TITLE PAGE

Citation Format:

C. Amendola, M. Zanoletti, M. Buttafava, T. Carteano, L. Contini, L. Cortese, T. Durduran, C. N. Guadagno, U. Karadeniz, M. Lacerenza, J. Mesquida, S. Parsa, R. Re, D. S. Garcia, S. K. V. Sekar, L. Spinelli, A. Torricelli, A. Tosi, U. M. Weigel, M. A. Yaqub, and D. Contini, "Diffuse Optics for Non-Invasive Endothelial Function Monitoring in ICU Patients," in *European Conferences on Biomedical Optics 2025*, Technical Digest Series (Optica Publishing Group, 2025), paper S4E.6.

Abstract link:

https://opg.optica.org/abstract.cfm?uri=ecbo-2025-S4E.6

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Diffuse Optics for Non-Invasive Endothelial Function Monitoring in ICU Patients

Caterina Amendola[1]*, Marta Zanoletti[2]*, Mauro Buttafava[3], Talyta Carteano[4], Letizia Contini[1], Lorenzo Cortese[2], Turgut Durduran[2,5], Claudia Nunzia Guadagno[6], Umut Karadeniz[2], Michele Lacerenza[3], Jaume Mesquida[7], Shahrzad Parsa[8], Rebecca Re[1,9], Diego Sanoja Garcia[4], Sanathana Konugolu Venkata Sekar[6], Lorenzo Spinelli[9], Alessandro Torricelli[1,9], Alberto Tosi[10], Udo M. Weigel[8], M. Atif Yaqub[2], Davide Contini[1]

All authors are listed in alphabetic order except for the first two and the last authors

*[1]Dipartimento di Fisica, Politecnico di Milano, Milan, Italy; [2]ICFO - Institut de Ciències Fotòniques, The Barcelona Institute of Science and Technology, Castelldefels (Barcelona), Spain; [3] PIONIRS s.r.l., Milan, Italy; [4]ASPHALION S.L., Barcelona, Spain;; [5]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain; [6]BioPixS Ltd – Biophotonics Standards, IPIC, Tyndall National Institute, Lee Maltings Complex, Cork, Ireland; [7]Critical Care Department, Parc Taulí Hospital Universitari. Institut D'Investigació i Innovació Parc Taulí I3PT, Sabadell, Spain; [8]HemoPhotonics S.L., Castelldefels, (Barcelona), Spain; [9]Istituto di Fotonica e Nanotecnologie, Consiglio Nazionale delle Ricerche, Milano, Italy; [10]Politecnico di Milano, Dipartimento di Elettronica, Informazione e Bioingegneria, Milan, Italy; *caterina.amendola@polimi.it, *marta.zanoletti@icfo.eu*

Abstract: We analyzed very-low-frequency signals of hemodynamic parameters in a distal muscle of 14 healthy volunteers and 10 ICU patients, measured using time-domain near-infrared and diffuse correlation spectroscopies. Significant differences were observed in their power spectral density. © 2025 The Author(s)

1. Introduction

1.1. Vascular endothelium

The vascular endothelium plays a crucial role in vasoregulation, homeostasis, and blood vessel barrier function. Endothelial dysfunction is a hallmark of various diseases, including septic shock, which disrupts vascular tone and homeostasis, leading to tissue hypoxia and potential fatality. While non-invasive techniques such as flow-mediated dilation (FMD), pulse wave analysis (PWA), and pulse contour analysis (PCA) are commonly used to assess endothelial function, they have limitations in reproducibility and operator dependence. Emerging methods like laser Doppler flowmetry (LDF) and photoplethysmography (PPG) analyze blood flow frequency components to evaluate endothelial activity. Indeed, previous LDF studies have shown that blood flow oscillations correlate with various physiological processes, depending on their frequency range [1]: [0.6–2.0 Hz] cardiac activity; [0.145–0.6 Hz] respiratory activity; [0.052–0.145 Hz] (I_3) myogenic activity;[0.021–0.052 Hz] (I_2, low frequency or LF) neurogenic (sympathetic) activity; [0.0095–0.021 Hz] (I_1, very low frequency or VLF) endothelial activity mediated by nitric oxide (NO). However, those technologies remain limited to superficial tissues.

1.2. Diffuse optics to assess vascular endothelium

Near-infrared spectroscopy (NIRS), particularly when combined with vascular occlusion tests (VOT), has shown promise in assessing endothelial health and microvascular reactivity in critical care settings [2,3]. However, conventional continuous-wave NIRS (CW-NIRS) suffers from motion artifacts and sensitivity to superficial tissue properties. The VASCOVID project (Horizon 2020) aims to overcome these limitations by integrating advanced optical techniques such as time-domain NIRS (TD-NIRS) and diffuse correlation spectroscopy (DCS).

1.3. Our approach

In this study, we explored a non-invasive, stationary diffuse optical (DO) monitoring approach to assess microvascular function without the need for VOT. By analyzing low- and very-low-frequency oscillations in hemodynamic parameters through TD-NIRS and DCS, we investigated spontaneous myogenic, neurogenic, and endothelial activity in skeletal muscle microvasculature. This method provides deeper insights into microvascular health beyond conventional approaches. While previous studies have used NIRS to examine low-frequency oscillations in cerebral autoregulation and post-exercise muscle oxygenation, no prior research has combined TD-NIRS and DCS to assess spontaneous vascular oscillations in resting skeletal muscles. We conducted a comparative analysis of measurements obtained from healthy subjects and 10 ICU patients, emphasizing the method's potential for distinguishing differences in microvascular functions across various health states. Additional patients, including those with sepsis, have also been measured, and data analysis is currently ongoing.

2. Methods

2.1 Hybrid diffuse optics technology

The study employed a hybrid TD-NIRS and DCS device to non-invasively monitor the hemodynamics of the thenar muscle of 14 healthy volunteers [4] and 10 ICU patients [5] at rest. They allow simultaneous measurements of hemoglobin concentrations and blood flow.

The TD-NIRS module used pulsed diode lasers (685 nm and 830 nm) to assess tissue absorption and scattering properties, while the DCS module used a continuous-wave laser (785 nm) to evaluate microvascular blood flow. A flexible, 3D-printed optical probe ensured optimal contact with the tissue surface. The device exploited in clinic to measure ICU patients differs only for the source-detector separation, that was 2.5 cm for both modules, from that used to measure healthy volunteers [4, 5]. We verified the agreement of those measurements testing on a sub-cohort of volunteers the use of the two different inter-fiber distances (data not shown).

Figure 1 Image of the VASCOVID device in use during measurements in the ICU.

2.2 Data analysis

Data processing included calculating absorption and scattering coefficients using a photon diffusion model, estimating hemoglobin concentrations via the Beer's law, and extracting the blood flow index (BFI) through a diffusion equation-based fitting procedure. Time-series data were normalized and detrended to remove baseline shifts. Frequency analysis was performed using the Welch algorithm, focusing on three key frequency intervals: endothelial (VLF), neurogenic (LF), and myogenic (LF) activity. Finally, spectra from ICU patients were compared with those from healthy volunteers, using the Wilcoxon rank sum test, to assess differences in microvascular functions.

3. Results and discussion

The power spectral density (PSD) of the blood flow index (BFI) was more than two orders of magnitude higher than that of hemoglobin concentrations, indicating stronger oscillatory components in the recorded DCS signal. We then compared the PSD of BFI measured on the thenar eminence of ICU patients with that of healthy volunteers (Figure 1a). ICU patients exhibited lower spectra in the very low-frequency (VLF) range, suggesting altered endothelial activity. As shown in Figure 1b, the absolute area within the endothelium-related frequency range (I1) was significantly lower ($p < 0.01$) in ICU patients compared to healthy volunteers.

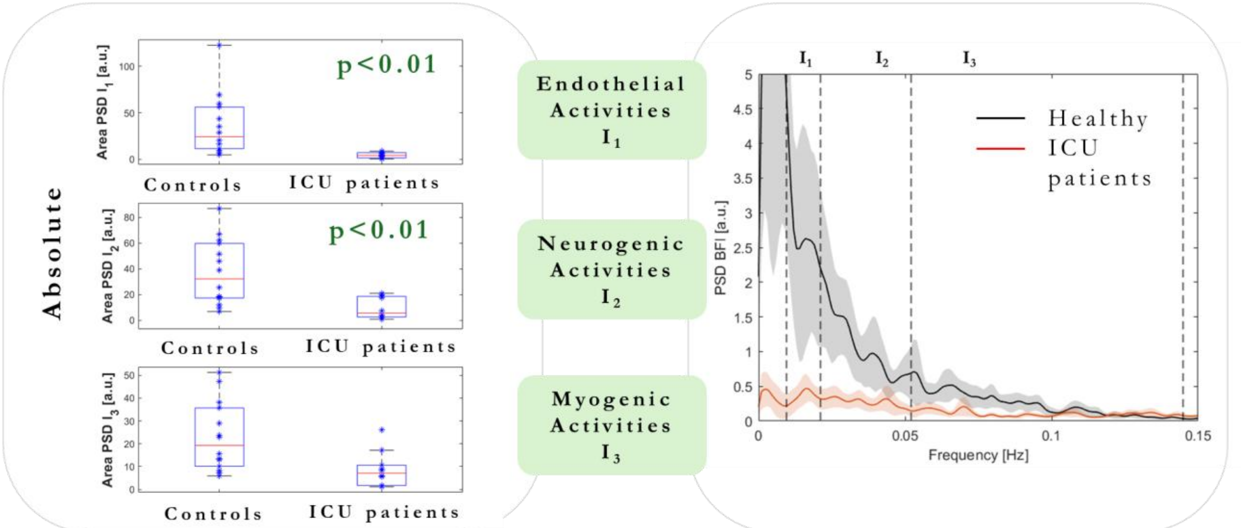

Figure 2 Panel a) absolute areas of PSD BFI in the three frequency ranges considered, I_1, I_2, I_3, of healthy volunteers compared to ICU patients. Panel b): comparison of the PSD of BFI measured on healthy volunteers and ICU patients, on the thenar eminence.

4. Conclusion

We explored the potential of using diffuse optical (DO) methods to non-invasively assess low-frequency (LF) and very-low-frequency (VLF) spontaneous oscillations in the microvasculature through resting-state measurements of skeletal muscle hemodynamics. Our frequency analysis demonstrated that both TD-NIRS (data not shown) and DCS effectively capture LF and VLF oscillations, with the BFI exhibiting a significantly higher power spectral density (PSD) than hemoglobin concentrations.

This study represents an important step toward assessing endothelial activity in skeletal muscles using DO technologies without requiring additional procedures. While the findings are encouraging, two main limitations must be considered: the age difference between the groups (27.1 years for healthy volunteers vs. 62.9 years for ICU patients) and the small sample size of ICU patients, who were also undergoing different treatments that could impact endothelial function. To enhance the reliability of our results, future work will focus on expanding the study with a larger, age-matched cohort of healthy volunteers and ICU patients, allowing for further validation and refinement of this approach.

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