OPINION/STATEMENT

by Assoc. Prof. Atanas Angelov Atanasov, MD, PhD
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regarding the dissertation
in Higher education Area 7. Healthcare and Sports
Professional field 7.1. Medicine
Scientific specialty: Cardiology

on the topic:
"TIME FOR CONTRAST TO PASS THROUGH THE MYOCARDIUM IN PAYIENTS WITH NON-OBSTRUCTIVE CORONARY ARTERY DISEASE"

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By Order No. P-109-479/20.11.2025 of the Rector of the Medical University of Varna, I was appointed as a member of the Scientific Jury, and on the basis of Protocol No. 1/03.12.2025, I was designated to prepare a formal statement within the procedure for awarding the degree of Doctor (PhD) to the candidate Dr. Rozen Krasimirov Grigorov.

Brief information on the doctoral candidate's professional development and qualifications: Dr. Rozen Grigorov graduated from the Medical University of Varna in 2021. Since 2021, he has been a cardiology resident at the Second Cardiology Clinic – Invasive Cardiology, University Hospital "St. Marina", Varna. Since 2023, he has been a full-time PhD candidate at the First Department of Internal Medicine. He participates in teaching the course Internal Medicine, Part I to fourth-year medical students. Dr. Grigorov demonstrates a strong affinity for scientific research and, within a relatively short period after graduation, has participated in more than 20 scientific publications and has presented posters or scientific presentations at more than 20 conferences.

Significance of the topic: The dissertation addresses a topic that is not historically new, yet remains highly relevant and continues to be the subject of active research. The concept of ischemia in the absence of obstructive coronary artery disease emerged following the introduction of coronary angiography in the 1960s. It was demonstrated that there was a subset of patients with clinical suspicion of ischemic heart disease (IHD), that did not have obstructive lesions in the epicardial coronary arteries. Registry data indicate that until approximately a decade ago, more than half of the patients referred for elective invasive coronary angiography (ICA) were found to have

non-obstructive coronary artery disease. With the introduction of coronary computed tomography angiography (CCTA) into routine clinical practice, invasive coronary angiography now reveals the absence of obstructive coronary artery disease in a significantly smaller proportion of patients. However, both imaging modalities (ICA and CCTA) are often unable to provide a clear answer as to whether microvascular angina is present in a given patient.

In recent years the definition of chronic coronary syndrome has evolved. The terms ANOCA (angina with non-obstructive coronary arteries) and INOCA (ischemia with non-obstructive coronary arteries) were introduced to describe, respectively, symptomatic patients and patients with objectively documented ischemia in the absence of obstructive (>50%) stenoses in the epicardial coronary arteries.

Invasive coronary angiography, although used to exclude obstructive coronary artery disease, does not allow direct assessment of the coronary microcirculation due to its limited spatial resolution. The European guidelines for the management of chronic coronary syndromes emphasize the importance of diagnosing microvascular angina through invasive assessment of coronary flow reserve (CFR) and the index of microvascular resistance (IMR) in patients with persistent symptoms and angiographically normal coronary arteries. Despite these recommendations, the widespread use of these techniques remains limited because of their relatively low availability, additional procedural risks and time requirements, and the need for well-trained personnel to correctly interpret the results and avoid errors.

Structure of the dissertation: The dissertation of Dr. Grigorov is prepared in accordance with the formal requirements and comprises 158 pages. It is illustrated with 28 figures, 31 tables, and 2 appendices. The dissertation is well balanced and includes an Introduction and Literature Review (48 pages), Aim and Objectives (1 page), Materials and Methods (7 pages), Original Results (30 pages), Discussion (19 pages), and Conclusions and Contributions (6 pages). The bibliography includes a total of 332 references. The thesis summary contains 22 figures and 23 tables.

Literature review: Dr. Grigorov systematically examines the historical development of the concept of angina/ischemia with non-obstructive coronary artery disease and provides data on the prevalence of this variant of ischemic heart disease. The functional anatomy of the coronary arteries is presented in detail, as well as the subtypes and pathophysiology of angina/ischemia with non-obstructive coronary artery disease. Contemporary invasive and non-invasive diagnostic modalities for the functional assessment of the coronary arteries are comprehensively reviewed, including the invasive diagnostic algorithm for ANOCA/INOCA.

In the subsequent chapter, Dr. Grigorov focuses on coronary microvascular dysfunction. The following aspects are addressed in a structured manner: risk factors for microvascular dysfunction; classification of microvascular dysfunction; and non-invasive diagnostic methods for its detection, with clear delineation of the advantages and limitations of the different techniques. The capabilities of invasive diagnostic methods for coronary microvascular dysfunction, based on coronary blood flow measurements, as well as fluoroscopic techniques for coronary flow assessment, are examined in great depth. In a separate chapter, Dr. Grigorov presents contemporary

therapeutic options for patients with angina/ischemia and non-obstructive coronary artery disease.

Aim and objectives: The doctoral candidate formulates the main aim of the scientific work as a logical continuation of the conducted literature review: to define a new, easily reproducible method, maximally refined and minimally influenced by external factors, for fluoroscopic assessment of the coronary microcirculation, termed indexed Time for Contrast to Pass through the Myocardium (iTCPM), in patients without significant epicardial coronary artery disease, and to analyze its relationship with the severity of anginal symptoms.

Materials and methods: To achieve the stated objectives, 102 participants were included in the study. The study is cross-sectional with prospective patient enrollment, observational, single-center, and conducted under real-world clinical conditions. The analyzed parameters include demographic characteristics; risk factors for atherosclerotic vascular disease; pharmacological therapy; comorbidities; anthropometric data; and laboratory parameters (blood glucose, lipid profile, creatinine, complete blood count, and coagulation status).
Based on clinical assessment, the presence or absence of anginal symptoms was determined, and patients were classified from functional class I to IV according to the Canadian Cardiovascular Society (CCS) classification. A standardized questionnaire for the assessment of chest pain, the Seattle Angina Questionnaire (SAQ), was also administered. All patients underwent transthoracic echocardiography to assess left ventricular dimensions, myocardial mass, systolic and diastolic function, valvular structure and function, and estimated pulmonary artery pressure.
Following coronary angiography and in the absence of obstructive coronary artery disease, TCPM was measured. The methodology for TCPM determination is described in detail. TCPM assessment was performed independently by two investigators for each patient. In cases where the interobserver difference exceeded 0.2 seconds (equivalent to two frames at a recording speed of 10 frames per second), a repeat assessment was conducted and a consensus value was established. Contemporary statistical methods were used for data analysis.

Results and discussion: Among the most significant findings of the study, the following should be highlighted:
1. The measurement of TCPM is technically feasible, quantitatively reproducible, and amenable to standardization. The use of a unified protocol, including fixed parameters of the automated contrast injection system, recording frame rate, and angiographic projections, as well as strictly defined criteria for identifying the initial and final frames, ensures a high degree of reliability in determining the value of this parameter.
2. This study is the first to describe TCPM in patients with angina and non-obstructive coronary anatomy.
3. The severity of anginal symptoms in the cohort is objectively significant despite the absence of obstructive coronary artery disease. The mean CCS functional class, as well as the results of the Seattle Angina Questionnaire, demonstrate clinically meaningful symptom burden, with values comparable to, or even worse than those observed in

patients with obstructive coronary artery disease (i.e., more pronounced symptoms and lower quality of life). This finding underscores that the absence of anatomical obstruction should not lead to underestimation of patient complaints.
4. TCPM values are influenced by certain physiological and anatomical variables. Correlation analysis revealed a weak but statistically significant positive association between TCPM and myocardial mass, as well as a negative association with mean arterial pressure. The relationship with heart rate was weak and not statistically significant; however, heart rate was included in the indexing process from a physiological standpoint, given its well-established influence on myocardial perfusion. The application of combined indexing of TCPM to these three parameters aims to minimize physiological variability and improve comparability between individual patients.
5. A statistically significant association exists between indexed TCPM and symptom severity, assessed by CCS functional class and the Seattle Angina Questionnaire. Patients with higher iTCPM values demonstrate higher CCS functional class and lower SAQ scores.
6. Regression analysis did not identify classical cardiovascular risk factors or pharmacological therapies as predictors of iTCPM values.

Based on the obtained results and the conducted analysis, Dr. Grigorov proposes the implementation of a standardized angiographic methodology and an automated contrast injection system for the measurement of TCPM under real-world clinical conditions. Unlike established methods for the assessment of coronary microcirculation, such as coronary flow reserve (CFR) and the index of microvascular resistance (IMR), indexed TCPM does not require the introduction of an additional catheter or guidewire into the coronary arteries, does not prolong procedure duration or increase radiation exposure, and is not associated with additional financial costs. These characteristics make it particularly suitable for routine clinical application. A diagnostic strategy based on iTCPM could serve as an initial step in the stratification of patients with angina and angiographically normal epicardial coronary arteries, guiding subsequent diagnostic interventions and therapeutic decision-making.

An additional strength of the dissertation is the author's critical appraisal of the conducted research. In a separate chapter, the doctoral candidate clearly outlines the limitations of the study, including:

- Lack of reporting of functional evidence of ischemia
- Limitations related to the methodology for TCPM measurement
- Absence of validation against established functional methods
- Possible influence of pharmacological therapy on iTCPM
- Low explanatory power of the applied regression models
- Lack of longitudinal follow-up and dynamic assessment

Dr. Grigorov further outlines the future perspectives following this study:

- The need for prospective studies with larger cohorts to allow more precise statistical evaluation and to improve the generalizability of the results

- Longitudinal follow-up of patients with respect to clinical evolution, response to therapy, and occurrence of cardiovascular events, which would enable assessment of the prognostic value of iTCPM and its potential role in risk stratification
- Validation of iTCPM against established invasive functional methods, including CFR and IMR, in order to determine its ability to reflect pathological values associated with microvascular dysfunction

In summary, future research should focus on validation of the method, risk stratification, integration of iTCPM into functional diagnostic assessment, and evaluation of the clinical benefit of therapeutic interventions guided by this index, in order for iTCPM to be established as a reliable tool for diagnosis and personalized treatment in patients with angina and non-obstructive coronary artery disease.

Contributions: From the proposed contributions, I consider the following to be the most substantial:

Contributions of original character:

- A new angiographic index been developed and theoretically substantiated – indexed Time for Contrast to Pass through the Myocardium (iTCPM). The index integrates three major physiological parameters: myocardial mass, mean arterial pressure, and heart rate. The method aims to eliminate individual hemodynamic variability and proposes a quantitative, standardized, and potentially reproducible approach for assessing myocardial contrast dynamics, with applicability in the diagnosis and treatment of patients with microvascular dysfunction.
- For the first time, a standardized methodology for measuring Time for Contrast to Pass through the Myocardium (TCPM) has been applied in patients with angina and non-obstructive coronary anatomy, incorporating an automated contrast injection system with fixed parameters, standardized frame rate, and recording speed.
- A new concept for the application of iTCPM as a diagnostic tool in patients with ANOCA and suspected microvascular dysfunction is presented. This approach enables quantitative assessment of myocardial contrast dynamics without the need for additional equipment, introduction of a pressure or flow wire into the coronary arteries, pharmacological provocation, or prolongation of the angiographic procedure. The method does not increase patient risk, procedural duration, or radiation exposure for either the patient or the operator and is not associated with additional costs.

Contributions of confirmatory character:

- The lack of a clear association between classical cardiovascular risk factors (age, sex, arterial hypertension, type 2 diabetes mellitus, dyslipidemia) and symptom severity in patients with ANOCA is confirmed, in agreement with published data from large studies involving patients with angina and non-obstructive coronary artery disease.

- It is confirmed that patients with ANOCA frequently present with pronounced symptoms and are subjected to intensive pharmacological therapy despite the absence of angiographically proven obstruction.

Publications and scientific presentations related to the dissertation: In relation to the dissertation, Dr. Grigorov presents three publications (two of which are published in peer-reviewed and indexed journals) and four participations in scientific forums.

Critical remarks: The bibliography does not include sources published in Cyrillic. While studies specifically addressing indexed myocardial contrast transit time are certainly lacking, publications related to angina/ischemia with non-obstructive coronary artery disease likely exist.

Conclusion: The scientific research conducted by Dr. Rozen Grigorov addresses a highly relevant problem in the field of cardiology, namely, the diagnostic approach in patients with suspected coronary microvascular dysfunction. A diagnostic method that is easily applicable in everyday clinical practice is proposed. The method is performed within the framework of invasive coronary angiography, does not require the introduction of an additional catheter or guidewire into the coronary arteries, does not prolong procedure duration or increase radiation exposure, and is not associated with additional financial costs. The dissertation of Dr. Grigorov fully satisfies the requirements for awarding the doctoral degree (PhD). This provides me with sufficient grounds to confidently propose that the esteemed Scientific Jury vote in favor of awarding the degree of Doctor (PhD) to Dr. Rozen Grigorov.

Varna, 04 January 2026