Flow and Oxygen Consumption by Near-Infrared Spectroscopy," *J. Appl. Physiol.* **76**, 1388-1393 (1994).
- Franceschini, M. A., S. Fantini, R. Palumbo, L. Pasqualini, G. Vaudo, E. Franceschini, E. Gratton, B. Palumbo, S. Innocente, and E. Mannarino, "Quantitative Near-Infrared Spectroscopy on Patients with Peripheral Vascular Disease," *Proc. SPIE* **3194**, 112-115 (1998).
- Homma, S., H. Eda, S. Ogasawara, and A. Kagaya, "Near-Infrared Estimation of O₂ Supply and Consumption in Forearm Muscles Working at Varying Intensity," *J. Appl. Physiol.* **80**, 1279-1284 (1996).
- Mannarino, E., G. Maragoni, L. Pasqualini, R. Sanchini, P. Rossi, and U. Orlandi "Transcutaneous Oxygen Tension Behavior in the Different Stages of Peripheral Vascular Disease and Its Correlation With Ankle/Arm Pressure Ratio and Calf Blood Flow," *Angiology* **38**, 463-468 (1987).
- McCully, K. K., C. Halber, and J. D. Posner, "Exercise-Induced Changes in Oxygen Saturation in the Calf Muscles of Elderly Subjects with Peripheral Vascular Disease," *J. Gerontol. BIOL. SCI.* **49**, B128-B134 (1994).
- McKenna, M., S. Wolfson, and L. Kuller, "The Ratio of Ankle and Arm Arterial Pressure as an Independent Predictor of Mortality," *Atherosclerosis* **87**, 119-128 (1991).
- Payne, K., "The Technique of Occlusive-Cuff Impedance Plethysmography," *J. Critical Illness* **7**, 1135-1143 (1992).
- Rooke, T. W., and P. J. Osmundson, "Variability and Reproducibility of Transcutaneous Oxygen Tension Measurements in the Assessment of Peripheral Vascular Disease," *Angiology* **40**, 695-699 (1989).
- van Beekvelt, M. C. P., W. N. J. M. Colier, B. G. M. van Engelen, M. T. E. Hopman, R. A. Wevers, and B. Oeseburg, "Validation of Measurement Protocols to Assess Oxygen Consumption and Blood Flow in the Human Forearm by Near-Infrared Spectroscopy," *Proc. SPIE* **3194**, 133-144 (1998).
- Wolf, U., M. Wolf, J. H. Choi, M. Levi, D. Choudhury, S. Hull, D. Coussirat, L. A. Paunescu, L. P. Safonova, A. Michalos, W. W. Mantulin, and E. Gratton, "Localized irregularities in hemoglobin flow and oxygenation in calf muscle in patients with peripheral vascular disease detected with near-infrared spectrophotometry," *J. Vasc. Surg.* **37**, 1017-1026 (2003).