REVIEW

by Prof. Dr. Yoto Trifonov Yotov, MD, PhD
Professor of Cardiology
First Department of Internal Medicine,
Medical University "Prof. Dr. P. Stoyanov" - Varna

By order No. P-109-479/20.11.25 of the Rector of the Medical University-Varna and by decision of the scientific jury with protocol 1/03.12.2025, I am appointed to prepare a review for the defense of a dissertation on the topic:

" TIME FOR CONTRAST TRANSITION THROUGH THE MYOCARDIUM IN PATIENTS WITH MINOR CORONARY DISEASE "

for acquiring the educational and scientific degree **" DOCTOR "**
by **Dr. Rozen Krasimirov Grigorov**

Scientific organization: First Department of Internal Medicine, Educational Sector of Cardiology, Faculty of Medicine, Medical University "Prof. Dr. P. Stoyanov" - Varna

Professional field **7.1. Medicine, Scientific specialty "Cardiology", doctoral program "Cardiology"**

Scientific supervisor: Prof. Dr. Svetoslav Georgiev, MD, PhD, Medical University "Prof. Dr. P. Stoyanov" - Varna.

Brief biographical data:

Dr. Rozen Grigorov was born in the city of Russe. From 2015-2021 he was a student at the Medical University "Prof. Dr. Paraskev Stoyanov"-Varna, where he obtained an educational and classification degree Master of Medicine with distinction. He started working at the Second Clinic of Cardiology-Invasive at the University Hospital "St. Marina"-Varna in 2021 as a resident physician. From February 2022 to the present, he is an Assistant Professor at the First Department of Internal Medicine, Educational Sector of Cardiology, Faculty of Medicine, MU-Varna and as a specializing physician in Cardiology. Since 2023 he has been a doctoral student in the full-time form of study in the doctoral program in Cardiology at MU-Varna.

Dr. Grigorov has a specialization under the Erasmus+ program at the Cardiology Clinic in Wroclaw, Poland, and a one-month visit to the Interventional Cardiology Department at the Cardiovascular Center, Aalst, Belgium, in October 2025. He has received numerous awards and scholarships since his student years.

From the provided reference, it is clear that Dr. Grigorov has shown interest in scientific activity since he was a student, as a result of which he has a significant number of publications and participation in scientific forums in our country and abroad.

Dr. Grigorov is fluent in English and Russian.

The submitted documentation for the competition for the educational and scientific degree "Doctor", announced by decision of the Faculty Council of the Faculty of Medicine, MU-Varna with protocol 49/10.11.2025, is in accordance with the requirements of the Law for Development of Academic Staff in Republic of Bulgaria and the Regulations for Development of Academic Staff of the Medical University-Varna.

Subject relevance

Ischemic heart disease (IHD) is one of the most common heart diseases worldwide. It is a common cause of death and disability in the world, and for Bulgaria it is one of the most fatal diseases. The clinical course is diverse and asymptomatic for a long time. On the other hand, IHD is the most common cause of sudden death, especially in people over 60 years of age.

Attention on this one pathology traditionally is focuses on obstructive coronary disease, defined as the presence on hemodynamically significant stenoses affecting epicardial coronary arteries. Despite this, a great number of patients with typical angina symptoms or with proven ischemia at functional test does not demonstrate significant stenoses at coronary angiography. Despite repeated changes in the terminology of non-obstructive coronary artery disease (most recently defined as ANOCA/MINOCA), it remains a common problem. About half of the cases of stable angina pectoris who undergo cardiac catheterization have minimal or no changes in the epicardial coronary vessels, with the relative proportion of ANOCA/MINOCA reaching 70% in women. Although there is great development and advances in understanding the pathogenesis of this process, the diagnosis of the condition remains a challenge. Routine coronary angiography, used as golden standard in obstructive CAD, does not allow direct assessment on the state on microcirculation, and various other imaging modalities have been proposed to assess microcirculation. In addition, patients with ANOCA/MINOCA have a worse prognosis than the general population. Several studies have shown that individuals with ANOCA have an increased risk from unfavorable cardiovascular events, including myocardial infarction and cardiovascular death, as well as significant worsened quality of life, persistent symptoms and increased frequency of hospitalizations in these patients .

All this makes the problem examined in this dissertation significant and dissertable.

Structure of the dissertation

The dissertation is contained in 158 standard typewritten pages. The bibliography includes a total of 332 paper sources, all in Latin. It is richly illustrated with 31 color and black-and-white figures and 28 tables, which provide sufficient information about the issues under consideration and are easy to understand.

The dissertation is structured as follows:

Introduction – 3 pages;
Literature review – 55 pages (35% of the dissertation volume);
Aim and objectives – 1 page;
Material and methods – 7 pages (4%);
Results – 30 pages (19%);
Discussion – 20 pages (13%);
Inferences – 2 pages;
Conclusion – 2 pages;
Contributions of the scientific work – 2 pages
List of publications related to the dissertation – 1 page
Appendices – 5 pages
References – 25 pages

This structure of the dissertation meets generally accepted requirements.

Literature review

It is written competently and shows excellent knowledge of the available information on the problem. The bibliography includes 324 titles, all in Latin.

The first part presents a detailed analysis of the problem of ischemic heart disease in the absence of significant coronary artery disease (ANOCA/MINOCA). The definition, historical

development of the problem, prevalence and significance of microvascular complications are presented. The main subtypes of ANOCA/MINOCA in the context of functional coronary anatomy are indicated, as well as the main pathophysiological mechanisms. The main diagnostic methods - invasive and non-invasive, and the proposed algorithm for functional tests for unmasking the main subtypes of ANOCA/MINOCA are presented.

The second part of the literature review focuses on microvascular dysfunction (MVD). It begins with an overview of the main risk factors that contribute to the occurrence of myocardial microcirculation disorders. The presented classification emphasizes that microvascular dysfunction can occur in different forms of cardiac damage - vascular, myocardial involvement (e.g. cardiomyopathies) or caused by iatrogenic interventions. In this section of the review, the non-invasive diagnostic methods of MVD are discussed in detail, such as with stress echocardiography, myocardial perfusion visualization through single-photon emission computer tomography (SPECT), positron emission tomography (PET), cardiovascular magnetic resonance (CMR) and CT perfusion angiography. The advantages and disadvantages of each method are presented. Methods for calculating invasive parameters used for assessment of CMD, such as coronary blood flow and resistance (CFR, MRR, IMR, HMR, RRR, etc.) are also revealed.

The third part is devoted to fluorographic methods for assessing coronary blood flow. It is shown that through certain techniques reliable information can be obtained not only about the degree of stenosis of the epicardial vessels, but also for assessing blood flow in the vessels. Advantages and disadvantages of various methods are presented, such as TIMI frame count, cTFC , MBG, TMPG, CCFC, CSFT, IMR. The main angiographic findings that can guide the examiner to the presence of ANOCA – tortuous vessels, ectasias, microfistulas are also considered.

Finally, the main methods of treatment of MVD are discussed, indicating non-drug means through lifestyle changes, basic medical therapy for decreasing risk factors and use of vasodilators. The place of invasive methods of treatment in the presence of a muscular bridge and in the presence of MVD is also revealed.

The rich literary material is purposefully synthesized, interpreted with skill, maturity, and criticality.

Purpose and objectives

The main aim of the dissertation is clearly defined: to define a new, easily reproducible, maximally devoted from external impacts method for fluoroscopic assessment on microcirculation, called indexed time for passage on contrast through myocardium (TPCM) at patients without significant epicardial coronary disease. As a second sub-objective, to analyze the relation with the severity of angina pectoris in these patients.

In connection with the main objectives, 7 specific tasks are also presented, related to standardization of the method in terms of number of frames, amount of contrast medium used and projections, establishment of average values indexed to TPCM in relation to HR, arteral pressure and myocardial mass, establishment of indicators with influence on TPCM, establishment of correlation between TPCM and severity of angina, defined by a standardized questionnaire and search for predictive factors for change in TPCM in patients with ANOCA.

Material and methods

The dissertation is based on a prospectively followed-up study of a total of 102 patients over the age of 18 who were indicated for coronary angiography due to anginal complaints for the period March 2023-April 2025. The inclusion and exclusion criteria are precisely described. It is noteworthy that the number of subjects studied was calculated in advance, which is a prerequisite for obtaining practical and statistically significant results.

The materials and methods section is well presented by Dr. Grigorov, as clinical, laboratory and echocardiographic data were systematically and adequately collected by trained medical personnel and validated scales and questionnaires were used. The design used was a prospective cross-sectional study, the only one possible to prove the hypothesis under study.

The methodology for calculating TPCM through invasive coronary angiography is described in detail, with all examinations performed by the doctoral candidate.

The obtained data were statistically processed using a very rich set of statistical methods. Various models were used, including linear regression techniques to assess the correctness of the hypotheses.

Results

The results are presented sequentially in several sections:

- Characteristics of the patients. The studied patients had a mean age of over 60 years and, as expected, are predominantly female. The risk characteristics are typical for patients with CHD. The clinical severity of CHD and the distribution of symptoms according to the different domains of the questionnaire used are examined in detail. The use of non-parametric analyses using clinical variables is justified by the lack of their normal distribution. Resting ECG changes are found in about half of the patients, and they correlate, as expected, with increased left ventricular muscle mass.
- Characteristics of the study. The presented results show an average value of the TPCM of nearly 5 seconds, between 2.5 and 7.7 seconds. The main indicator of MVD is indexed for the HR, APN and LVMM in two different ways - by correlation coefficients and by linear regression. Indexing, however, does not significantly change the time for contrast washout, since the baseline has a close to normal distribution, and the correlation between the selected variables and the TPCM is weak. *As a remark, it can be noted that the dissertation candidate preferred the correlation equation to the regression one, which is not particularly correct, since a lower evidential method of establishing interdependence was chosen, despite the reasons for its choice indicated in the discussion*.
- Contrast washout time showed a moderate correlation with the severity of angina pectoris and with some of the angina domains of the Seattle questionnaire - physical limitation, frequency of anginal symptoms and perception of illness. This relationship was strengthened after excluding patients with anatomical abnormalities. Subgrouping according to iTPCM values below and above the mean value showed a significantly more delay in washout in the presence of severe angina and in the presence of significant impairment in quality of life.
- Analysis of predictors of TPCM. The comparisons performed did not show a significant influence of the usual risk factors for IHD, ECG changes and the applied therapy on the time for contrast medium washout. This was also confirmed by the multivariate linear regression analysis, in which the only borderline significance was reached by the presence of ventricular-coronary microfistulas. The non-randomly selected indicators explain only slightly over 2% of the variability of TPCM.

As a recommendation, I would point out avoiding presenting the same results in tabular and graphical form.

The discussion discusses in detail the methodology used, compares the demographic characteristics of the subjects included in the present study with those from other studies, and shows the methodological advantages of the present methodology compared to other fluoroscopic methods used so far. The uniqueness of the methodology used for indirect assessment of MVD is emphasized. The lack of association between the time of passage of the contrast medium and traditional risk factors for IHD is again discussed, as well as the correlation with the severity of anginal symptoms and with some aspects of quality of life in

patients with ANOCA. I would like to point out that in this part there is some repetition of the discussion with what has already been done in the Results section.

The limitations of the study, which are related to the angiographic examination methodology itself, the iTPCM method used, and the lack of functional determination of IHD and MVD, are correctly indicated. The need for dynamic follow-up is also emphasized. In connection with the indicated limitations, **future perspectives** for the development of the study are also outlined.

Inferences are 6 in total and they are in line with the set goal and objectives.

The conclusion summarizes the entire work on the dissertation and the conclusions drawn as a result of the work done and the results obtained. *Here, however, some repetition is allowed with what has already been mentioned in the discussion and inferences sections. I would also recommend a conclusion that the angiographic methods are initial and indicative and should be followed by a more detailed examination of the MVD with laboratory and other methods for more accurate and personalized treatment.*

There are **8 contributions – 1 with fundamental value, 6 with original character and 2 confirmatory**, all of them are of theoretical, scientific and practical value and which I fully accept.

The bibliography covers the problem of studying IHD without significant coronary pathology and microvascular dysfunction in a multifaceted way, with detailed knowledge of the methods used for this. It is impressive that the majority of titles are from the last 5 and 10 years. **A disadvantage is the lack of citation of works by Bulgarian authors, as they are available. In addition, the bibliographical material is arranged in the order of mentioning, not in alphabetical order.**

The well-written text, with a precise scientific style and good layout, should be noted. The dissertation is well illustrated, which complements the main text.

The abstract is 72 pages in total and is prepared according to standards It correctly presents the main problems and results discussed in the dissertation.

In connection with the dissertation work, 3 articles have been **published**: 1 in an indexed in international database journal and 2 in refereed Bulgarian journals. Dr. Grigorov is the first author in the publications.

In conclusion, I believe that the dissertation presented by **Dr. Rozen Krasimirov Grigorov,** on the topic **" TIME FOR CONTRAST TRANSITION THROUGH THE MYOCARDIUM IN PATIENTS WITH MINOR CORONARY DISEASE ",** is original scientific research, which presents a new standardized method for indirect assessment of microvascular involvement in patients with coronary artery disease with the advantages of being easy to perform, without the need for expensive equipment and additional consummatives, with good resolution according to the severity of angina. This study can be used for initial screening of patients with "sick" arteries, who are referred for coronary angiography and in whom it makes sense to have further detailed examination and personalized treatment. The dissertation has significant scientific and practical value in the everyday clinical practice in the angiography laboratory. It possesses all the qualities and **MEETS THE REQUIREMENTS** of the law on the development of the academic staff in the Republic of Bulgaria and the regulations for its application at MU-Varna, **FOR AWARDING THE EDUCATIONAL and SCIENTIFIC DEGREE "DOCTOR"**; that is why I confidently give **a POSITIVE assessment.**

Varna
05.12.2026

/ Prof. Dr. Yoto Yotov, MD