To the Rector of MU

Prof. Dr. Paraskev Stoyanov,

Varna

STATEMENT

On the doctoral dissertation titled “Time for contrast to pass through the myocardium in patients with non-obstructive coronary artery disease ”, submitted for public defense before a scientific jury for the award of the educational and scientific degree “Doctor”, Professional field 7.1 Medicine, Specialty Cardiology

Author of the dissertation: Dr. Rozen Krasimirov Grigorov, PhD candidate in full-time doctoral studies in the doctoral programme Cardiology, Professional Field 7.1 Medicine, enrolled by Order № P-109-74 / 31.01.2023 at the Medical University of Varna.

Reviewer: Prof. Dr. Zhaneta Georgieva Tyaneva, MD, PhD, Medical University of Varna, member of the Scientific Jury, approved by Order № P-109-479 / 20.11.2025 of the Rector of the Medical University of Varna.

Biographical Information: Dr. Grigorov was born on 04 October 1996. He completed his higher education in 2021 at the Medical University “Prof. Dr. Paraskev Stoyanov”, Varna. In the same year, he was appointed as a physician at the Second Clinic of Cardiology—Invasive Cardiology, University Hospital “St. Marina”, Varna. Since 2022, he has been a resident physician at the clinic and an assistant at the First Department of Internal Medicine, Educational and Scientific Unit of Cardiology. He has completed training under the Erasmus programme at the Department of Interventional Cardiology and the Department of Cardiac Surgery in Wrocław, Poland, as well as training in the Department of Interventional Cardiology at the Cardiovascular Center, Aalst, Belgium (2025).

Since January 2023, he has been enrolled as a full-time PhD candidate in the Doctoral Programme in Cardiology at the Medical University of Varna.

Research Activity

The dissertation titled “ **Time for contrast to pass through the myocardium in patients with non-obstructive coronary artery disease** ” addresses a relevant

issue and highlights several contemporary challenges during coronary angiography. It emphasizes the need for methods to assess terminal coronary blood flow and microcirculation in order to support diagnostic evaluation and therapeutic stratification in patients with anginal symptoms in the absence of obstructive epicardial coronary artery disease.

Structure of the Dissertation: The dissertation comprises 158 pages and includes 31 tables and 28 figures. The bibliography contains 332 literature sources. The study was conducted at the Second Clinic of Cardiology, University Hospital "St. Marina", Varna.

The PhD candidate has authored three full-text publications related to the dissertation topic in specialized journals, serving as first author in all of them, and has participated in four scientific forums and congresses.

The literature review demonstrates a good understanding of the available sources and a rigorous extraction of in-depth information from them. Early reports in the literature initially provided limited evidence regarding the clinical significance of ischemia in the absence of obstructive coronary artery disease; these issues have been discussed in greater depth following the implementation and wider adoption of coronary angiography.

The aim of the study is clearly defined and specific: to establish a novel, easily reproducible method for assessing the coronary microcirculation in patients without significant epicardial coronary artery disease, and to analyze its relationship with the severity of anginal symptoms in this patient population.

The objectives are precisely formulated and aligned with achieving the stated aim. These include standardization of the methodology for measuring TCPM, as well as the angiographic projections required for visualization of the coronary sinus; assessment of anginal symptom burden using a standardized questionnaire and indexing of TCPM; and evaluation of factors predicting indexed TCPM values, including classical cardiovascular risk factors and ongoing pharmacological therapy.

Statistical methods: Data analysis was performed using Python, employing multiple libraries. Data derived from coronary angiography, echocardiography, questionnaires, and laboratory parameters were entered and pre-validated within a structured electronic database.

The results and the conclusions drawn from them are convincing and demonstrate scientific value and originality. The discussion effectively contextualizes the study findings by integrating them with evidence derived from the literature review.

The conclusions are logically derived from the results of the study. The author demonstrates that the methodology for measuring TCPM can be standardized and applied in clinical practice. The investigation shows that the measurement is technically feasible, quantitatively reproducible, and amenable to standardization. The distribution of values exhibits a clear central tendency, with well-defined minimum and maximum values. The present study is the first to describe this parameter in patients with angina and non-obstructive coronary anatomy.

The severity of anginal symptoms is objectively significant despite the absence of anatomically demonstrable obstruction. The mean CCS functional class, as well as the questionnaire-based scores, demonstrate clinically meaningful symptom burden, comparable to, or even more severe than, that observed in patients with obstructive coronary artery disease, underscoring that the absence of anatomical obstruction should not lead to underestimation of patients' complaints. A statistically significant association exists between indexed TCPM and symptom severity, assessed by CCS functional class and the Seattle Angina Questionnaire.

Scientific contributions of the dissertation: A novel angiographic index – the indexed Time for Contrast to Pass through the Myocardium (iTCPM) has been developed and theoretically substantiated. This method eliminates individual hemodynamic variability and provides a quantitative, standardized, and reproducible approach for assessing myocardial contrast dynamics, with applicability in the diagnosis and management of patients with microvascular dysfunction. For the first time, a standardized methodology for TCPM has been applied in patients with angina and non-obstructive coronary anatomy, incorporating an automated injection system with fixed parameters, standardized frame rate, and acquisition speed. An indexed TCPM has been developed, accounting for the influence of myocardial mass, arterial pressure, and heart rate on contrast dynamics. A statistically significant association has been established between higher iTCPM values and greater anginal symptom severity, supporting the applicability of iTCPM as a marker of the degree of microvascular dysfunction in patients with ANOCA. A new conceptual framework for the application of iTCPM as a diagnostic tool is presented.

I agree with the conclusions drawn and with the summary of the candidate's scientific contributions.

Conclusion

The presented doctoral dissertation by Dr. Grigorov is highly relevant to contemporary cardiology. It combines an in-depth analysis of the literature with original investigations and well-substantiated conclusions. The dissertation and the related scientific publications meet the required scientometric criteria for the award of the educational and scientific degree "Doctor" in accordance with the Law on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations of the Medical University of Varna. The dissertation includes both original and confirmatory scientific contributions.

I give a positive vote for the award of the scientific degree "Doctor" to Dr. Rozen Krasimirov Grigorov

10.01.2026

Varna

Reviewer:

Prof. Dr. Zhaneta Georgieva, MD, PhD