REVIEW

In connection with the procedure for awarding the scientific and educational degree "Doctor" in the field of Higher Education 7. Health and Sports in the professional field 7.1 "Medicine" and scientific specialty "Cardiology", Medical University-Varna, FACULTY OF MEDICINE, FIRST DEPARTMENT OF INTERNAL DISEASES, DEPARTMENT OF CARDIOLOGY

Member of the Scientific Jury, who prepared the review – Prof. Dr. Arman Shnork Postadjian, MD

The competition for the Scientific Jury for the competition was appointed by order of the Rector of the Medical University-Varna No. R-109-479/ 20.11.2025

The review was prepared in accordance with the Academic Staff Development Act (ASDA), the Regulations for the Implementation of ASDA (PRASDA) and the Regulations on the Conditions and Procedures for Acquiring Scientific Degrees and Holding Academic Positions (PURPNSZAD) at MU-Varna.

The presented set of materials on paper/electronic media is in accordance with the procedure for acquiring the academic position of "professor" and the regulations of MU - Varna.

The dissertation was developed by Dr. Rozen Krasimirov Grigorov, a full-time doctoral student at the Medical University of Varna, FIRST DEPARTMENT OF INTERNAL DISEASES, DEPARTMENT OF CARDIOLOGY with the topic "Time for contrast to pass through the myocardium in patients with minor coronary disease", scientific supervisor Prof. Dr. Svetoslav Georgiev, MD.

I declare the absence of a conflict of interest in preparing the review.

I have not identified plagiarism in the works submitted to me for review.

Relevance and significance of the topic

Ischemic heart disease is a leading cause of morbidity and mortality worldwide, often as a clinical manifestation of concomitant risk factors and their combination. Several factors determine the health consequences of its widespread prevalence - the severity of the onset of symptoms, the presence, severity and localization of coronary lesions on the epicardial coronary arteries, the concomitant state of left ventricular function, etc. The concept of ischemia in the absence of obstructive coronary disease gradually emerged after the introduction of coronary angiography in the 1960s. Even then, it became clear that obstructive lesions in the epicardial vessels were not detected in some patients with clinical suspicion of CHD. In an attempt to introduce a clear distinction and emphasize the significance of this clinical phenotype, the terms ANOCA (angina in non-obstructive coronary disease) and INOCA (ischemia in non-obstructive coronary disease), which describe respectively symptomatic patients and/or patients with proven ischemia in the absence of obstructive stenoses >50% in the epicardial arteries. The pathophysiological basis of ANOCA/INOCA includes a wide range of disorders in the coronary circulation, which can be conditionally classified as epicardial vasomotor dysfunction and coronary microvascular dysfunction (CMD), and in some cases as their combinations. Some patients experience vasospastic phenomena, while in others the leading role is played by abnormal regulation of

vascular tone and remodeling of the arterioles and capillary network, determining reduced coronary blood flow reserve (CFR) and increased Additionally, the presence of myocardial bridging may contribute to ischemic symptoms in some patients.

Angiographic techniques such as TIMI frame count and myocardial blush grade (MBG) are used to assess epicardial coronary blood flow and indirectly assess microvascular function.microvascular resistance. Studies have shown their potential benefit in diagnosing MVD, with patients demonstrating increased TIMI scores and reduced MBG values. From a clinical perspective, it is important that, in parallel with the diagnosis of a particular abnormality, there is a clearly defined algorithm for its favorable impact and individualization of the approach in these patients. The CorMicA (CORonary MICrovascular Angina trial) study demonstrated that invasive functional profiling and treatment adaptation according to the established ANOCA endotype leads to significant improvement in symptoms and quality of life compared to the standard approach not supported by functional diagnostics. This highlights the need for accessible, reliable, and routinely applicable methods for microcirculation assessment to aid in the diagnosis and therapeutic stratification of patients with ANOCA. The above largely determines the conduct of this dissertation work, defining it as particularly relevant in an area with unmet clinical needs.

Analysis of the dissertation work

The dissertation work includes 158 pages and contains an introduction, a literature review, goals and objectives of the study, materials and methods, results and discussion, conclusions, conclusion, contributions, applications and bibliography. It is illustrated with 31 tables and 28 figures. The bibliography contains 332 cited titles, with over 90% of the cited sources being from the last 10 years. In connection with the dissertation, the author presents 3 publications in journals and 4 presentations at scientific forums.

The dissertation is structured as follows:

The literature review is presented on 55 pages and is structured in several directions - angina/ischemia in non-obstructive coronary disease (with an Algorithm for invasive diagnosis in ANOCA/INOCA); coronary microvascular dysfunction (MVD); Fluoroscopic methods for assessing coronary blood flow; treatment of patients with angina/ischemia in non-obstructive coronary artery disease (ANOCA/INOCA). The good structure of the presentation and the detailed critical analysis of the parameters used are impressive. Based on the literature review, the goals and objectives of the dissertation work are derived

Goal and objectives

Dr. Grigorov sets as the goal of his research work the definition of a new, easily reproducible, maximally free from external influences method for fluoroscopic assessment of microcirculation, called indexed myocardial contrast transit time (ICT) in patients without significant epicardial coronary disease and to analyze its relationship with the severity of anginal symptoms in these patients.

The following tasks were formulated:

1. Standardization of the methodology for measuring myocardial contrast transit time (MCT), including: recording speed, contrast agent used, parameters of the automatic injection system (speed and volume), as well as standard angiographic projections for visualization of the coronary sinus.
2. To determine the mean value of the VPCM in the study cohort.
3. To assess the severity of anginal symptoms using a standardized questionnaire and clinical assessment by the treating team.

4. Record variables that may influence the value of the VPCM, including: myocardial mass, hemodynamic conditions during the study.

5. Index the VPCM to myocardial mass, heart rate, and mean arterial pressure at the coronary artery ostium during the study.

6. To analyze the relationship between the indexed VPCM and the severity of anginal symptoms, assessed by CCS class and a standardized angina questionnaire.

7. To search for factors that could predict the value of the indexed VPCM such as classic cardiovascular risk factors and accepted drug therapy.

The study was conducted at the Clinic of Invasive Cardiology at the University Hospital "St. Marina" - Varna in the period March 2023 - April 2025, after approval by the Research Ethics Committee (№128/02.03.2023) at the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna. All included patients signed an informed consent to participate.

Methodology

A cross-sectional observational study was conducted including 102 patients with a mean age of 61.5±9.9 years, of whom 59% were women (n = 60). Information was collected regarding cardiovascular risk factors: age, body mass index (BMI), presence of diabetes mellitus, arterial hypertension, dyslipidemia, smoking. Additionally, concomitant diseases and previous coronary angiographies were documented. Patients were classified from first to fourth functional class according to the CCS (Canadian Cardiovascular Society), using a standardized questionnaire for assessing chest symptoms - the Seattle Angina Questionnaire (SAQ), translated into Bulgarian, which assesses five aspects of functional status. After coronary angiography and in the absence of obstructive coronary disease, patients underwent myocardial contrast transit time (MCT). The invasive examination, clinical assessment, and questionnaire completion were performed while receiving continuous anti-ischemic therapy.

The endpoint is to determine the mean indexed myocardial transit time (iMTRT) in patients with nonstenotic coronary artery disease and to investigate the correlation of iMTRT with the severity and frequency of anginal symptoms assessed by CCS and SAQ functional class. and variables that may influence the iVPCM value were analyzed, such as classic cardiovascular risk factors and the type and number of medications taken.

The results obtained are presented clearly, well illustrated with figures and tables, and appropriate statistical data processing has been appropriately selected for the tasks set.

The following main results of the study can be summarized:

1. The methodology for measuring myocardial contrast transit time (MCT) can be standardized and applied in clinical practice through a unified protocol, including fixed parameters of the automatic injection system, recording speed and angiographic projections, as well as strictly defined criteria for determining the initial and final frame. This provides a high degree of reliability in determining the value of the indicator.

2. The value of the VPKM is influenced by some physiological and anatomical variables. The conducted correlation analysis found a weak but statistically significant positive correlation between VPCM and myocardial mass, as well as a negative correlation with mean arterial pressure. The relationship with heart rate was weak and statistically insignificant, but rate was included in the indexing process from a physiological perspective, given its well-established influence on myocardial perfusion. The application of combined indexing of VPCM to these three parameters aims to eliminate physiological variability and improve comparability between different patients.

3. There is a statistically significant relationship between the indexed VPCM and the severity of symptoms assessed by the CCS functional class and the Seattle Angina Questionnaire (SAQ). Patients with higher iVPCM values demonstrate a higher CCS class and lower SAQ scores – especially in the categories of physical limitation and frequency of anginal symptoms, which supports the applicability of the index as an objective marker of symptom severity.

4. No classic cardiovascular risk factors or drug therapies have been identified to predict the value of iVPCM. Despite the inclusion of data on gender, age, classic risk factors such as arterial hypertension, diabetes mellitus and dyslipidemia, as well as drug treatment in the regression analysis, none of these factors showed a statistically significant influence on iVPCM values.

Contributions

Eight contributions are listed, mostly of an original scientific nature, which I fully accept. The listed contributions demonstrate the relevance of the topic and the precision of the dissertation.

Fundamental contributions:

1. A new angiographic index – the indexed myocardial contrast transit time (iMCT) – was developed and theoretically substantiated, integrating three main physiological parameters – myocardial mass, mean arterial pressure and heart rate. The method aims to eliminate individual hemodynamic variability and offers a quantitative, standardized and potentially reproducible approach for assessing myocardial contrast dynamics, with potential application in the diagnosis and treatment of patients with microvascular dysfunction.
   Scientific contributions:
   1. A standardized methodology for measuring the time for contrast to pass through the myocardium (TCPM) has been applied in patients with angina and non-obstructive coronary anatomy for the first time. The protocol includes the use of an automated contrast injection system with fixed parameters, frame rate, and recording speed.
   2. For the first time, an average TCPM value has been reported in a cohort of patients with angina and no significant epicardial stenoses, establishing a basis for its use as a quantitative variable in both clinical and research settings.

3. An indexed time for contrast to pass through the myocardium (iTCPM) has been developed, incorporating myocardial mass, arterial pressure, and heart rate to account for physiological variability in contrast dynamics. This indexing improves the objectivity and comparability of results between individual patients.
4. A statistically significant relationship between higher iTCPM values and more severe anginal symptoms has been demonstrated, supporting the applicability of iTCPM as a marker of microvascular dysfunction severity in patients with ANOCA.
5. A new conceptual approach has been proposed for using iTCPM as a diagnostic tool in patients with ANOCA and suspected microvascular dysfunction. The method allows quantitative assessment of myocardial contrast dynamics without requiring additional equipment, intracoronary guidewires, pharmacological provocation, or prolongation of the angiographic procedure. The approach does not increase procedural risk, examination time, radiation exposure for either patient or operator, and entails no additional costs.
The abstract is well structured, presents the most important part of the dissertation work and meets the requirements of the ZRASRB and PPZRASRB. The figures and tables provided help to easily understand the results.

In conclusion
In conclusion, the dissertation presented by Dr. Rozen Krasimirov Grigorov contains scientific, scientifically applied and applied results that represent an original contribution to science and exceed the requirements for the award of the educational and scientific degree "DOCTOR". The dissertation demonstrates that the doctoral student possesses in-depth theoretical knowledge and professional skills in the scientific specialty, demonstrating qualities and skills for independently conducting and discussing scientific research. I believe that this dissertation meets the requirements for awarding the educational and scientific degree "Doctor" set forth in the Act on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations on the Development of the Academic Staff of the Medical University-Varna.
On these grounds, I propose to the esteemed members of the Scientific Jury to vote positively and propose to the Rector of the Medical University of Varna to award the scientific and educational degree "doctor" in the doctoral program in cardiology to Dr. Rozen Krasimirov Grigorov.

01/08/2026

Prof. Dr. Arman Postajian, MD
MU – Sofia
Member of the Scientific Jury