Conference materials
UDC 616.13/14-008.46-073.75:543.42; 577.3
DOI: https://doi.org/10.18721/JPM.183.256

Development of an optical spectroscopy-based non-invasive vasodilation assessment method

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Abstract. This study investigates feasibility of a novel spectrophotometric method for the assessment of endothelial dysfunction (ED) in substitution for standard ultrasound flow-mediated dilation test (FMD). Using an 18-channel optical analyzer (410–940 nm), tissue optical spectra during reactive hyperemia were assessed in 21 patients with ED-related condition (atherosclerosis, coronary heart disease, post-COVID syndrome) and 11 control subjects. Vascular occlusion test (VOT) was performed on the subjects with 3-minute ischemia of the brachial artery at 180 mmHg. Statistical analysis revealed significant differences ($p < 0.05$) in absorption of light at specified wavelengths (410, 560, 585, 610, 680, 705, 760, 860 nm) between groups with most pronounced differences in atherosclerosis patients. Results show promise for ED detection without operator-dependent ultrasound measurements, but further validation against FMD is required.

Keywords: endothelial dysfunction, spectrophotometry, non-invasive diagnostics, reactive hyperemia

Funding: The study was supported by a grant from the Russian Science Foundation Project No. 24-21-00404.

Citation: Liamina Ju.V., Mazing M.M., Glebov G.S., Zaitceva A.Yu., Davydov V.V., Development of an optical spectroscopy-based non-invasive vasodilation assessment method, St. Petersburg State Polytechnical University Journal. Physics and Mathematics. 18 (3.2) (2025) 280–283. DOI: https://doi.org/10.18721/JPM.183.256

Материалы конференции
УДК 616.13/14-008.46-073.75:543.42; 577.3
DOI: https://doi.org/10.18721/JPM.183.256

Разработка неинвазивной спектрофотометрической методики диагностики эндотелиальной дисфункции

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Аннотация. В ходе работы проведен сбор данных изменения оптических спектров тканей в ходе окклюзионной пробы. Использован 18-канальный оптический анализатор, работающий в диапазоне 940–410 нм. На нескольких длинах волн были обнаружены статистически значимые ($p < 0,05$) различия между двумя группами испытуемых.

Ключевые слова: эндотелиальная дисфункция, спектрофотометрия, неинвазивная диагностика

Финансирование: Исследование проводилось при поддержке гранта Российского научного фонда № 24-21-00404.

Ссылка при цитировании: Лямина Ю.В., Мазинг М.С., Глебов С.Н., Зайцева А.Ю., Давыдов В.В. Разработка неинвазивной спектрофотометрической методики диагностики эндотелиальной дисфункции // Научно-технические ведомости СПбГПУ. Физико-математические науки. 2025. Т. 18. № 3.2. С. 280–283. DOI: https://doi.org/10.18721/JPM.183.256

Introduction

Endothelial dysfunction (ED) serves as a significant predictor of vascular wall morphological changes in various cardiovascular diseases including hypertension, atherosclerosis, and coronary artery disease [1]. This pathological condition exhibits systemic manifestation, affecting both large vessels and microcirculatory networks [2–3]. While flow-mediated dilation (FMD) remains the gold standard diagnostic approach, its clinical application faces limitations due to substantial costs and significant operator dependence, creating a demand for alternative diagnostic solutions. Current research focuses on developing non-invasive, accessible, wearable, and precise methods for ED detection, with spectrophotometric techniques emerging as particularly promising.

The primary objective of this study was to explore feasibility of a spectrophotometric approach for non-invasive ED diagnosis. To achieve this, several key tasks were accomplished. A series of tissue optical spectra were recorded using a vascular occlusion test (VOT). Statistical analysis was then performed to access differences between ED patients and healthy controls. Finally, method's potential utility in monitoring therapeutic efficacy was evaluated.

Materials and Methods

The study included 18 patients with endothelial dysfunction and 18 healthy controls (< 45 years). Participants underwent comprehensive screening for risk factors including atherosclerosis, ischemic heart disease, severe COVID-19 (past year) [4–5], cancer, diabetes, advanced age, and obesity BMI > 40 (body mass index).

All the measurements were performed using an 18-channel optical analyzer (410–940 nm), [6–7] developed in the Institute of Analytical Instrumentation RAS (Russian Academy of Sciences) St. Petersburg, featuring three multi-spectral LEDs [38] and an array of wave-specific photodetectors. To assess tissue light interactions device utilizes reflectance-mode absorption spectroscopy principles with both the light source and detector positioned on the same side of the examined tissue, recording back-scattered radiation with a maximum penetration depth of 2.5 mm. two configurations (refers to the physical setup of the probe, specifically the distance between the light source and the detector) were developed (5 mm and 10 mm) for measurements at different tissue depths (2.5 mm and 5 mm respectively), with this study employing the 5 mm sensor configuration. The key measured parameter was surface energy flux density (Ee), representing the radiant flux per unit area incident on the photodetector surface, which quantifies the intensity of back-scattered tissue radiation.

To achieve the study objectives, we used VOT to record induced changes in microcirculatory response. Experimental protocol comprised three sequential phases: rest (30 seconds seated rest), loading (3-minute cuff inflation to 180 mmHg on the mid-upper arm), and recovery (10-second decompression followed by 3-minute 50-second rest), totaling 7 minutes 30 seconds. For the seated occlusion test, the sensor unit was fixed securely on the inner right forearm with LEDs facing the skin, maintaining full contact with minimal pressure. Continuous measurements were recorded every 5 seconds throughout the procedure. All acquired data was transmitted in real-time to a laptop for storage and further analysis.

Statistical analysis consisted of several steps. First, each measurement was normalized to a range of 1 and shifted so that the starting point was set to zero. Linear interpolation was then used to bring each measurement to a length of 100 points. Inspired by the classical approach, area under the curve (AUC) was calculated to form an experimental and study groups for every wavelength, measured using the formula:

$$y_{ij} = \sum_{k=1}^{100} \square x_{ijk},$$

where i stands for a wavelength and j for a measurement. Finally, a non-parametric Mann–Whitney U-test was used to compute statistical significance in differences between groups, followed by a false discovery control using Benjamini-Hochberg method, with 0.05 being chosen as a threshold.

Results and discussion

Several wavelengths were found to have statistical difference between groups (Fig. 1). Notably, patients with endothelial dysfunction-associated conditions (hypertension, atherosclerosis, coronary artery disease, post-COVID sequelae) exhibited significant spectral deviations at 410, 560, 585, 610, 680, 705, 760 and 860 nm, compared to control group, demonstrating the method's sensitivity to pathological microcirculatory changes.

This hints that a classification algorithm can be used for automatic ED detection with potential success. Further work would include validation studies comparing this approach with the conventional FMD method and a development of method to detect ED. These advancements could significantly improve early detection and management of endothelial dysfunction in clinical practice.

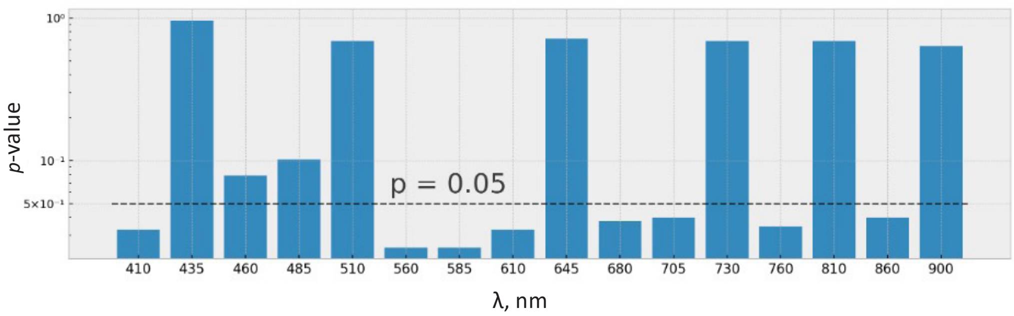

Fig. 1. Calculated p-values at various wavelengths (410–900 nm) after multiple-hypothesis correction procedure. Dashed line represents a threshold of statistical significance (0.05)

Conclusion

The spectrophotometric method is widely acclaimed [9–10] and in this work it is shown that is promising for non-invasive endothelial dysfunction diagnosis by detecting optical spectral changes during reactive hyperemia. It identifies significant differences between high-risk patients and healthy individuals, with advantages over FMD such as reduced variability, portability, and multi-parameter assessment. Further validation, protocol optimization, diagnostic criteria development, and exploration of therapeutic monitoring potential are needed, alongside machine learning integration.

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Received 12.09.2025. Approved after reviewing 02.10.2025. Accepted 24.10.2025.