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Time for contrast to pass through the myocardium in patients with non-obstructive coronary artery disease

Thesis summary

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The dissertation consists of 158 pages and is illustrated with 31 tables and 28 figures. The bibliography includes 332 references. The study was conducted at the Second Clinic of Cardiology, St. Marina University Hospital – Varna.

The dissertation was reviewed and approved for defense by the departmental council of the First Department of Internal Medicine at the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna on November 6, 2025.

The official defense of the dissertation will take place on ..... 2026 in hall .... during an open session of the scientific jury. The materials related to the defense are available at the library of the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna.

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CONTENTS

LIST OF ABBREVIATIONS

ACEi – Angiotensin-Converting Enzyme inhibitor

ANOCA – Angina with Non-Obstructive Coronary Arteries

ARB – Angiotensin II Receptor Blocker

ASA – Acetylsalicylic acid

BMI – Body Mass Index

CAD – coronary artery disease

CCB – Calcium Channel Blocker

CCFC – Coronary Clearance Frame Count

CCS – Canadian Cardiovascular Society

CMD – coronary microvascular dysfunction

CFR – Coronary Flow Reserve

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration

CMR – Cardiovascular Magnetic Resonance

CSFT – Coronary Sinus Filling Time

cTFC – corrected TIMI Frame Count

ESC – European Society of Cardiology

FFR – Fractional Flow Reserve

ECG – electrocardiogram

HDL – High Density Lipoprotein

IHD – ischemic heart disease

IMR – Index of Microcirculatory Resistance

INOCA – Ischemia with Non-Obstructive Coronary Arteries

LAD – Left Anterior Descending artery / лява предна десцендентна артерия

LDL – Low Density Lipoprotein / липопротеини с ниска плътност

MBG – Myocardial Blush Grade

MVA – microvascular angina

PCI – Percutaneous Coronary Intervention

PET – Positron Emission Tomography

SAQ – Seattle Angina Questionnaire / Сиатълски въпросник за ангина

TIMI – Thrombolysis In Myocardial Infarction

TMPG – TIMI Myocardial Perfusion Grade

TTE – transthoracic echocardiography

VSA – vasospastic angina

I. INTRODUCTION

Ischemic heart disease (IHD), and in particular stable angina pectoris, affects more than 100 million people worldwide, and a substantial proportion of patients undergoing coronary angiography due to anginal symptoms or a positive ischemia test do not have obstructive coronary artery disease (CAD) (Perera et al. 2023; Vrints et al. 2024; Jansen et al. 2021). Clinical attention toward this pathology has traditionally focused on obstructive coronary disease, defined by the presence of hemodynamically significant stenoses affecting the epicardial coronary arteries. However, a large number of patients with typical anginal symptoms or with documented ischemia on functional testing do not demonstrate significant stenoses on coronary angiography (Perera et al. 2023; Vrints et al. 2024; Jansen et al. 2021). This clinical scenario, initially described as early as the mid-1970s, raises important questions regarding alternative mechanisms underlying myocardial ischemia in the absence of obstructive CAD (Kemp et al. 1967).

The concept of ischemia in the absence of obstructive coronary disease developed gradually following the introduction of coronary angiography in the 1960s. It soon became evident that a subset of patients with clinical suspicion of IHD did not exhibit obstructive lesions in the epicardial vessels. In 1967, Likoff et al. reported a group of 15 women aged 30 to 53 years with chest pain and normal coronary angiograms but with electrocardiographic changes at rest and during exertion (Likoff et al. 1967). In 1973, Kemp et al. published the first systematized study defining this phenotype as "Syndrome X," reflecting the uncertainty surrounding the etiology of anginal symptoms in these patients (Kemp et al. 1967). Over the following decades, multiple authors contributed to expanding understanding of this condition, including descriptions of impaired vasodilatory capacity of the coronary microvasculature, endothelial dysfunction, inflammatory mechanisms, and hormonal factors such as estrogen deficiency (Rosano et al. 1995; Opherk et al. 1981; Cannon et al. 1983; Motz et al. 1991). Gradually, the term "microvascular angina" (MVA), proposed by Cannon and Epstein in 1988, replaced the concept of "syndrome X," emphasizing the vascular nature of the underlying abnormality (Cannon and Epstein 1988). Significant advances in understanding the pathophysiology of this condition have occurred over the past two decades, facilitated by the development of invasive and noninvasive techniques for evaluating the coronary microcirculation, enabling more precise diagnosis and a correspondingly individualized therapeutic approach.

In an effort to establish clearer terminology and emphasize the importance of this clinical phenotype, the terms ANOCA (angina with non-obstructive coronary arteries) and INOCA (ischemia with non-obstructive coronary arteries) have gained acceptance in recent years. These describe, respectively, symptomatic patients and/or patients with documented ischemia in the absence of obstructive stenoses >50% in the epicardial arteries (Kunadian et al. 2021). Data from large registries

and studies, including the WISE (Women's Ischemia Syndrome Evaluation) program, indicate that up to 50% of patients referred for angiographic investigation due to angina or a positive stress test fall into the ANOCA/INOCA category (Vrints et al. 2024; Pepine et al. 2010). This condition is particularly common among women, where its prevalence reaches up to 70%, compared with 30–50% among men (Jespersen et al. 2012).

For many years, angina without obstructive lesions was considered a relatively benign condition. Subsequent observations, however, clearly demonstrate that ANOCA/INOCA is associated with markedly impaired quality of life, frequent hospitalizations, persistent symptoms despite treatment, and an increased risk of adverse cardiovascular events, including myocardial infarction and cardiac death (Samuels et al. 2023; Camici and Crea 2007).

The pathophysiological basis of ANOCA/INOCA comprises a broad spectrum of abnormalities in coronary circulation, which can be broadly classified as epicardial vasomotor dysfunction and coronary microvascular dysfunction (CMD), and in some patients as a combination of both (Kunadian et al. 2021). Some patients exhibit vasospastic phenomena, whereas in others the predominant mechanism involves abnormal regulation of vascular tone and remodeling of arterioles and the capillary network, leading to reduced coronary flow reserve (CFR) and increased microvascular resistance. Additionally, the presence of myocardial bridging may contribute to ischemic symptoms in a subset of patients (Pepine 2023).

Despite significant progress in elucidating the mechanisms underlying ANOCA/INOCA, diagnosis in these patients remains challenging. Routine coronary angiography, used to exclude obstructive CAD, does not allow direct assessment of microcirculatory function due to its limited spatial resolution (Thomas J Ford et al. 2018). The European guidelines for chronic coronary syndromes emphasize the importance of diagnosing microvascular angina through invasive assessment of CFR and the index of microvascular resistance (IMR) in patients with persistent symptoms and angiographically normal coronary arteries (Vrints et al. 2024). Despite these recommendations, widespread use of these techniques remains limited due to their relatively low availability, additional procedural risks and time, and the requirement for well-trained personnel to ensure accurate interpretation and avoid diagnostic errors. Noninvasive methods such as Doppler echocardiographic assessment of CFR in the proximal left anterior descending artery (LAD), cardiac magnetic resonance imaging (CMR), and positron emission tomography (PET) are also used to evaluate CFR, but they lack sufficient sensitivity and specificity and carry lower levels of recommendation, limiting their clinical applicability (Escobar et al. 2024).

Angiographic techniques such as TIMI frame count and myocardial blush grade (MBG) are used to assess epicardial coronary blood flow and provide indirect evaluation of microvascular function. Studies have demonstrated their potential utility in diagnosing CMD, with affected patients

exhibiting increased TIMI frame counts and reduced MBG values (Gibson et al. 1996; Van 'T Hof et al. 1998). Other fluoroscopic indices, such as Coronary Clearance Frame Count (CCFC) and Coronary Sinus Filling Time (CSFT), have also been investigated as possible tools for assessing microvascular function, with varying clinical and prognostic significance (Yildirim et al. 2018; Haridasan et al. 2013).

It is important to emphasize that ANOCA does not represent a "benign" disease. On the contrary, published data from large studies, including WISE (Pepine et al. 2010; Kunadian et al. 2021), demonstrate an increased risk of adverse cardiovascular events, including myocardial infarction and cardiac death, as well as significantly impaired quality of life, persistent symptoms, and an increased frequency of hospitalizations in these patients (Pepine et al. 2010; Kunadian et al. 2021). The clinical significance of this condition remains underestimated, and diagnostic uncertainty contributes to empirical or inadequate treatment.

Multiple lines of evidence support the importance of individualized therapy tailored to the underlying pathophysiological mechanism. The CorMicA (CORonary MICrovascular Angina) trial demonstrated that invasive functional profiling and treatment stratification based on the identified ANOCA endotype results in significant improvement in symptoms and quality of life compared with the standard approach (Thomas J. Ford et al. 2018). This underscores the need for accessible, reliable, and routinely applicable methods for assessing the microcirculation to support diagnosis and therapeutic stratification of patients with ANOCA.

The aforementioned issues, the substantial proportion of patients with anginal symptoms referred for coronary angiography who lack obstructive epicardial coronary disease, the poorer prognosis of these patients compared with the general population, and the absence of a reliable, easily applicable, and accessible method for evaluating the coronary microcirculation constitute the rationale for conducting the present study.

II. AIM AND TASKS

AIM

The aim of the study is to define a new, easily reproducible method for fluoroscopic assessment of the microcirculation that is as free as possible from external influences, referred to as the indexed time for contrast to pass through the myocardium (iTCPM), in patients without significant epicardial coronary artery disease, and to analyze its association with the severity of anginal symptoms in these patients.

TASKS

1. To standardize the methodology for measuring TCPM, including frame rate of recording, type of contrast agent used, parameters of the automatic injection system (rate and volume), and standard angiographic projections for visualization of the coronary sinus.
2. To determine the mean TCPM value in the study cohort.
3. To assess the severity of anginal symptoms using a standardized questionnaire and a clinical evaluation.
4. To record variables that may influence the TCPM value, including myocardial mass and hemodynamic conditions during the examination.
5. To index TCPM relative to myocardial mass, heart rate, and mean aortic pressure at the ostium of the coronary artery during the examination.
6. To analyze the relationship between indexed TCPM and the severity of anginal symptoms, assessed by CCS class and a standardized angina questionnaire.
7. To identify factors that may predict the value of indexed TCPM, such as classical cardiovascular risk factors and concurrent pharmacological therapy.

III. MATERIALS AND METHODS

1. Material base for the implementation of the dissertation

The study was conducted at the Clinic of Interventional Cardiology, St. Marina University Hospital, Varna, Bulgaria, between February, 2023, and April, 2025. The study was approved by the institutional ethics committee of the Medical University of Varna (№128/02.03.2023 г.). Written informed consent was obtained from all participants.

2. Study population

The required sample size was pre-calculated using Pearson's correlation test (Pearson's r), with a predefined effect size ($r = 0.3$), a statistical power of 80% ($Z = 0.84$), and a significance level ($\alpha = 0.05$; $Z = 1.96$). The minimum required number of participants was calculated to be 87. To compensate for potential exclusion of patients from the analysis due to anatomical variations of the coronary arteries or technical limitations, a total of 102 patients were included in the study. The participants were patients with anginal symptoms, aged over 18 years, referred for invasive coronary angiography.

Inclusion criteria:

- age ≥18 years
- presence of angina warranting diagnostic angiography
- signed informed consent

Exclusion criteria:

- prior myocardial infarction
- previous coronary revascularization (interventional or surgical)
- ≥50% stenosis in any epicardial coronary artery
- elevated biomarkers of cardiac necrosis
- significant valvular heart disease
- echocardiographic evidence of pulmonary hypertension
- atrial fibrillation during angiography
- hematocrit outside the 0.35–0.45 range.

3. Study design

The study is cross-sectional with prospective enrollment of patients, observational, and single-center, conducted under real clinical conditions. Data were collected once during hospitalization, without an additional follow-up period. No control group was used. The study design is presented in Figure 2.

The initial assessment included the collection of clinical and demographic data. Trained medical professionals conducted structured interviews with participants regarding their cardiac symptoms, documenting the location, character, duration, radiation, and frequency of symptoms, as well as precipitating and relieving factors. Based on clinical evaluation, anginal symptomatology was either accepted or refuted, and patients were classified from first to fourth functional class according to the CCS (Canadian Cardiovascular Society). A standardized questionnaire for the assessment of symptoms was used – the Seattle Angina Questionnaire (SAQ), translated into Bulgarian (Spertus et al., 1995).

We collected information on cardiovascular risk factors: age, body mass index (BMI), presence of diabetes mellitus, arterial hypertension, dyslipidemia, and smoking status. Additionally, comorbidities and any prior coronary angiographies were documented.

A complete clinical examination and electrocardiogram (ECG) recording were performed at rest. The ECGs were analyzed for signs of ischemia (T-wave inversion, pathological Q waves, ST-segment depression, left or right bundle branch block) and for the presence of arrhythmia.

Blood samples were analyzed for levels of total, LDL-, and HDL-cholesterol, serum creatinine, complete blood count, and coagulation status.

Transthoracic echocardiography

Transthoracic echocardiography (TTE) was performed in all patients to assess left ventricular dimensions, myocardial mass, systolic and diastolic function, valvular structures, and the estimated pulmonary artery pressure. The examinations were conducted using a Philips EPIQ CVx Premium Cardiovascular Ultrasound System (2023 model), equipped with an X5-1c xMatrix transducer. Patients were positioned in the left lateral decubitus position. Images were obtained in standard views: parasternal long-axis (PLAX) with the transducer placed in the fourth left intercostal space adjacent to the sternum, parasternal short-axis, apical four-chamber, and apical two-chamber views.

Endocardial contours of the left ventricle were traced in end-diastole and end-systole at the level of the papillary muscles or chordae in the PLAX view using M-mode. End-diastolic and end-systolic diameters were measured, and ejection fraction was calculated using the Teichholz formula.

From the apical four-chamber view, endocardial contours of the left ventricle were traced in end-diastole and end-systole, and left ventricular ejection fraction was also calculated using the Simpson method. Left ventricular myocardial mass was calculated using the Devereux formula based on measurements obtained in end-diastole (Devereux et al., 1986):

$$\text{Myocardial mass} = 0.8 \times \{1.04 \times [(\text{LVEDD} + \text{IVSd} + \text{PWd})^3 - \text{LVEDD}^3]\} + 0.6$$

Measurements of right ventricular dimensions, aortic root diameter, and left atrial size were also performed. The valvular apparatus was evaluated using standard echocardiographic modalities: 2D, M-mode, Color Doppler, Pulsed Wave Doppler (PW), and Continuous Wave Doppler (CW). All measurements and interpretations were conducted in accordance with current recommendations of the European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology (ESC).

Obtaining the time for contrast to pass through the myocardium (TCPM)

After completion of the coronary angiography and confirmation of the absence of obstructive coronary artery disease, the time for contrast to pass through the myocardium (TCPM) was measured in all patients. The invasive procedure was performed using a Siemens Axiom Artis system. The contrast agent used was Iomeron 350 (BRACCO). Selective contrast injection into the left coronary artery (LCA) was performed through selective engagement of the LCA. Invasive measurement of mean pressure was obtained from the catheter tip positioned in the ascending aorta and in the LCA. An automated injection system, Acist CVi, was used.

The projection for TCPM assessment was FAS CAU 15–30°. A total of 6 ml of contrast (volume) was injected at a flow rate of 2 ml/s, with a rise time of 0.5 s, a pressure of 450 psi, and a recording speed of 10 frames/s, using a Terumo Radial TIG 5F diagnostic catheter or a Judkins Left 3/5F catheter.

Definition of TCPM: the time in seconds required for the contrast medium to pass from the catheter tip through the epicardial arteries and microcirculation and reach the venous coronary sinus.

Method for calculating TCPM: the number of frames was counted from the moment the contrast exited the catheter tip (with the catheter pre-filled with contrast) to the first appearance of contrast in the venous coronary sinus.

$$TCPM\ (s) = \frac{(last\ frame - first\ frame)}{frame\ rate\ (fps)}$$

TCPM assessment was performed by two independent investigators for each patient. In cases where the difference between observers exceeded 0.2 seconds (equivalent to 2 frames at a recording speed of 10 frames per second), a repeated evaluation was performed and a consensus value was established. Differences below this threshold were considered negligible.

Figure 1 shows the first and last frames used for measurement. The obtained value in seconds was then adjusted for heart rate, pressure in the LCA ostium, and myocardial mass, thereby yielding the indexed time for contrast to pass through the myocardium (iTCPM).

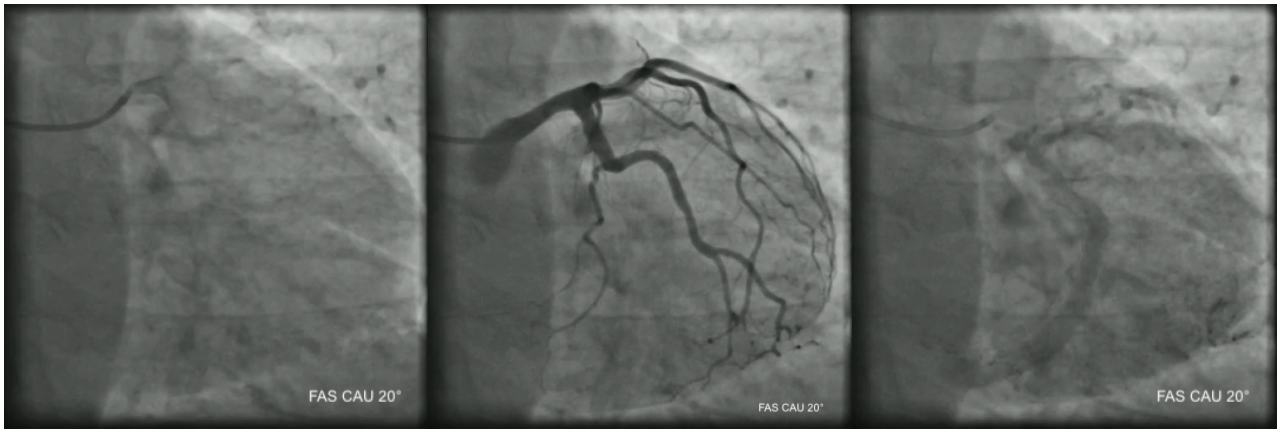

Figure 1. First frame – passage of contrast from the catheter tip into the left coronary artery. Second frame – maximal opacification of the left coronary artery. Final frame – first visualization of the coronary sinus.

The coronary angiography, clinical assessment, and completion of the questionnaire were performed without discontinuation of the patients ambulatory-prescribed anti-ischemic therapy, when such therapy was present.

4. End point

The endpoint is the determination of the mean indexed time for contrast to pass through the myocardium (iTCPM) in patients with non-obstructive coronary artery disease in the cohort, and the investigation of the correlation between iTCPM and the severity and frequency of anginal symptoms, assessed by CCS functional class and the Seattle Angina Questionnaire (SAQ). Additional aims include identifying variables that may influence the value of iTCPM, including classical cardiovascular risk factors, and the type and number of medications taken.

5. Statistical analysis

Statistical analyses were performed using Python, employing the following libraries: Pandas for data manipulation, NumPy for numerical operations, SciPy for statistical tests, and Matplotlib/Seaborn for data visualization. Data from angiography, echocardiography, questionnaires, and laboratory parameters were entered into and pre-validated within a structured electronic database. Preliminary analysis of the main continuous variables included assessment of distribution normality using the Shapiro–Wilk test, as well as visual inspection via Q–Q plots and histograms. It was determined that the time for contrast to pass through the myocardium (TCPM) demonstrated an approximately normal distribution, whereas all subscales of the SAQ showed statistically significant deviation from normality. Therefore, to preserve consistency and avoid assumptions of normality in correlation and comparative analyses, nonparametric statistical methods were used. Continuous variables are presented as mean ± standard deviation (SD) or as median and interquartile range (IQR). Categorical variables as absolute and relative frequencies (%).

To assess the relationship between iTCPM and angina severity according to CCS functional class, Spearman's rank correlation coefficient was used. The analysis additionally included separate Spearman correlations between iTCPM and each of the five SAQ scales.

In a supplementary subanalysis, the same statistical tests were repeated after excluding 13 patients in whom angiography revealed structural anatomical variants of the coronary circulation (myocardial bridges or coronary–cameral microfistulae). These findings may represent potential causes of ischemia and anginal symptoms without necessarily affecting iTCPM, and therefore could introduce structural bias into the evaluation of the association between iTCPM and symptom severity.

A between-group comparative analysis was performed, dividing participants into two groups according to the mean iTCPM value. The first group included patients with iTCPM below the mean ("fast" group), and the second included patients with iTCPM above the mean ("slow" group). The purpose of this analysis was to assess whether statistically significant differences existed in the severity of anginal symptoms, measured by CCS functional class and the five SAQ subscales, between the two groups. Given the non-normal distribution of SAQ scores and the ordinal nature of CCS classification, the Mann–Whitney U test was used for statistical comparison. The analysis aimed to test the hypothesis that patients with a longer time for contrast to pass through the myocardium ("slow" group) exhibit higher CCS class and lower SAQ scores, reflecting more severe symptoms and poorer quality of life.

Two separate multivariable linear regression analyses were conducted to identify independent predictors of iTCPM. The first model included demographic and clinical characteristics, as well as structural anatomical features identified by coronary angiography. The second model evaluated the

influence of pharmacological therapy, examining the effect of different classes of anti-ischemic medications and medications for cardiovascular event prevention on iTCPM.

In both models, refinement was achieved through backward elimination, removing variables without statistical contribution to explaining the variation in the dependent variable. Compliance of the final models with assumptions of linearity, homoscedasticity, and independence of residuals was assessed, and the normality of residuals was evaluated visually using Q–Q plots. The coefficient of determination (R^2) and the p-values of the regression coefficients were used to assess explanatory power and statistical significance of individual predictors.

A predefined significance level of $\alpha = 0.05$ was used. A wide range of graphical methods was used for visualizing the results, including boxplots, correlation plots with superimposed linear regression lines, and graphical representations of distributions using Kernel Density Estimation (KDE).

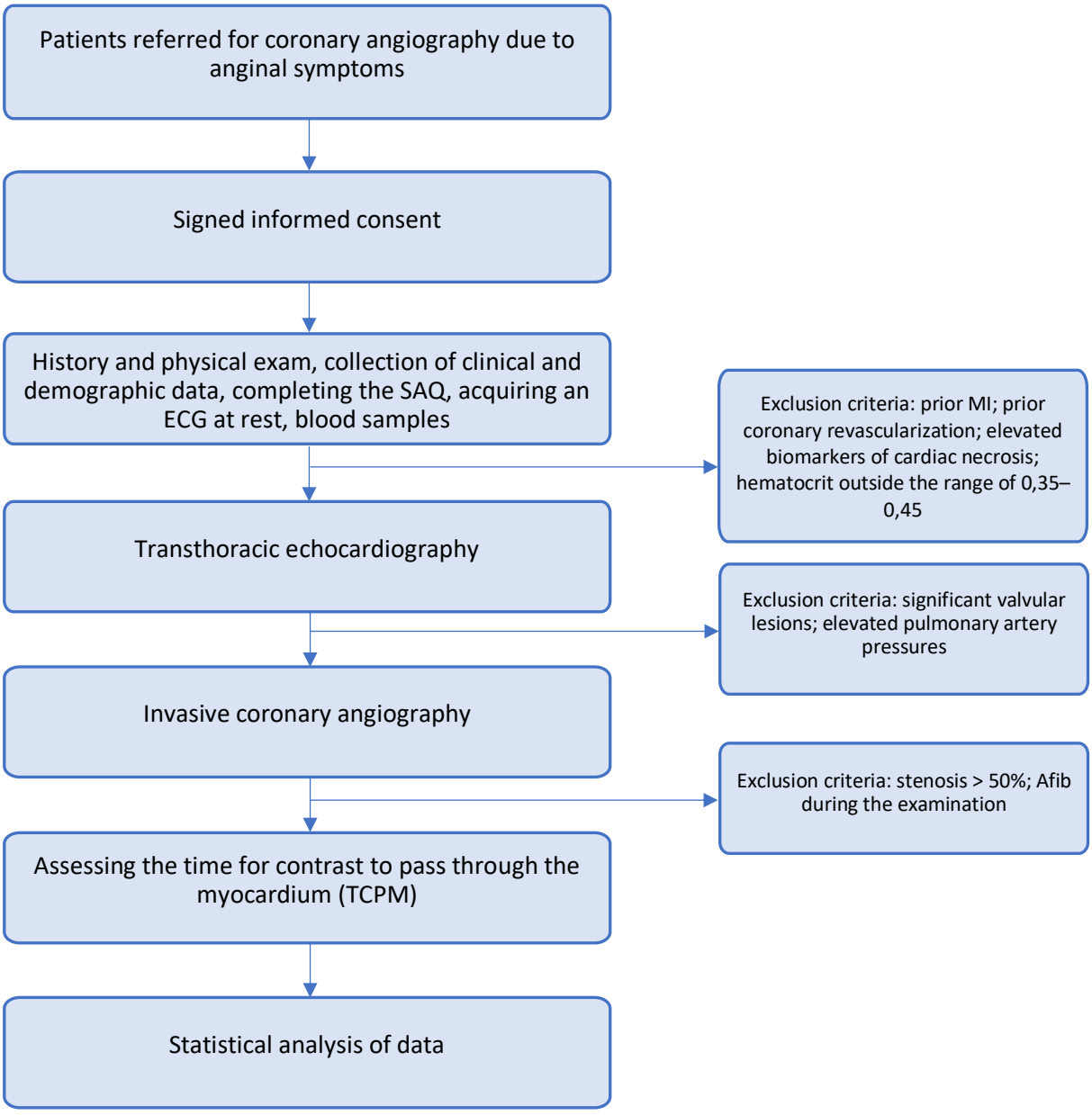

Figure 2. Study design
ECG – electrocardiography; SAQ – Seattle Angina Questionnaire; MI – myocardial infarction; Afib – atrial fibrillation

IV. RESULTS

Patient characteristics

A total of 102 patients meeting the inclusion criteria were included in the final analysis. The mean age of the cohort was 61.5 ± 9.9 years, and women accounted for 59% of all participants (n = 60). The most prevalent cardiovascular risk factors in the group were arterial hypertension and dyslipidemia, each present in 94% of the patients (n = 96). The next most frequent were smoking (57%) and type 2 diabetes mellitus (22%). The mean body mass index (BMI) was 30.5 ± 6.3 kg/m², and the estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI formula) was 86.5 ± 14.8 ml/min/1.73m². The mean LDL-cholesterol level in the study population was 2.76 ± 1.12 mmol/L. Nearly all patients (97%) had preserved left ventricular systolic function, defined as an ejection fraction greater than 50%. The demographic characteristics and major cardiovascular risk factors of the study population are presented in Table 1.

Assessment of the functional class of anginal symptoms according to the Canadian Cardiovascular Society (CCS) classification showed that more than half of the patients (54.4%) fell into functional class II or higher. The most frequently observed categories were CCS II (23.3%) and CCS II–III (20.4%) (Table 2).

Results from the Seattle Angina Questionnaire (SAQ), translated and adapted for the Bulgarian population, demonstrated the following mean scores across its subscales: physical limitation – 61.85 ± 15.08, angina stability – 25.74 ± 19.09, angina frequency – 74.11 ± 13.96, treatment satisfaction – 85.40 ± 12.28, and disease perception – 34.15 ± 19.14. Full SAQ results for each category are presented in Table 3. Figure 3 illustrates the density distribution of the scores across the five SAQ subcategories using KDE curves. Figure 4 shows the distribution of scores in the five SAQ categories using box-plot diagrams. To determine the appropriate statistical approach for analyzing the SAQ results, a Shapiro–Wilk test for normality was performed. Statistically significant deviations from normality were observed for all five subscales (all $p < 0.05$), with W coefficients ranging from 0.8173 to 0.9442 (Table 4).

Fourteen patients had undergone previous coronary angiography demonstrating non-significant coronary atherosclerosis; in three of these patients, the examination had been performed twice.

Resting electrocardiography (ECG) at admission was pathological in 49% of the cohort, showing significant ST-segment depression in 23.5%, negative T waves in 27.4%, and both abnormalities concurrently in 9.8%. Left and right bundle branch block were identified in 2.9% and 5.9% of patients, respectively.

Left ventricular myocardial mass was calculated for all participants using the Devereux formula. The mean myocardial mass for the cohort was 195.75 ± 53.84 grams, and the mean indexed myocardial mass was 97.96 ± 23.07 g/m².

To investigate whether the ECG abnormalities could be explained by increased myocardial mass, the cohort was dichotomized using the mean indexed myocardial mass (98 g/m²) as a cut-off value. The analysis did not identify a significant association between increased myocardial mass and the presence of pathological ECG findings ($\chi^2 = 0.03$, $p = 0.866$).

Table 1. Baseline characteristics and risk factors in the cohort.

Variable	Absolute value (n=102)	Percentage (%)
Age	61.5 ± 9.9 years	-
BMI	30.5 ± 6.3 kg/m².	-
eGFR (CKD-EPI)	86.5 ± 14.8 ml/min/1,73m^2	-
Female sex	60	59
Hypertension	96	94
Diabetes	23	22
Dyslipidemia	96	94
LDL	2,76 ± 1.12 mmol/L	-
Smoking	58	57
Preserved ejection fraction (EF > 50%)	99	97

Table 2. Distribution of patients according to CCS class.

Characteristic	Absolute value (n=102)	Percentage (%)
CCS class 0-I	10	9.7
CCS class I	23	22.3
CCS class I-II	13	12.6
CCS class II	24	23.3
CCS class II-III	21	20.4
CCS class III	11	10.7
CCS class IV	0	0.0

Table 3. Results from the Seattle angina questionnaire (SAQ)

	Mean	SD	Minimal value	25-th percentile	Median	75-th percentile	Maximal value
Physical limitation	61.85	15.08	31.11	49.44	66.67	75.0	84.44
Angina stability	25.74	19.09	0.0	25.0	25.0	25.0	100.0
Angina frequency	74.11	13.96	30.0	60.0	70.0	90.0	100.0
Treatment satisfaction	85.4	12.28	37.93	79.31	88.1	96.55	100.0
Disease perception	34.15	19.14	0.0	25.0	33.33	41.67	91.67

**SD – standard deviation*

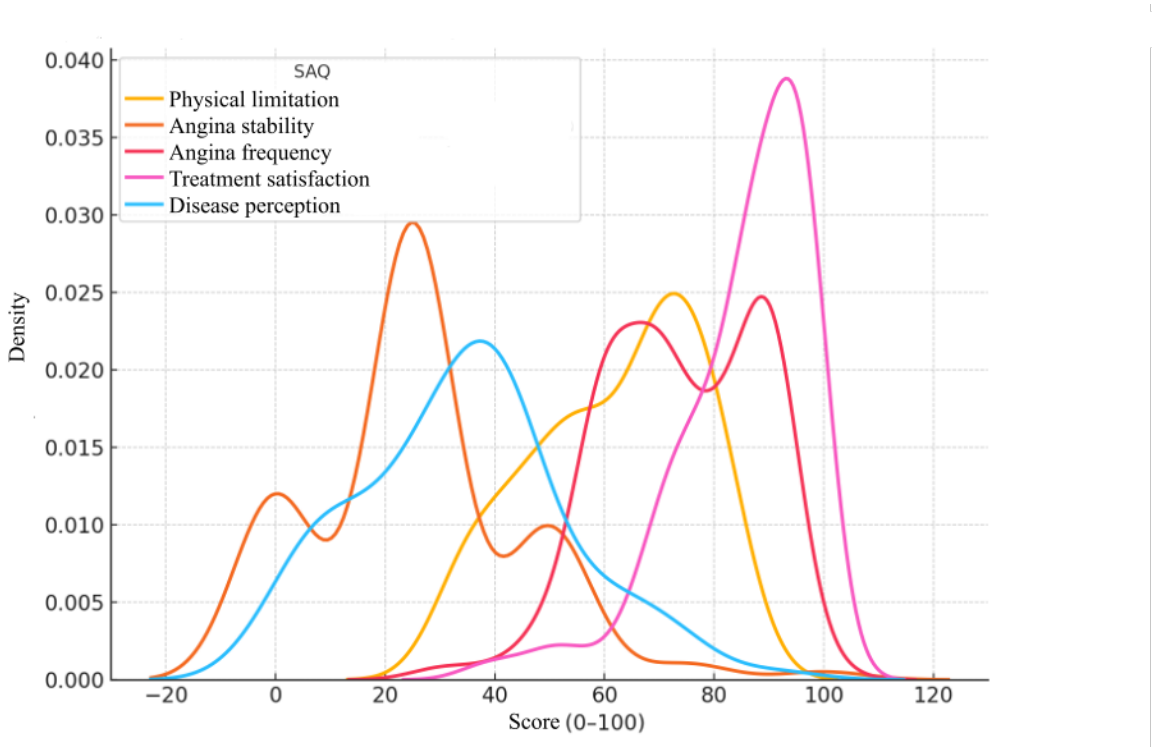

Figure 3. Density distribution (Bell curve) of the results in the Seattle Angina Questionnaire (SAQ) categories. The density distribution of the results in the five subcategories of the SAQ is presented using Kernel Density Estimation (KDE) curves.

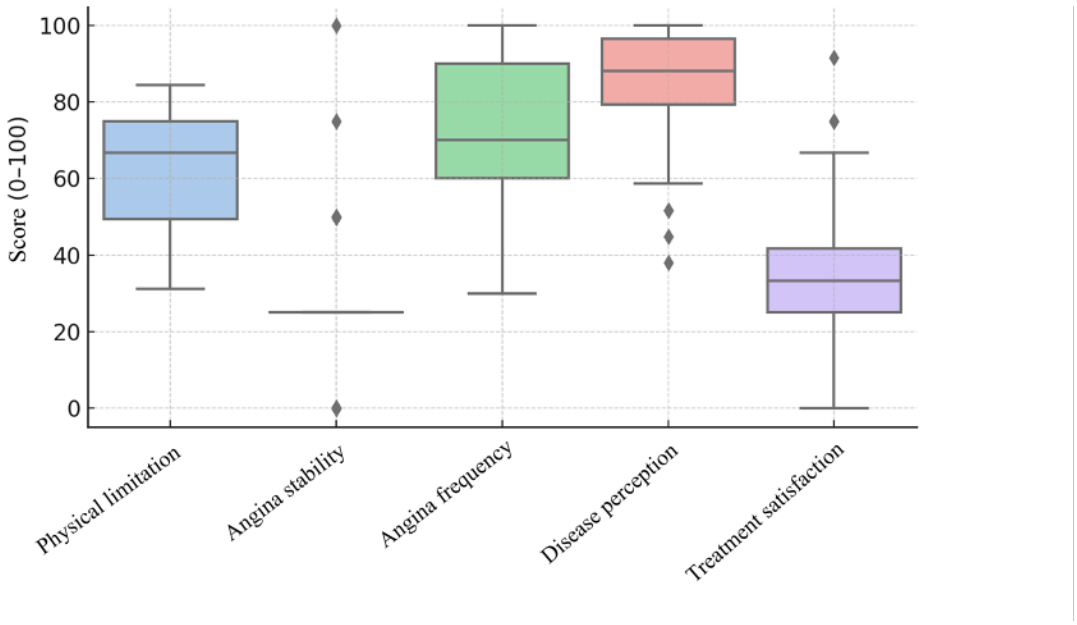

Figure 4. Box-plot diagram of the results across the Seattle Angina Questionnaire (SAQ) categories. The distribution of results in the five categories of the SAQ is presented. In the "Angina Stability" category, a clustering of patients around a score of 25 is evident, resulting in the "box" collapsing into a line.

Table 4. Results from the Shapiro-Wilk test for normality in the five categories of the Seattle angina questionnaire (SAQ)

	W Coefficient (Shapiro-Wilk)	**p-value**
Angina stability	0,8173	< 0.000001
Treatment satisfaction	0,8437	< 0.000001
Angina frequency	0,8985	< 0.000001
Physical limitation	0,9441	0,000296
Disease perception	0,9619	0,005

Study characteristics

All patients were in sinus rhythm during the examination. The mean heart rate was 71 beats per minute, and the mean perfusion pressure (mean arterial pressure), measured at the ostium of the left coronary artery, was 98 mmHg, with verification of no pressure drop relative to the mean aortic

pressure. In all patients, the examination was performed according to the protocol described in the materials and methods section.

The mean value of the time for myocardial contrast transit (TCPM) in the study population was 4.96 seconds, with a standard deviation (SD) of ±1.12. The minimum recorded value was 2.40 seconds, and the maximum was 7.70 seconds. The median was 4.80 seconds, with an interquartile range (IQR) of 4.20 to 5.68 seconds. Figure 5 presents the density distribution and histogram of TCPM.

Vessel tortuosity was observed in 21 patients, a myocardial bridge of the left anterior descending artery (LAD) in four patients, and coronary–cameral microfistulae were visualized in 10 patients. One patient exhibited both anomalies concurrently (myocardial bridge and microfistulae).

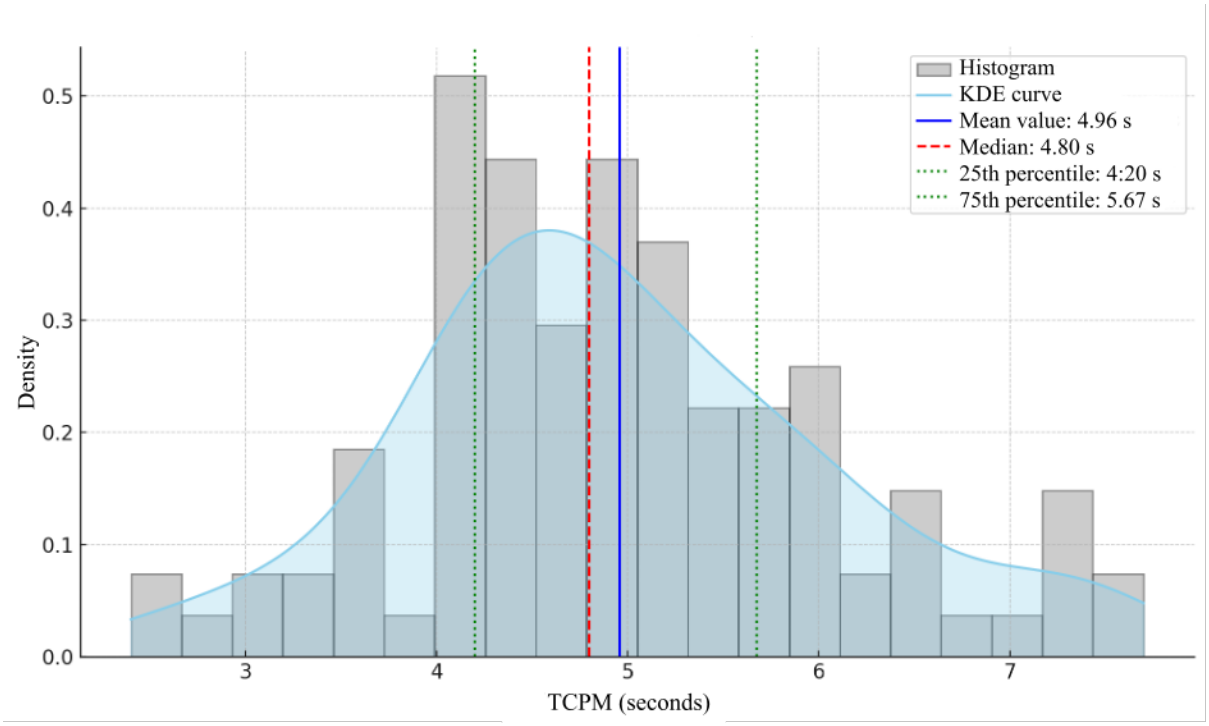

Figure 5. Density distribution and histogram of the time for contrast to pass through the myocardium (TCPM)

Indexing of the time for contrast to pass through the myocardium (TCPM)

It is well established that myocardial mass, mean arterial pressure (MAP), and heart rate (HR) influence the velocity of contrast transit through the coronary arteries.

To account for the impact of these physiological factors on the measured TCPM, two approaches to indexing were considered:

1. Indexing using relative correlation coefficients

A correlation analysis was performed between TCPM, myocardial mass, mean arterial pressure, and heart rate. A weak positive correlation was observed between myocardial mass and TCPM (r = 0.230; p = 0.020), as well as a weak negative correlation between MAP and TCPM (r = –0.269; p = 0.006). A weak, statistically non-significant negative correlation was demonstrated between TCPM and heart rate (r = –0.161; p = 0.103). The results are presented in Table 5.

To avoid the influence of these factors on the measured TCPM, we applied a standardization formula in which TCPM is multiplied by MAP and HR and divided by myocardial mass, with each variable normalized to the cohort mean and raised to the power corresponding to its relative correlation coefficient with TCPM.

Table 5. Corelation between the time for contrast to pass through the myocardium (TCPM), myocardial mass, mean arterial pressure and heart rate

	TCPM (r)	**p-value**
Myocardial mass	0,230	0,019
Mean arterial pressure	-0,269	0,006
Heart rate	-0,161	0,103

r – корелационен коефициент

Formula used:

$$iTCPM = \frac{TCPM \times \left(\frac{MAP}{Mean\ MAP}\right)^{RCC\ MAP} \times \left(\frac{HR}{Mean\ HR}\right)^{RCC\ HR}}{\left(\frac{Myocardial\ mass}{Mean\ myocardial\ mass}\right)^{RCC\ MM}}$$

Where:

RCC MAP – relative correlation coefficient MAP $= \frac{0.269}{0.269+0.230+0.161} = 0.407$

RCC HR – relative correlation coefficient HR $= \frac{0.161}{0.269+0.230+0.161} = 0.244$

RCC MM – relative correlation coefficient Myocardial mass $= \frac{0.230}{0.269+0.230+0.161} = 0.349$

The relative correlation coefficients were derived from the relative contribution of each variable based on its level of correlation with TCPM.

The correlation analysis between TCPM and the three physiological parameters – myocardial mass, MAP, and HR is illustrated in Figures 6–8.

For the indexed time for contrast to pass through the myocardium (iTCPM), which accounts for the influence of mean arterial pressure, heart rate, and myocardial mass, the mean value was 4.97

seconds with a standard deviation of 1.02 seconds. The minimum recorded value was 2.44 seconds, and the maximum reached 7.69 seconds. The interquartile range extended from 4.38 seconds (25th percentile) to 5.72 seconds (75th percentile), with a median value of 4.94 seconds (Figure 9).

To determine the appropriate statistical approach for the analysis of iTCPM, a Shapiro–Wilk test for normality was performed. A p-value of 0.390 was observed, indicating no statistically significant deviation from a normal distribution (W = 0.9865). Figure 10 presents the Q–Q plot, demonstrating that the empirical data closely follow the theoretical normal line, with only minimal deviations at the extreme values.

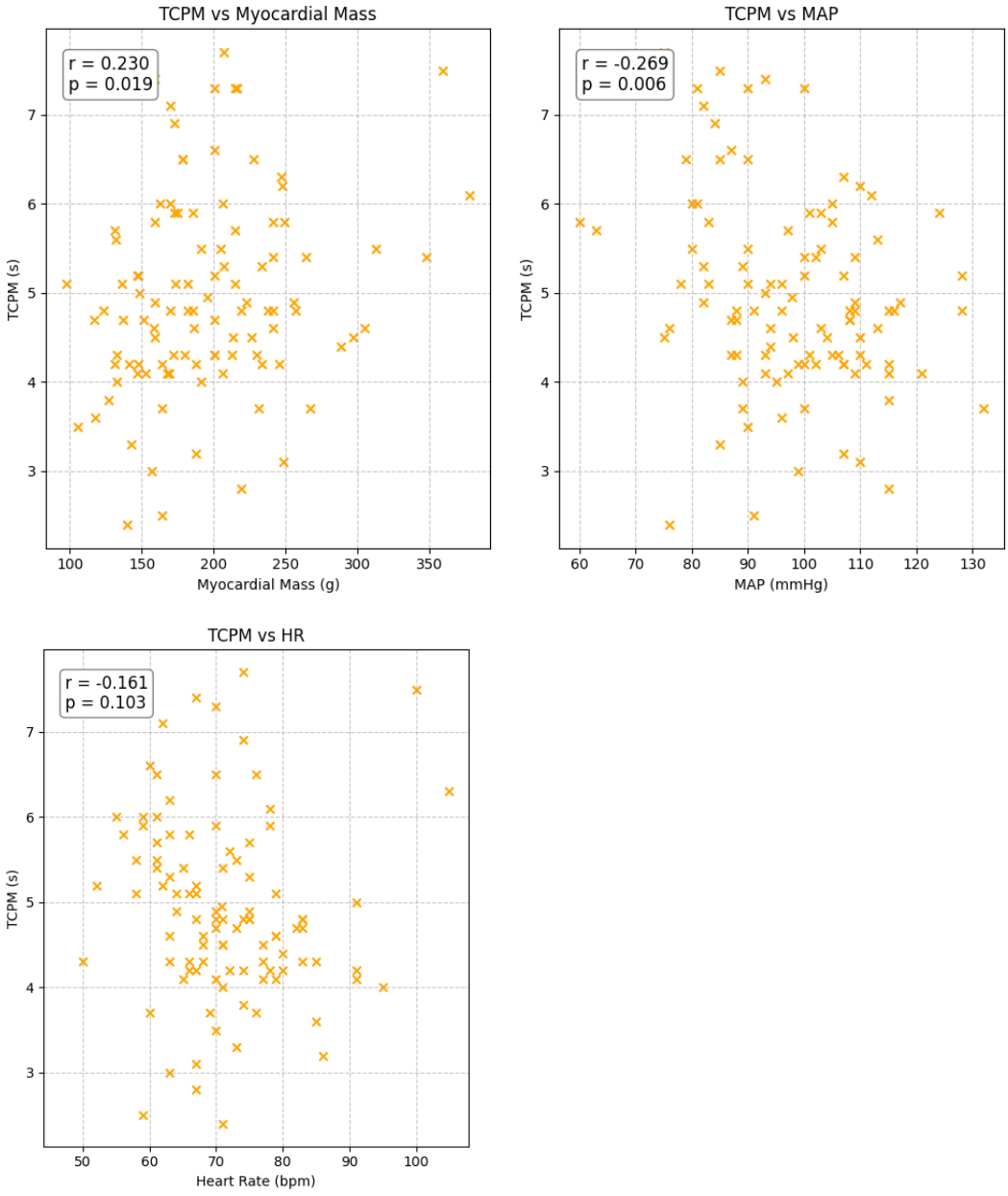

Figure 6. Scatter plot illustrating the relationship between TCPM (y) and myocardial mass (x). A weak positive correlation is observed.

Figure 7. Scatter plot illustrating the relationship between TCPM (y) and mean arterial pressure (MAP) (x). A weak but statistically significant negative correlation is identified.

Figure 8. Scatter plot illustrating the relationship between TCPM (y) and heart rate (HR) (x). The correlation is weak and statistically non-significant.

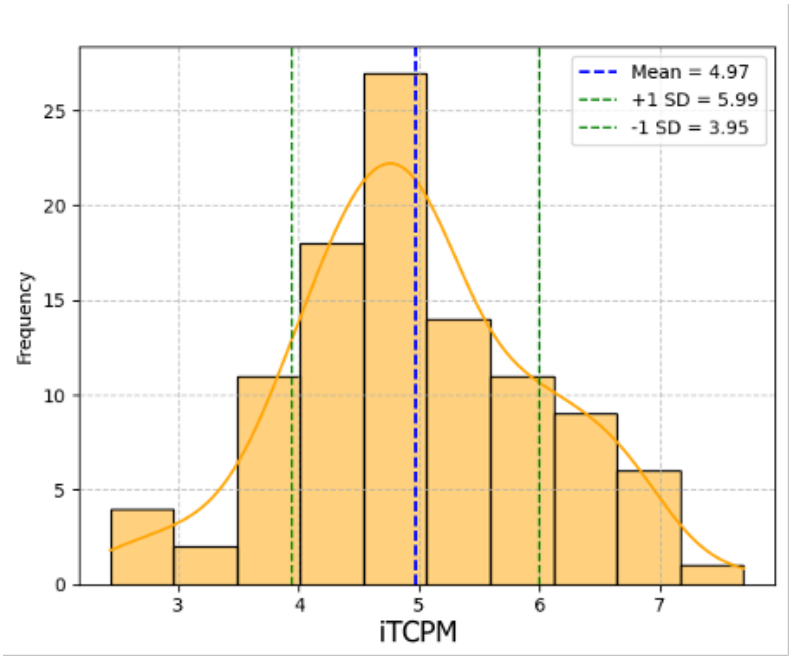

Figure 9. Distribution of the indexed time for contrast to pass through the myocardium (iTCPM) in the study cohort. The diagram includes a histogram displaying the frequency of different iTCPM values and a smoothed density curve (KDE).

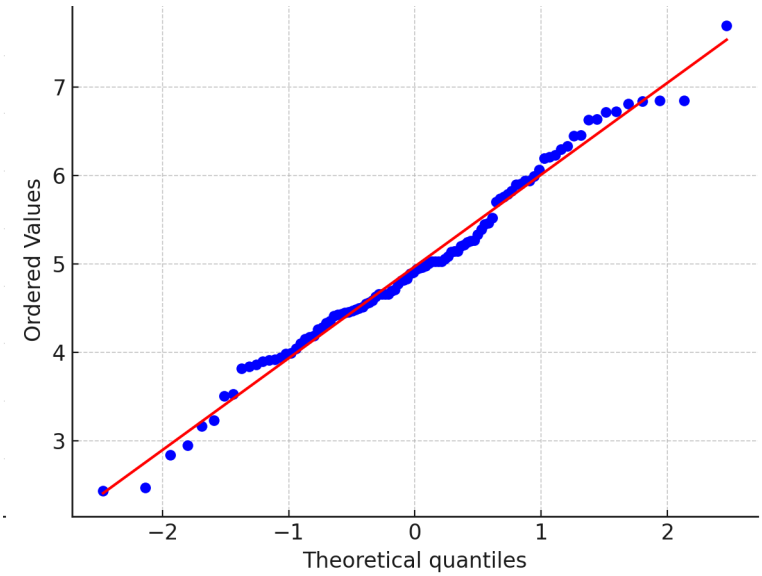

Figure 10. Q–Q plot of the indexed time for contrast to pass through the myocardium (iTCPM). The plot shows empirical data that closely follow the theoretical normal line, with minimal deviations at the extreme values.

2. Indexing using regression coefficients

As an alternative approach for indexing TCPM, a linear multivariable regression was performed, including mean arterial pressure (MAP), heart rate (HR), and myocardial mass (MM) as independent variables. The resulting coefficients showed that higher MAP was associated with a shortening of TCPM (β = −0.0214; p = 0.006), greater myocardial mass was associated with a prolongation of TCPM (β = +0.00526; p = 0.0079), while heart rate demonstrated a negative trend without reaching statistical significance (β = −0.0132; p = 0.206). The intercept of the equation was 6.959 (p < 0.001).

The following formula was used for indexing TCPM:

$$irTCPM = 6{,}959 - 0{,}0214 \times MAP - 0{,}0132 \times HR + 0{,}00526 \times MM + \varepsilon$$

where ε represents the residual component reflecting the portion of TCPM variability not explained by the included variables.

The overall explanatory ability of the model was: $R^2 = 0.149$, adjusted $R^2 = 0.23$, $F(3,98) = 5.74$, $p = 0.0012$. The AIC and BIC values were 302.4 and 312.9, respectively. Diagnostic analysis revealed no issues with multicollinearity (VIF: MAP = 1.04, HR = 1.03, MM = 1.01).

Based on this, an index was defined using the recentered residuals of the model, in which for each patient the difference between observed and predicted TCPM is calculated, and the cohort mean TCPM value is added to the residual. In this way, the regression-indexed TCPM (irTCPM) preserves

the original measurement units while accounting for individual physiological variability and eliminating the influence of MAP, HR, and MM.

For irTCPM, the mean value was 4.96 seconds with a standard deviation of 1.03 seconds. The minimum recorded value was 2.23 seconds, and the maximum was 7.44 seconds. The interquartile range extended from 4.34 seconds (25th percentile) to 5.47 seconds (75th percentile), with a median of 4.81 seconds. The Shapiro–Wilk test for normality yielded a p-value of 0.194 (W = 0.982), indicating no statistically significant deviation from a normal distribution.

For the purposes of the present study, the first method of indexing using relative correlation coefficients was employed.

Correlation analysis between the indexed time for contrast to pass through the myocardium (iTCPM) and the CCS functional class

To evaluate the relationship between the iTCPM and the severity of anginal symptoms, we performed a correlation analysis between iTCPM values and the patients' functional class according to the CCS classification. The analysis included all patients enrolled in the study (n = 102) and was conducted using Spearman's rank correlation coefficient due to the ordinal nature of the CCS variable. The results demonstrated a moderate positive association between iTCPM and CCS class, with a correlation coefficient of $r_s = 0.443$ and a p-value < 0.0001, indicating high statistical significance.

To further refine the analysis, the correlation was recalculated after excluding 13 patients in whom anatomical variations of the coronary circulation were identified (myocardial bridges or coronary–cameral microfistulae), as these anomalies could potentially influence symptom presentation independently of intrinsic coronary microcirculatory function. After excluding these patients, a stronger correlation between iTCPM and CCS class was observed – $r_s = 0.545$ with $p < 0.0001$, indicating a moderate to strong positive association with very high statistical significance (Tables 6 and 7).

Figures 11 and 12 present the box plots depicting the relationship between iTCPM and CCS class before and after exclusion of patients with anatomical variations.

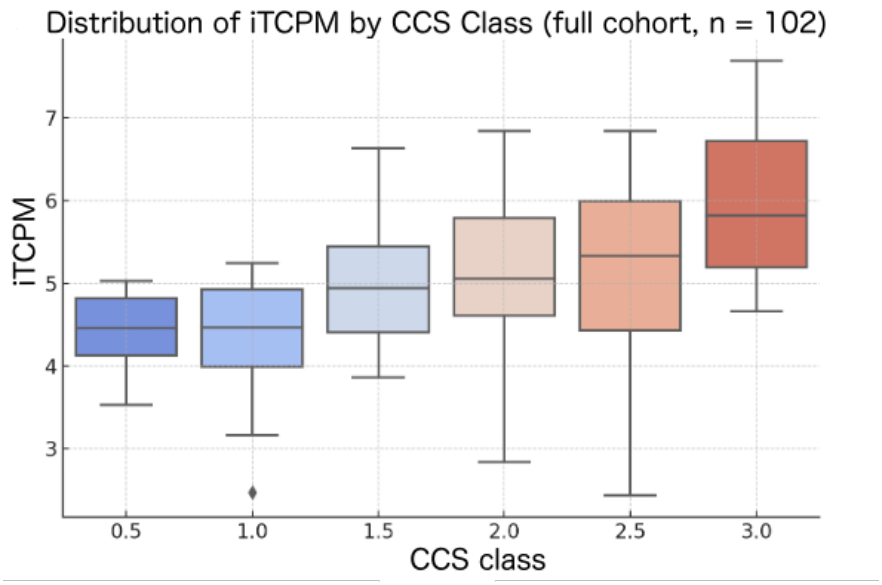

Figure 11. Boxplot showing the distribution of iTCPM across CCS classes in the full study cohort (n = 102).

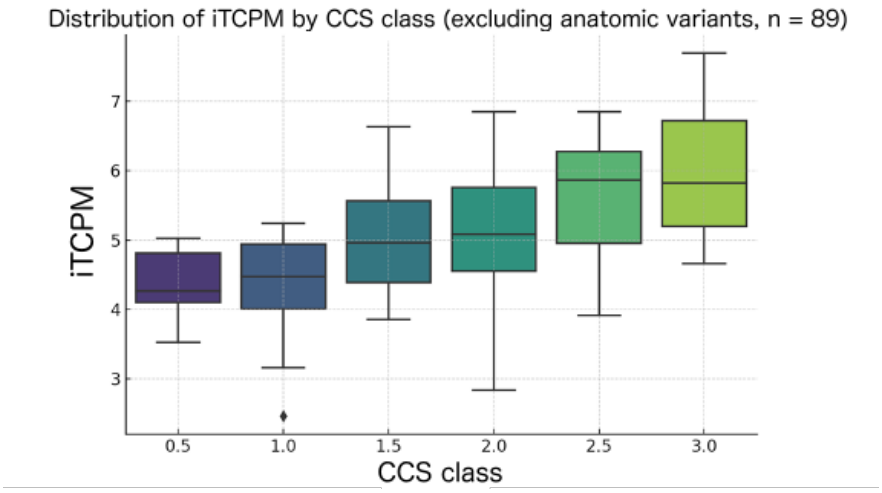

Figure 12. Boxplot showing the distribution of iTCPM across CCS classes after excluding patients with anatomic variants (n = 89).

Table 6. Distribution of the indexed time for contrast to pass through the myocardium (iTCPM) across CCS class categories in the full cohort (n=102).

CCS клас	count	mean	std	min	25%	50%	75%	max
0.5	10.0	4.42	0.51	3.53	4.12	4.46	4.82	5.03
1.0	23.0	4.35	0.71	2.47	3.99	4.47	4.92	5.24
1.5	13.0	5.09	0.9	3.86	4.41	4.94	5.45	6.63
2.0	24.0	5.14	1.05	2.84	4.61	5.06	5.79	6.85
2.5	21.0	5.14	1.14	2.44	4.43	5.33	5.99	6.84
3.0	11.0	5.94	0.95	4.66	5.2	5.82	6.72	7.69

Table 7. Distribution of the indexed time for contrast to pass through the myocardium (iTCPM) across CCS class categories after exclusion of patients with anatomic variants (n=89).

CCS клас	count	mean	std	min	25%	50%	75%	max
0.5	9.0	4.36	0.5	3.53	4.1	4.26	4.81	5.03
1.0	22.0	4.4	0.68	2.47	4.0	4.48	4.94	5.24
1.5	12.0	5.1	0.93	3.86	4.39	4.96	5.56	6.63
2.0	21.0	5.09	1.08	2.84	4.55	5.08	5.76	6.85
2.5	14.0	5.59	0.88	3.92	4.95	5.87	6.27	6.84
3.0	11.0	5.94	0.95	4.66	5.2	5.82	6.72	7.69

Correlation between the indexed time for contrast to pass through the myocardium (iTCPM) and the Seattle angina questionnaire (SAQ)

A correlation analysis using Spearman's coefficient was performed to assess the relationship between iTCPM and the five subcategories of the Seattle Angina Questionnaire (SAQ). The analysis was conducted both for the full sample (n = 102) and after excluding 13 patients with identified anatomical variations (myocardial bridge or microfistulae).

In the complete dataset, a statistically significant moderate negative correlation was found between iTCPM and the "Physical Limitation" category ($r_s = –0.317$, $p = 0.001$), as well as a moderate negative correlation with "Angina Frequency" ($r_s = –0.460$, $p < 0.00001$). In addition, the "Disease Perception" category showed a weak but statistically significant negative association ($r_s = –0.206$, $p = 0.038$). No statistically significant correlation was observed for the remaining two categories: "Angina Stability" ($r_s = –0.135$, $p = 0.176$) and "Treatment Satisfaction" ($r_s = +0.163$, $p = 0.102$).

After excluding the 13 patients with anatomical variations, the strength of the correlation between iTCPM and the SAQ categories increased. The strongest negative correlation remained with "Angina Frequency" ($r_s = –0.533$, $p < 0.00001$), followed by "Physical Limitation" ($r_s = –0.378$, $p = 0.0003$) and "Disease Perception" ($r_s = –0.289$, $p = 0.006$). Once again, no statistically significant relationship was observed with "Angina Stability" ($r_s = –0.175$, $p = 0.101$) or "Treatment Satisfaction" ($r_s = +0.099$, $p = 0.357$).

The correlation values are presented in Tables 8 and 9. Figure 13 displays combined scatter plots with regression lines illustrating the relationship between iTCPM and each of the five SAQ scales.

Table 8. Correlation coefficients between the indexed time for contrast to pass through the myocardium (iTCPM) and the categories of the Seattle Angina Questionnaire (SAQ) in the full cohort (n=102)

SAQ categories	Spearman coefficient (rs)	p-value
Physical limitation	-0.317	0.00116
Angina stability	-0.135	0.17562
Angina frequency	-0.46	<0.00001
Treatment satisfaction	0.163	0.10181
Disease perception	-0.206	0.03826

Table 9. Correlation coefficients between the indexed time for contrast to pass through the myocardium (iTCPM) and the categories of the Seattle Angina Questionnaire (SAQ) after exclusion of patients with anatomic variants (n=89)

SAQ categories	Spearman coefficient (rs)	p-value
Physical limitation	-0.378	0.00026
Angina stability	-0.175	0.10105
Angina frequency	-0.533	<0.00001
Treatment satisfaction	0.099	0.35727
Disease perception	-0.289	0.00605

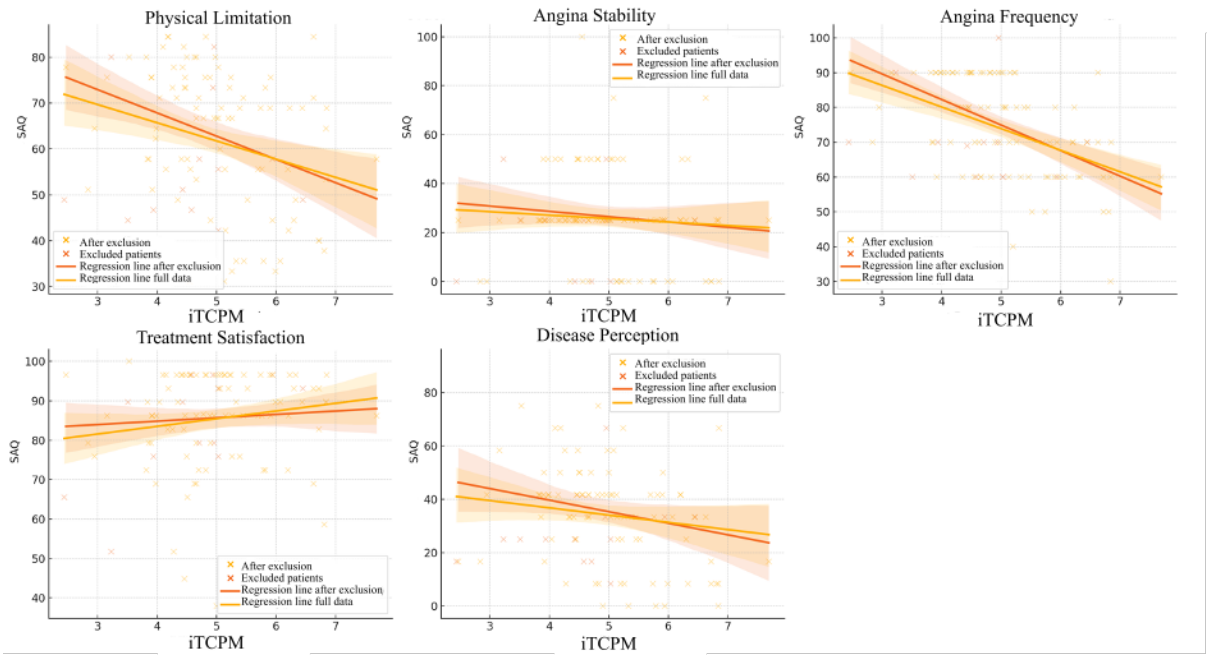

Figure 13. Combined scatter plots with regression lines illustrating the relationship between iTCPM and each of the five SAQ subscales, before and after exclusion of patients with anatomical variants (n = 13). The yellow line represents the regression model for the full cohort (n = 102), while the orange line represents the model after filtering. Strengthening of the negative association is observed for the subcategories "Physical Limitation", "Angina Frequency" and "Disease Perception" corresponding to higher Spearman correlation coefficients. For the subscales "Angina Stability" and

“Treatment Satisfaction,” the regression lines remain nearly identical, confirming the absence of a statistically significant correlation.

Group analysis of the results

The patients were categorized into two groups, "fast" and "slow," based on the mean iTCPM value. The mean iTCPM for the entire study population was 4.97 seconds.

The "fast group" (iTCPM ≤ 4.97 s) included 54 patients, with a mean iTCPM of 4.21 s, a standard deviation of 0.62 s, a minimum value of 2.44 s, and a maximum of 4.96 s.

The "slow group" (iTCPM > 4.97 s) comprised 48 patients, with a mean iTCPM of 5.82 s, a standard deviation of 0.67 s, a minimum value of 4.98 s, and a maximum of 7.69 s.

Comparative Analysis of CCS Class Between Groups

To assess the relationship between iTCPM and the severity of anginal symptoms, a comparative intergroup analysis of the CCS functional class was performed between the two groups of patients divided according to the mean iTCPM value. Patients with iTCPM ≤ 4.97 s constituted the "fast" group, while those with iTCPM > 4.97 s formed the "slow" group.

Results of the Mann–Whitney U test demonstrated a statistically significant difference in the distribution of CCS class between the two groups ($U = 712.5$; $p < 0.0001$). The mean CCS class in the "fast" group was 1.48, whereas in the "slow" group it reached 2.10.

An illustration of the results from the intergroup comparative analysis of CCS class between patients with lower and higher iTCPM values is presented in Figure 14.

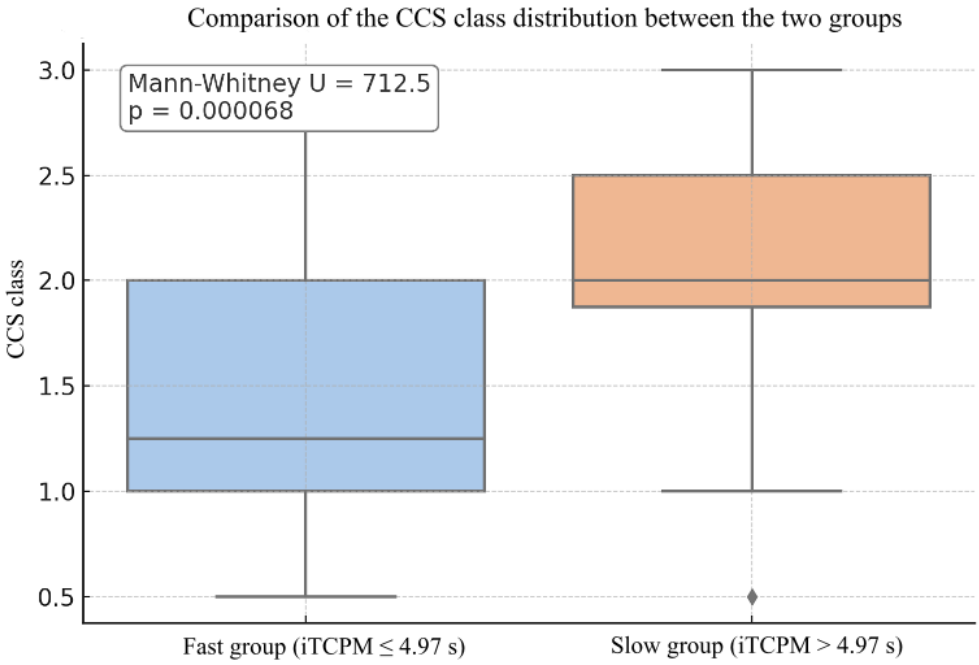

Figure 14. Boxplot diagram illustrating the distribution of CCS class in the two groups.

Comparative analysis of Seattle Angina Questionnaire (SAQ) results between groups

Anginal symptoms were assessed using the five subcategories of the Seattle Angina Questionnaire (SAQ): physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception. For each subcategory, the mean and standard deviation were calculated for both groups, and a comparative analysis between the two groups was performed using the Mann–Whitney U test.

Patients in the fast group demonstrated better functional capacity, with a mean physical limitation score of 66.42 ± 13.77, compared to 56.71 ± 14.97 in the slow group. The difference between groups was statistically significant (U = 1795.5, p = 0.00081).

Regarding angina stability, the mean score in the fast group was 28.70 ± 18.43, while in the slow group it was 22.40 ± 19.46. Although the slow group showed lower values, the difference did not reach statistical significance (U = 1547.0, p = 0.06165), though a trend toward less stable symptoms was observed in patients with slower myocardial contrast transit.

The “angina frequency” subcategory showed the most pronounced difference between groups. The mean score in the fast group was 79.80 ± 11.75, compared to 67.71 ± 13.56 in the slow group. The difference was highly statistically significant (U = 1919.0, p = 0.00002).

Patients in the slow group reported higher treatment satisfaction (87.65 ± 11.58) compared to those in the fast group (83.40 ± 12.64). The difference approached statistical significance (U = 1013.5, p = 0.05521).

Patients in the slow group also demonstrated a lower score for disease perception (30.73 ± 20.85) compared with the fast group (37.19 ± 17.11), suggesting a poorer subjective perception of their health status. The difference was statistically significant (U = 1587.5, p = 0.04826).

The results of the comparative analysis of the five SAQ subcategories between the "fast" and "slow" groups are presented in Tables 10 and 11. Figure 15 graphically depicts the SAQ questionnaire results for both groups using boxplot diagrams.

Distribution of electrocardiographic changes between groups

To examine the relationship between the myocardial contrast transit velocity and electrocardiographic findings, a comparative intergroup analysis was performed. No statistically significant difference was found in the frequency of pathological ECG changes between the two groups ($\chi^2 = 0.65$; $p = 0.421$).

Table 10. Mean values and standard deviation of the five Seattle Angina Questionnaire categories in the "slow" and "fast" group.

SAQ scale	Slow group (mean ± SD)	Fast group (mean ± SD)
Physical limitation	56.71 ± 14.97	66.42 ± 13.77
Angina stability	22.40 ± 19.46	28.70 ± 18.43
Angina frequency	67.71 ± 13.56	79.80 ± 11.75
Treatment satisfaction	87.65 ± 11.58	83.40 ± 12.64
Disease perception	30.73 ± 20.85	37.19 ± 17.11

Table 11. Results of the Mann–Whitney U test assessing the statistical differences between the two groups for each subcategory.

SAQ scale	U-value	p-value
Physical limitation	1795.5	0.00081
Angina stability	1547.0	0.06165
Angina frequency	1919.0	0.00002
Treatment satisfaction	1013.5	0.05521
Disease perception	1587.5	0.04826

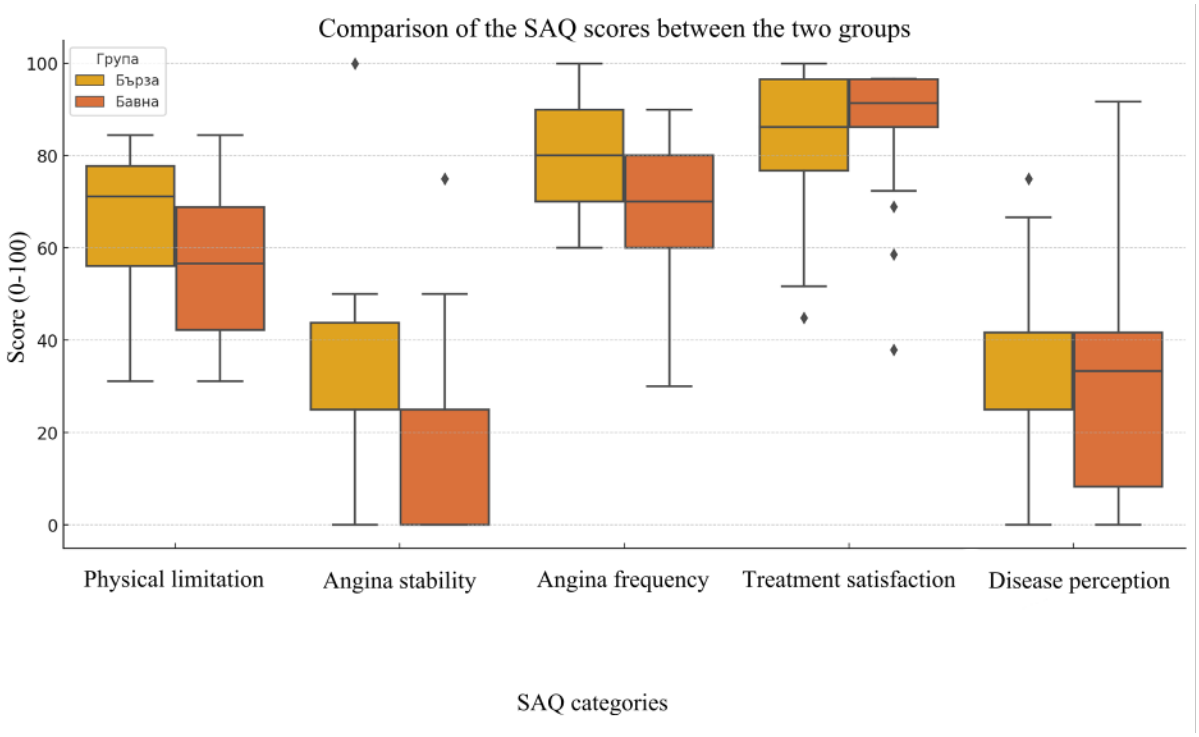

Figure 15. Boxplot diagram illustrating each of the five subcategories compared between the "fast" and "slow" groups according to iTCPM value (iTCPM < 4.97 s and > 4.97 s).

Regression analysis for the evaluation of risk factors and anatomical variations influencing the indexed time for contrast to pass through the myocardium (iTCPM)

To assess the influence of classical cardiovascular risk factors and anatomical variants on iTCPM values, a multivariable linear regression analysis was performed. The dependent variable was the iTCPM value (in seconds). The following factors were included as independent predictors: age, female sex, body mass index (BMI), estimated glomerular filtration rate by the CKD-EPI formula (eGFR), presence of arterial hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol consumption, and three observed anatomical features – myocardial bridge of the LAD, coronary–cameral microfistulae, and coronary ectasia.

Categorical variables were coded as binary: value 1 indicating the presence of the characteristic and 0 indicating its absence. Initially, a full model including all predictors was constructed. A backward stepwise regression method was applied, in which variables with $p > 0.05$ were sequentially excluded from the model. In the final model, only one variable remained – the presence of coronary–cameral microfistulae with a coefficient of –0.57 and $p = 0.0951$. Although this variable did not reach statistical significance, a trend toward association with lower iTCPM values was observed. Tables 12 and 13 present the results of the full multivariable linear regression analysis

and the final reduced model obtained after backward elimination, respectively. Figure 16 visualizes the regression coefficients with 95% confidence intervals from the full model.

The explanatory power of the model, evaluated using the coefficient of determination, showed $R^2 = 0.028$ and adjusted $R^2 = 0.018$, indicating that only 2.8% of the variation in iTCPM could be explained by the variables included in the model. This highlights the limited predictive value of classical risk factors and anatomical features regarding myocardial contrast dynamics.

Graphical assessment of residuals versus predicted values (Figure 17) revealed no systematic deviations but confirmed the limited explanatory capacity of the model. The Q–Q plot of the residuals (Figure 18) demonstrated an approximately normal distribution with minor deviations at the extremes (tails). The calculated Variance Inflation Factor (VIF) values for all independent variables were below 2, indicating no significant multicollinearity in the model (Table 14).

In summary, the results of the linear regression analysis did not identify any statistically significant independent predictors of iTCPM values.

Table 12. Results of the multivariable linear regression analysis identifying the relationship between classical cardiovascular risk factors and anatomical variations of the coronary circulation with iTCPM.

Variable	Coefficient	Std. error	t-value	p-value	Lower 95%	Upper 95%
const	6.1387	1.522	4.0332	0.0001	3.114	9.1635
Age	0.0071	0.0136	0.521	0.6036	-0.0199	0.034
Female	0.0093	0.286	0.0326	0.9741	-0.5591	0.5777
BMI	-0.0087	0.0181	-0.4779	0.6339	-0.0447	0.0273
eGFR CKD EPI	-0.0113	0.0082	-1.3872	0.1689	-0.0275	0.0049
Alchohol	-0.0619	0.3122	-0.1985	0.8431	-0.6823	0.5584
Smoking	-0.0384	0.2449	-0.1568	0.8758	-0.525	0.4483
LDL	0.0341	0.1056	0.3227	0.7477	-0.1758	0.2439
Dyslipidemia	-1.0279	0.5062	-2.0306	0.0453	-2.0339	-0.0219
Hypertension	0.6902	0.5812	1.1875	0.2382	-0.4648	1.8451
Diabetes	-0.1443	0.2829	-0.5101	0.6112	-0.7066	0.4179
LAD Bridge	-0.032	0.6117	-0.0523	0.9584	-1.2475	1.1836
Coronary-cameral mcrofistulae	-0.9071	0.3971	-2.2843	0.0248	-1.6962	-0.1179
Coronary ectasia	0.6961	0.5671	1.2274	0.2229	-0.4309	1.823

Table 13. Final regression model after stepwise backwards elimination.

Variable	Coefficient	Std. error	t-value	p-value	Lower 95%	Upper 95%
const	5.0266	0.1064	47.2418	0.0	4.8155	5.2377
Coronary-cameral mcrofistulae	-0.5725	0.3398	-1.6848	0.0951	-1.2467	0.1017

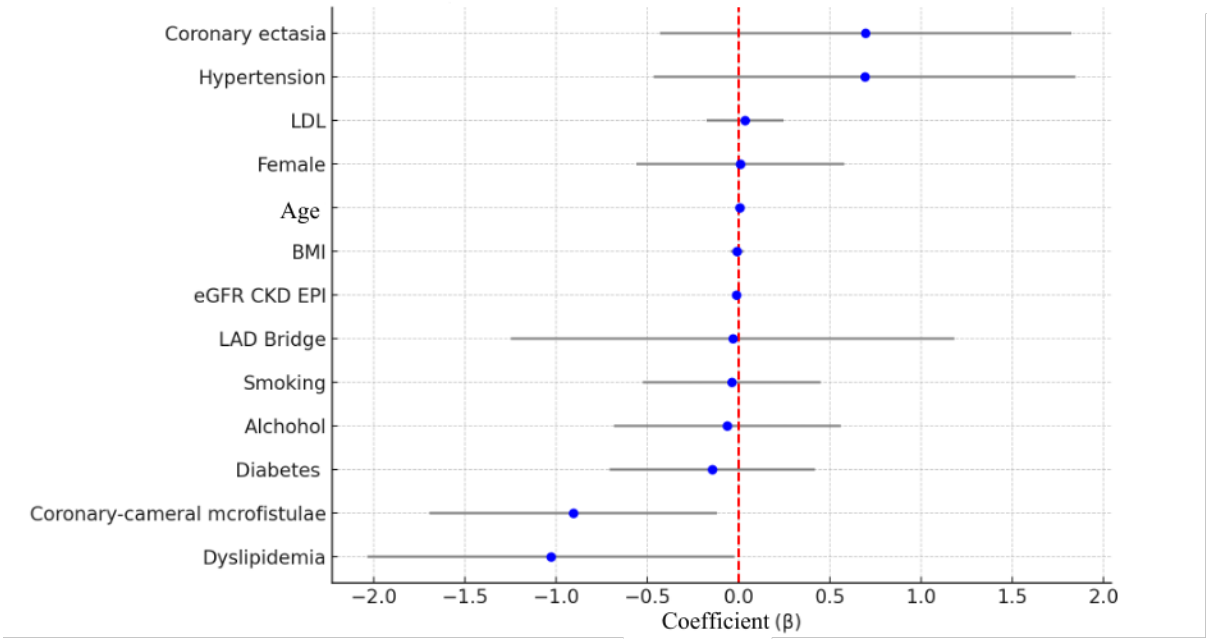

Figure 16. Visualization of regression coefficients (β) with 95% confidence intervals for all independent variables included in the full multivariable model.

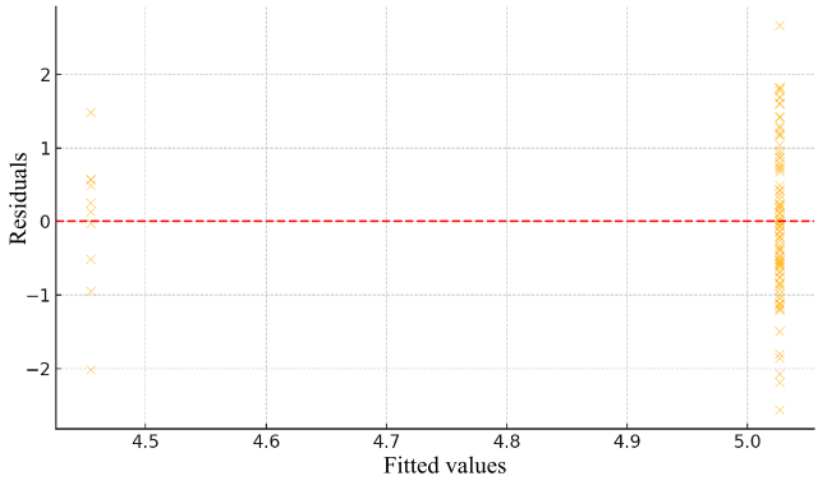

Figure 17. Residuals vs. fitted values plot from the linear regression model. The residuals are randomly distributed around the zero line without a discernible pattern but with low variation in the fitted values, which is consistent with the low R^2 value.

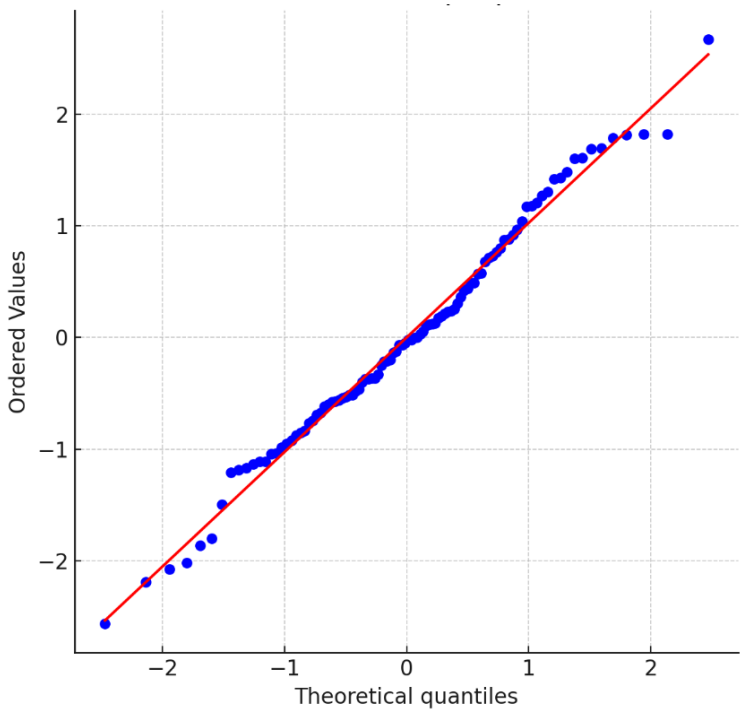

Figure 18. Q–Q plot of the residuals from the linear regression model. The residuals closely follow the theoretical normal line in the central portion, with moderate deviations observed at the extreme values.

Table 14. Values of the Variance Inflation Factor (VIF) for the independent variables in the regression model.

Variable	VIF
const	224.23
Age	1.73
Female	1.92
BMI	1.27
eGFR CKD EPI	1.4
Alchohol	2.13
Smoking	1.42
LDL	1.35
Dyslipidemia	1.37
Hypertension	1.81
Diabetes	1.39
LAD Bridge	1.36
Coronary-cameral mcrofistulae	1.35
Coronary ectasia	1.17

Group analysis of risk factors and anatomical variants among patients categorized by iTCPM

Patients were categorized into two groups based on the mean iTCPM value (4.97 s): a "fast group" (iTCPM < 4.97 s) and a "slow group" (iTCPM ≥ 4.97 s). To assess potential differences in classical cardiovascular risk factors and anatomical characteristics of the coronary circulation between the two groups, a comparative analysis was performed. Both categorical and continuous variables were examined.

Categorical variables

The following variables were analyzed: sex (female), arterial hypertension, diabetes mellitus, dyslipidemia, smoking, alcohol consumption, and the presence of anatomical variants such as myocardial bridge of the LAD, vascular tortuosity, coronary–cameral microfistulae, and coronary ectasia. Frequencies and percentages were calculated for each variable in both groups. Statistical significance was assessed using the χ^2 test, and Fisher's exact test was applied when expected frequencies were small.

The results revealed no statistically significant differences between the groups for any of the analyzed categorical variables (all $p > 0.2$). For instance, the prevalence of arterial hypertension in the "slow" group was 95.8%, compared to 92.6% in the "fast" group ($p = 0.785$). Smoking was present in 56.2% of patients in the "slow" group and 57.4% in the "fast" group ($p = 1.000$), clearly indicating a lack of association between iTCPM and these factors. Regarding sex, the proportion of women was 64.6% in the "slow" group and 53.7% in the "fast" group ($p = 0.361$), which did not reach statistical significance. Diabetes mellitus was observed in 25.9% of patients in the "slow" group and 20.8% in the "fast" group ($p = 0.710$), while dyslipidemia was present in 96.3% and 91.7%, respectively ($p = 0.569$), also without significant differences. Vascular tortuosity was detected in 14.6% of patients in the "slow" group and 9.3% in the "fast" group ($p = 0.449$).

The results of the comparative analysis of categorical variables are presented in Table 15, and a graphical summary of these categorical variables is shown in Figure 19.

Continuous variables

The following continuous variables were compared: age, body mass index (BMI), eGFR by CKD-EPI, and LDL cholesterol. The comparison between groups was performed using the Mann–Whitney U test.

The mean age in the "slow" group was higher (63.3 ± 8.9 years) compared with the "fast" group (59.8 ± 10.6 years), with a p-value of 0.0828 – borderline but not statistically significant. No substantial differences were observed between the two groups with respect to BMI, eGFR, or LDL cholesterol. The U statistics and p-values for each variable are presented in an additional table and visualized through boxplot diagrams (Table 16 and Figure 20).

Table 15. Results of the comparative analysis of categorical variables between the "fast" and "slow" patient groups, defined according to the mean iTCPM value (4.97 s). Absolute counts, relative proportions (%), results of the χ^2 test for independence (blank fields indicate use of Fisher's exact test), and p-values are presented.

Variable	n=48 (Slow)	n=54 (Fast)	Percent (Slow)	Percent (Fast)	χ^2 -value	p-value
Female	31	29	64.6	53.7	0.8333	0.3613
Hypertension	46	50	95.8	92.6		0.6814
Diabetes	10	14	20.8	25.9	0.1379	0.7104
Dyslipidemia	44	52	91.7	96.3		0.4165
Smoking	27	31	56.2	57.4	0.0	1.0
Alchohol	15	20	31.2	37.0	0.1645	0.6851
LAD Bridge	1	3	2.1	5.6		0.6202
Coronary-cameral mcrofistulae	3	7	6.2	13		0.328
Coronary ectasia	3	1	6.2	1.9		0.34
Vessel tortuosity	11	10	22.9	18.5	0.0918	0.7619

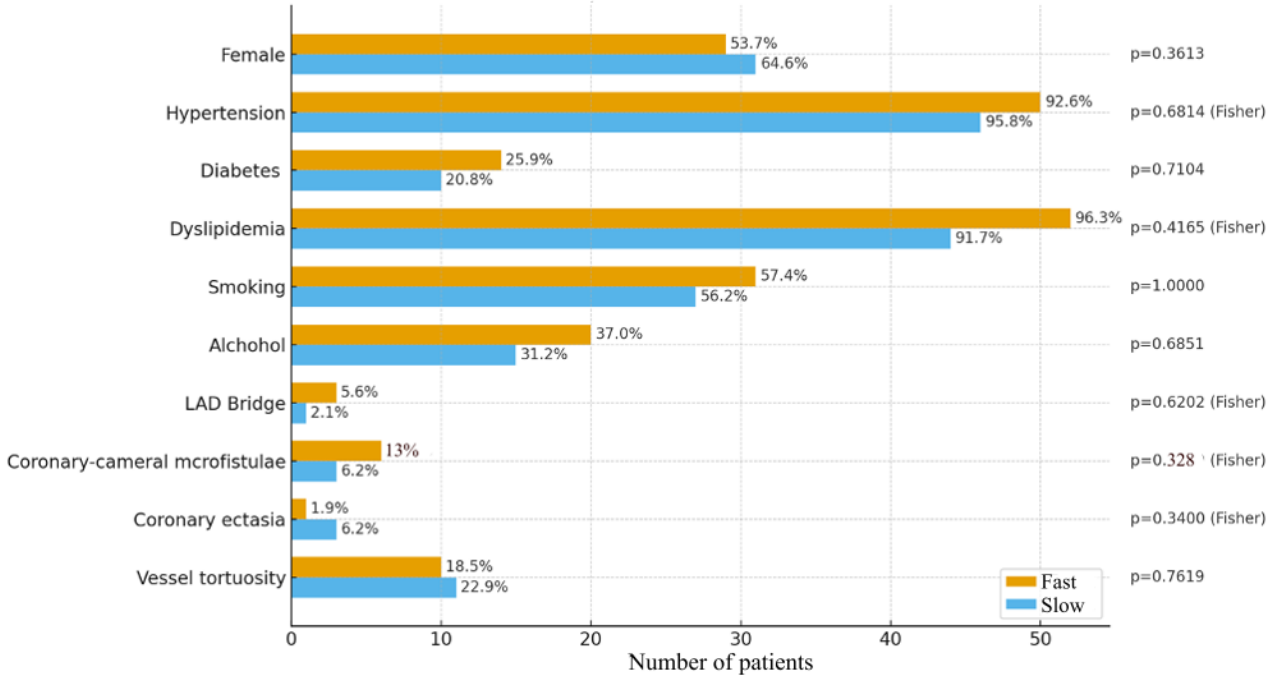

Figure 19. Graphical comparison of the frequency of categorical variables between the "fast" and "slow" groups. The number and percentage of patients for each group are shown, along with p-values from the χ^2 test or Fisher's exact test.

Table 16. Results of the comparative analysis of continuous variables between the "fast" and "slow" patient groups, defined according to the mean iTCPM value (4.97 s). Absolute values, standard deviations, and U statistics are presented.

Variable	Mean value (Fast)	Mean value (slow)	Std. deviation (Fast)	Std. deviation (Slow)	U-statistic	p-value(Mann-Whitney)
Age	59.81	63.33	10.57	8.89	1037	0.0828
BMI	30.80	30.23	6.76	5.91	1336	0.7911
eGFR CKD EPI	88.35	84.46	14.66	14.84	1473	0.2352
LDL	2.83	2.68	1.10	1.16	1416	0.4230

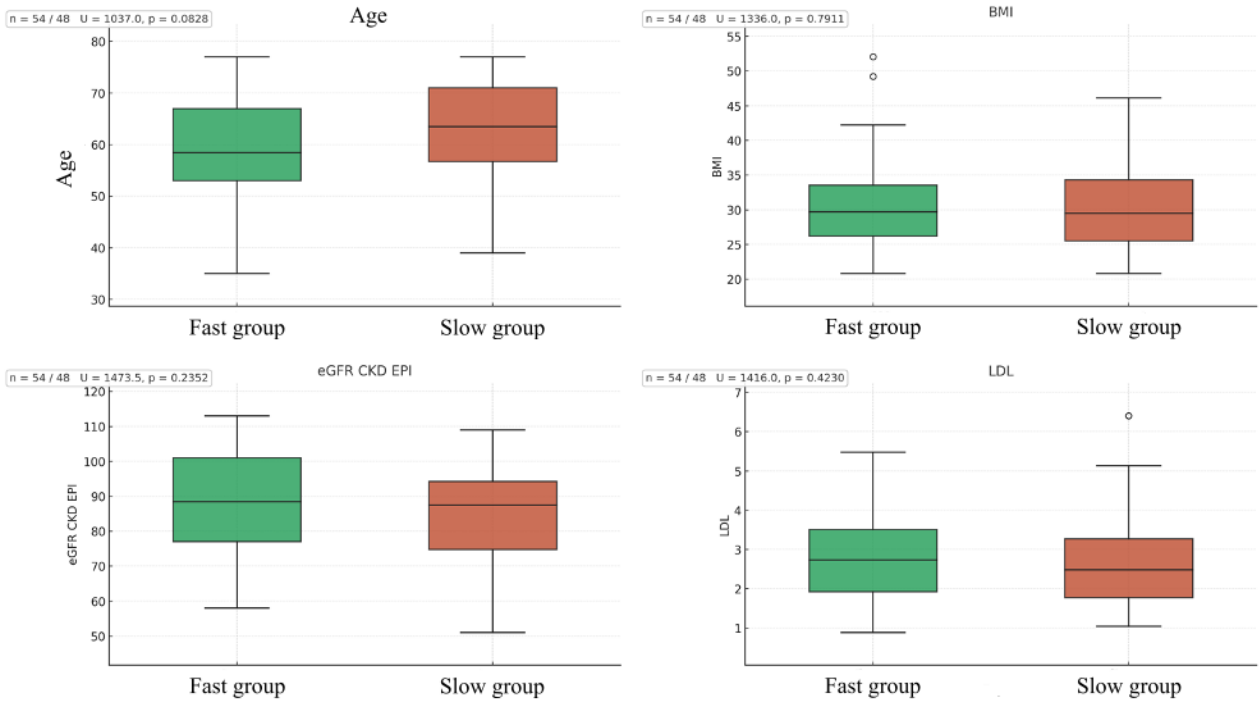

Figure 20. Boxplot diagram comparing the distribution of continuous variables between the two groups. A visual trend toward higher age is observed in the slow group, with no substantial differences in the other parameters.

Analysis of the used pharmacological therapy

In the studied population, the most commonly used antianginal medications were β-blockers (59.8%), followed by calcium channel blockers (44.1%). Regarding concomitant cardiovascular therapy, the highest prevalence was observed for ACE inhibitors/ARBs, used by 70.6% of patients, and statins, taken by 58.8%. Acetylsalicylic acid (ASA) was used by 22.5% of patients, and trimetazidine by 20.6%. Nitrate use was documented in 16.7% of participants, while clopidogrel was taken by 7.8%. None of the patients were receiving ranolazine at the time of study inclusion.

With respect to the number of concomitant medications, 8.8% of participants were not receiving any pharmacological therapy, while 15.7% were on monotherapy. Dual and triple therapy were recorded in 14.7% and 16.7% of patients, respectively, and quadruple therapy in 21.6%. The total number of participants taking five or more medications was 22.6%, reflecting a substantial therapeutic burden among part of the cohort.

Detailed information on the frequency of prescribed medications and combined regimens is presented in Tables 17 and 18 and illustrated in Figure 21.

Table 17. Distribution of patients according to the type of medication use.

Medication	Number of patients	Percent (%)
ASA	23	22.5
Clopidogrel	8	7.8
Trimetazidine	21	20.6
Statin	60	58.8
Beta-blocker	61	59.8
CCB	45	44.1
ACEi/ARB	72	70.6
Nitrate	17	16.7
Ranolazine	0	0.0

Table 18. Distribution of patients according to the number of prescribed medications.

Category	Number of patients	Percent (%)
0 medications	9	8.8
Monotherapy	16	15.7
Dual therapy	15	14.7
Triple therapy	17	16.7
Quadruple therapy	22	21.6
5 medications	16	15.7
6 medications	7	6.9

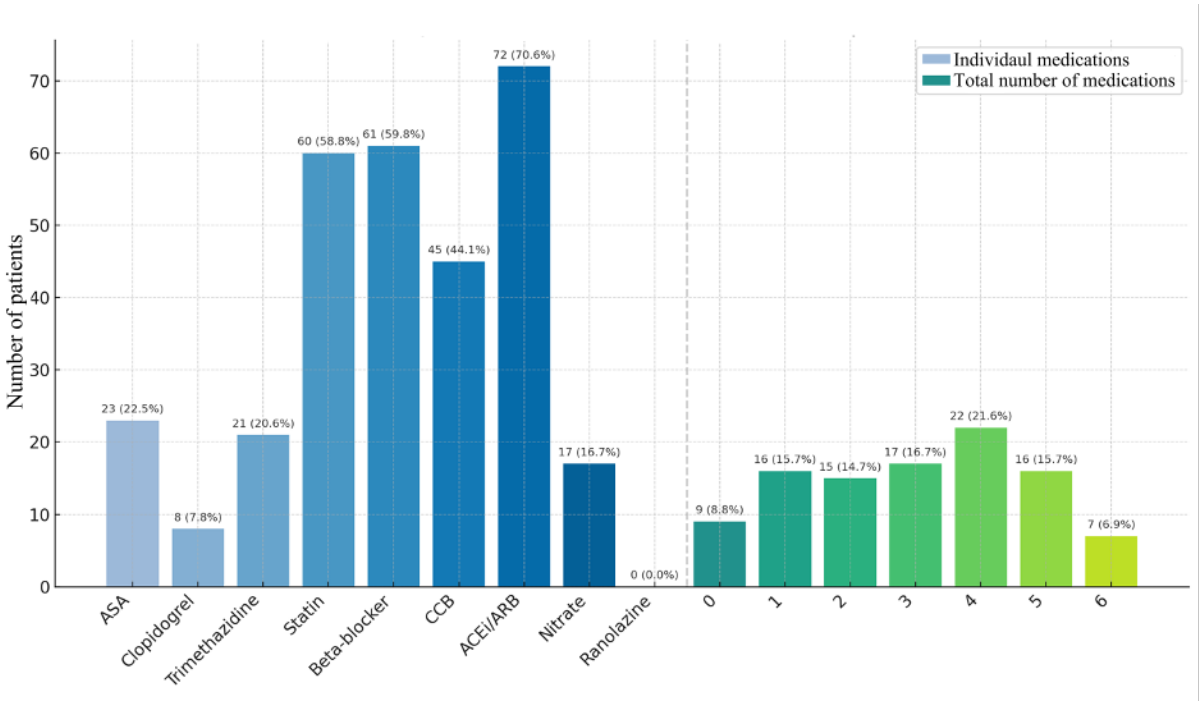

Figure 21. Frequency of administered medications and distribution of patients according to the number of prescribed therapies. The diagram illustrates both the number of patients taking each individual medication (in light blue) and the distribution by the number of medications used (in green).

Relationship between the number of administered medications and CCS functional class

To evaluate whether the severity of anginal symptoms, as measured by the CCS classification, was associated with more intensive pharmacological therapy, an analysis of the number of administered medications was performed across CCS class subgroups. The mean number of medications ranged from 2.20 in patients with CCS 0–I to 3.43 in those with CCS II–III, showing a slight trend toward a higher number of medications with increasing CCS class (Table 19).

To assess the statistical significance of this relationship, the Kruskal–Wallis H test was applied. The analysis did not reveal a statistically significant difference: $H = 5.786$, $p = 0.3276$.

These findings suggest that, in the present cohort, no strong association was observed between the degree of anginal symptom severity and the number of prescribed medications.

Table 19. Distribution of the number of medications used between the CCS class categories.

CCS class	Number of patients	Mean number of medications used	Standard deviation
0-I	10	2.2	1.87
I	23	2.78	1.98
I-II	13	3.08	1.5
II	24	3.42	1.53
II-III	21	3.43	1.69
III	11	2.45	1.86

Multivariable linear regression analysis of the effect of pharmacological therapy and the number of medications used on iTCPM

To investigate whether the type or number of administered medications influenced iTCPM, a multivariable linear regression analysis was performed. The dependent variable was iTCPM, while the independent variables included all major classes of medications used in patient treatment (acetylsalicylic acid – ASA, clopidogrel, trimetazidine, statin, beta-blocker, calcium channel blocker, ACE inhibitor/ARB), as well as the total number of administered medications.

Medications were entered into the model as binary variables (1 = taking, 0 = not taking), and the "number of medications" variable was included as a continuous quantitative variable. Patients taking ranolazine were excluded from the analysis due to lack of variation (0 patients taking the drug).

The results showed that none of the included medications, nor the total number of medications, demonstrated a statistically significant association with iTCPM, with all p-values exceeding 0.05 (Table 20).

The overall explanatory power of the model was low: $R^2 = 0.034$, adjusted $R^2 = –0.049$, confirming that the model did not improve predictive capability compared to a baseline model without predictors.

The visual representation of the model through a plot of regression coefficients with 95% confidence intervals likewise demonstrated the absence of a significant effect (Figure 22).

Table 20. Results of the multivariable linear regression analysis of the effect of the type of medication used and the number of medications on iTCPM.

	Coef.	Std.Err.	t	P>|t|	[0.025	0.975]
const	5.0506	0.2224	22.7118	0.0	4.609	5.4922
ASA	-0.0849	0.2691	-0.3157	0.753	-0.6193	0.4494
Clopidogrel	0.0949	0.3666	0.2589	0.7963	-0.6332	0.823
Trimetazidine	-0.3597	0.2592	-1.3878	0.1685	-0.8743	0.155
Statin	-0.0156	0.2754	-0.0566	0.955	-0.5624	0.5313
Beta-blocker	0.1632	0.2415	0.6757	0.5009	-0.3164	0.6428
CCB	-0.0796	0.2177	-0.3658	0.7154	-0.5119	0.3526
ACEi/ARB	0.0706	0.2656	0.266	0.7908	-0.4568	0.598
Nitrate	0.1694	0.2853	0.5935	0.5543	-0.3973	0.736
Number of medications	-0.0417	0.0695	-0.5996	0.5502	-0.1798	0.0964

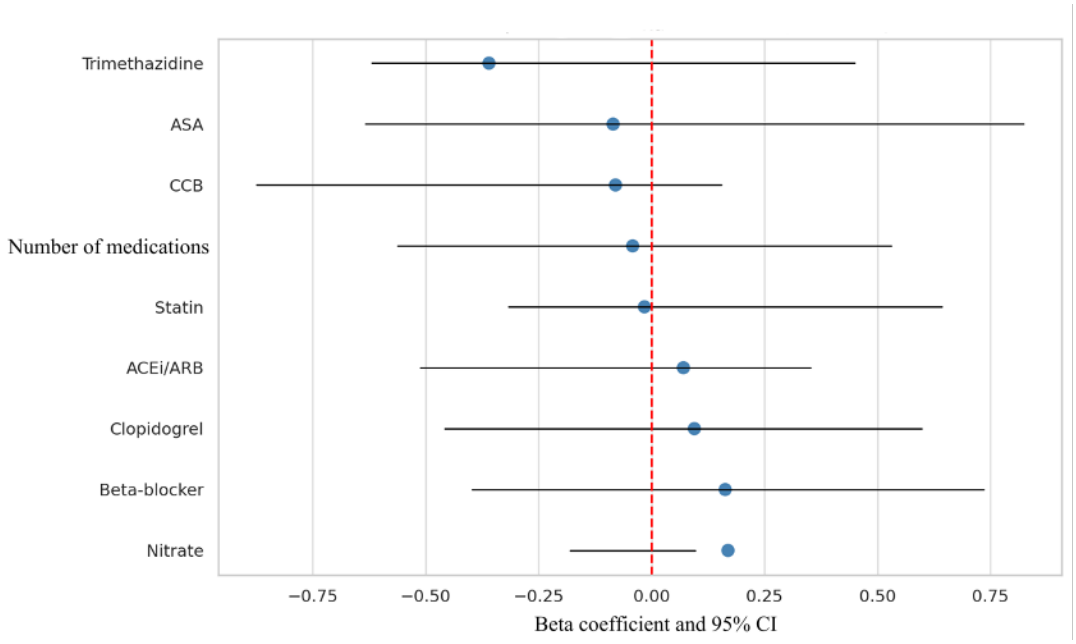

Figure 22. Visualization of regression coefficients (β) with 95% confidence intervals for each medication and for the total number of medications.

V. DISCUSSION

The present study introduces a novel approach for evaluating coronary microcirculation in patients with angina and no significant epicardial coronary artery disease, through the use of the indexed time for contrast to pass through the myocardium (iTCPM). The method is quick and technically simple to perform during routine coronary angiography, is not associated with additional risk to the patient, and does not incur extra procedural cost. The principal findings highlight a clear relationship between prolonged myocardial contrast transit time and the severity of anginal symptoms, as assessed by both the Canadian Cardiovascular Society (CCS) functional class and the Seattle Angina Questionnaire (SAQ).

Technical aspects and indexing methods

In this study, we applied an innovative and standardized angiographic approach to evaluate myocardial contrast dynamics by measuring the time for contrast to pass through the myocardium (TCPM), followed by indexing (iTCPM) that accounts for three key physiological determinants of perfusion – mean arterial pressure (MAP), heart rate (HR), and myocardial mass (MM). Two principal approaches to indexing were considered:

Indexing by relative correlation weights

When indexing the TCPM, we considered that a larger myocardial mass would be expected to result in a longer contrast transit time through the myocardium, whereas higher mean arterial pressure (MAP) and heart rate (HR) would be expected to accelerate the passage of contrast through the microcirculation. Therefore, we normalized the transit time by dividing it by myocardial mass and multiplying by MAP and HR. To isolate the influence of each variable, a correlation analysis was performed between TCPM and each of the three physiological parameters. The results showed a weak positive correlation between myocardial mass and TCPM, a weak negative correlation between mean arterial pressure and TCPM, and a weak but statistically non-significant negative relationship between heart rate and TCPM. Although heart rate did not reach statistical significance, it was included in the indexing equation for physiological completeness.

To isolate the contribution of each parameter to the observed TCPM, we implemented a two-step approach. First, we accounted for the deviation of each parameter from its cohort mean by dividing the individual value by the average cohort value and adjusting the time according to this ratio. Second, recognizing that each parameter exerts a different degree of influence on TCPM, we

raised each to a power equal to its relative correlation coefficient with TCPM, thus weighting its effect according to its observed strength of association.

Indexing by multivariable linear regression

As an alternative approach, a regression model was constructed with TCPM as the dependent variable and MAP, HR, and MM as independent variables. The resulting equation enabled the calculation of a predicted TCPM value and the derivation of an indexed value through the residuals (re-centered relative to the cohort mean).

Although the regression model is statistically more rigorous, it is highly model-dependent and requires re-analysis when applied to different cohorts. Regression-derived data tend to be less stable in smaller samples and more difficult to generalize. In contrast, the method based on relative correlation weights is conceptually simpler, easily reproducible, and more broadly applicable beyond the studied cohort, making it more suitable for clinical use and for comparisons across populations. Given the identical directions of association, the nearly identical distributions (mean values of 4.97 vs. 4.96 s), and the normality observed with both methods, the regression analysis effectively serves to validate the use of the first formula.

For these reasons, the method of indexing using relative correlation coefficients was chosen as the primary approach in the present study.

Comparison with established fluoroscopic methods

Unlike previously published studies that have employed various fluoroscopic techniques to assess microcirculation using manual contrast injection with a syringe, a method inherently associated with significant variability in applied force, volume, and injection rate, we utilized an automated injection system (Acist CVi) with precisely defined parameters: contrast volume of 6 mL, injection rate of 2 mL/s, and rise time (time to peak flow rate) of 0.5 s. This eliminated the heterogeneity arising from operator-dependent manual injection variability and the associated measurement inconsistencies, thereby ensuring a higher degree of standardization and reproducibility compared with earlier techniques.

The TIMI flow grade and corrected TIMI frame count are well-established fluoroscopic methods for evaluating epicardial coronary blood flow following reperfusion in patients with myocardial infarction and have been shown to correlate with patient prognosis. However, these parameters depend on the condition of the microvascular network and therefore can only indirectly reflect microcirculatory function (Cannon et al. 1998; Chesebro et al. 1987). The Myocardial Blush

Grade (MBG) and TIMI Myocardial Perfusion Grade (TMPG) are visual scales for assessing myocardial contrast opacification following reperfusion in acute coronary syndrome and are used to infer microvascular dysfunction or "no-reflow." Both indices have been linked to infarct size, biomarker release, and patient survival (Van 'T Hof et al. 1998; Gibson et al. 2000). The Coronary Clearance Frame Count (CCFC) was proposed as a method for evaluating microvascular function after reperfusion in both acute coronary syndrome and "Syndrome X." The authors reported significantly higher mean index values in patients with non-significant epicardial disease and proven myocardial ischemia compared with controls (Yildirim et al. 2018; De Prado et al. 2005). The Coronary Sinus Filling Time (CSFT) represents the difference in the number of frames between maximal opacification of the LAD and initial contrast appearance in the coronary sinus. Prior studies have shown that this time interval is significantly prolonged in patients with angina and non-obstructive coronary artery disease, who also exhibit more frequent hospitalizations for chest pain (Haridasan et al. 2013; Kadermuneer et al. 2015; Shakerian and Panahifar 2019; Ibrahim et al. 2021; Ramakrishnudu and Rao 2019).

The TIMI Frame Count (TFC) and its corrected version (cTFC) provide quantitative measures of flow velocity in the epicardial arteries, which can be used as indirect indicators of microcirculatory function. Despite their simplicity and reproducibility, these methods do not provide direct information on microcirculation and are limited to the arterial phase of contrast passage. They do not account for hemodynamic variables such as perfusion pressure and heart rate, both of which influence contrast transit velocity. Moreover, they do not standardize for injection rate between operators (Gibson et al. 1996).

The MBG and TMPG are visual grading systems for microvascular assessment. However, they were not designed or validated for evaluating microcirculation in patients with ANOCA. These scales are inherently subjective, and their application does not account for hemodynamic conditions or injection rate (Van 'T Hof et al. 1998; Gibson et al. 2000).

The CCFC is a dedicated technique for evaluating microvascular function in both acute coronary syndrome and Syndrome X. Nevertheless, this method remains limited to the arterial phase, lacks adequate physiological normalization, does not consider patient-specific parameters such as myocardial mass, and is not standardized in terms of injection technique (Yildirim et al. 2018; De Prado et al. 2005).

The Coronary Sinus Filling Time (CSFT) method is conceptually similar to the approach proposed in our study and has also been used to assess microcirculation in patients with microvascular angina. In CSFT, the measurement is defined as the frame difference between maximal opacification of the LAD and the first appearance of contrast in the coronary sinus. In contrast, in the present study, we defined iTCPM as the time interval between the first appearance of contrast at the catheter tip(

after the catheter was prefilled with contrast) and the moment the contrast reached the coronary sinus. We believe this approach provides several key advantages.

First, the initial measurement point (contrast appearance at the catheter tip) is objective and easily identifiable, which minimizes subjectivity and reduces interobserver variability compared with the more ambiguous identification of "maximal LAD opacification." Second, the time required for contrast to travel through the epicardial arteries to reach the LAD is itself influenced by the state of the microcirculation, as well documented in the phenomenon of "no-reflow." Therefore, including this component in the measurement may more accurately reflect the global microvascular flow. Third, in the available CSFT studies, no automated injection systems were used, introducing variability related to manual injection technique (volume, speed, pressure). Moreover, previous reports lack adjustment for hemodynamic parameters during angiography or for individual myocardial mass – both of which significantly affect contrast transit time (Haridasan et al. 2013; Kadermuneer et al. 2015; Shakerian and Panahifar 2019; Ibrahim et al. 2021; Ramakrishnudu and Rao 2019).

In this context, the methodology proposed in our study, based on a strictly standardized injection protocol and indexing for physiological parameters should offer superior reproducibility, precision, and physiological interpretability of results.

In summary, our study provides a methodological solution to the main limitations of previous fluoroscopic techniques by standardizing both contrast delivery and interpretation, while indexing transit time for MAP, HR, and myocardial mass. This indexing minimizes the influence of individual variations associated with hypo- or hyperdynamic circulation and anatomic differences, providing a more objective basis for patient-to-patient comparison. The indexed TCPM aims to minimize individual variability and to reflect the true efficiency of microcirculatory perfusion. In this context, the proposed method advances existing approaches by combining technical feasibility, standardized contrast administration, and physiologically grounded normalization, offering a technique that is both clinically practical and scientifically valid.

Demographic characteristics, risk profile, and angina severity in the study population

The studied cohort included 102 patients presenting with clinical manifestations of stable or unstable angina and angiographically excluded obstructive coronary artery disease, consistent with the contemporary definition of ANOCA.

When comparing the baseline characteristics of our population with those reported in major clinical trials involving patients with obstructive (ISCHEMIA and ORBITA) and non-obstructive coronary artery disease (CorMicA and iPOWER), an interesting intermediate profile emerges. The mean age in our population (61 years) closely matches that in CorMicA and iPOWER (61–62 years)

and is slightly lower than in ISCHEMIA and ORBITA (64–66 years). The mean body mass index (BMI 30.5 kg/m²) is somewhat higher than in all reference cohorts, underscoring the high prevalence of overweight and obesity among patients with angina in our population (Thomas J. Ford et al. 2018; Maron et al. 2020; Mygind et al. 2016; Al-Lamee et al. 2018).

The mean age of participants (61 years) and the predominance of women (59%) are consistent with existing evidence that ANOCA is more common in postmenopausal women (Kunadian et al. 2021). Compared with other large studies in patients with obstructive and non-obstructive coronary disease, our cohort demonstrates a female proportion substantially higher than that in ISCHEMIA (23%) and ORBITA (27%), yet lower than in CorMicA (73.5%). This pattern reflects the well-recognized epidemiologic characteristic of microvascular angina being more prevalent among women, while also suggesting broader inclusion criteria in our study (Maron et al. 2020; Al-Lamee et al. 2018; Thomas J. Ford et al. 2018).

The prevalence of smoking (57%) in our cohort is markedly higher than the rates reported in ORBITA (13%), CorMicA (17.9%), and iPOWER (19%), and approximates the combined rate of current and former smokers in ISCHEMIA (~57%). This finding may reflect either a higher overall risk burden or regional behavioral differences. Similarly elevated values were observed for arterial hypertension and diabetes mellitus – 94% and 22%, respectively, both exceeding those reported in CorMicA (treated hypertension ~45%; diabetes 19.2%) and iPOWER (hypertension 45%; diabetes 11%), and closer to the rates observed in obstructive CAD cohorts (ISCHEMIA: hypertension 77%, diabetes 35%; ORBITA: hypertension 69%, diabetes 18%) (Thomas J. Ford et al. 2018; Maron et al. 2020; Mygind et al. 2016; Al-Lamee et al. 2018). The comparative data summarizing the risk profile in our study versus major ischemic heart disease trials are presented in Table 21.

In summary, published studies on patients with microvascular angina generally report a lower prevalence of traditional cardiovascular risk factors compared with populations with obstructive coronary disease. In contrast, our cohort demonstrates a substantial cardiometabolic risk burden, distinguishing it as a high-risk population despite the absence of angiographically significant stenoses. This observation holds important pathophysiological implications: arterial hypertension, insulin resistance, dyslipidemia, and chronic inflammation – conditions closely linked to elevated vascular risk are believed to contribute to endothelial dysfunction and microvascular remodeling. Therefore, the baseline characteristics observed in our cohort support the hypothesis that microvascular angina in this population is not a benign or merely “functional” entity, but rather reflects underlying structural and/or functional alterations of the vascular wall that warrant targeted diagnostic and therapeutic strategies.

Table 21. Comparison of baseline characteristics between the present study and trials involving non-obstructive and obstructive coronary artery disease.

Variable	Present study	ISCHEMIA	ORBITA	CorMicA	iPOWER
Mean age (years)	61	64	66	61 (median)	62 (median)
BMI (kg/m²)	30.5	30	28.7	29.7 (median)	26.6
Smoking (%)	57%	57% (incl. ex smokers)	13%	17.9%	19%
Diabetes (%)	22%	35%	18%	19.2%	11%
Hypertension (%)	94%	77%	69%	~45% (treated with ACEi)	45%
Female sex (%)	59%	23%	27%	73.5%	100% (by design)

The clinical burden of angina symptoms in patients with non-obstructive coronary artery disease is often underestimated in clinical practice due to the absence of angiographically significant stenoses. Comparison of baseline Seattle Angina Questionnaire (SAQ) scores between our population and published cohorts from studies involving obstructive (ORBITA, ISCHEMIA) and microvascular angina (CorMicA) reveals that the symptomatic burden in ANOCA may be comparable to or even greater than that in obstructive CAD.

In our study, the mean SAQ scores for the Physical Limitation and Angina Frequency categories were 61.9 ± 15.1 and 74.1 ± 14.0, respectively – lower than those reported in patients with obstructive CAD in ISCHEMIA (78.5–80.2 and 80.8–82.1), similar to ORBITA (71.3–69.1 and 63.2–60.0), but notably higher than those in patients with microvascular angina from CorMicA (52.1 and 59.3). Conversely, our cohort demonstrated markedly lower scores in the Angina Stability (25.7 ± 19.1) and Disease Perception (34.2 ± 19.1) domains, highlighting the subjective instability and emotional burden of symptoms among ANOCA patients (Thomas J. Ford et al. 2018; Maron et al. 2020; Mygind et al. 2016; Al-Lamee et al. 2018). The SAQ results are summarized in Table 22.

From the perspective of the Canadian Cardiovascular Society (CCS) classification, in ORBITA nearly 40% of participants were in CCS class III and 59% in class II. Similarly, in our cohort, the majority of patients were in CCS class II and II–III (combined 43.7%), with an additional 10.7% in class III. This distribution indicates that, despite the absence of anatomically significant

stenoses, a considerable proportion of patients in our study experienced moderate to severe angina, comparable in severity to that observed in stable obstructive CAD (Al-Lamee et al. 2018).

Taken together, these findings challenge the common perception that the absence of angiographic stenoses in patients with anginal symptoms implies "low risk." On the contrary, both the SAQ results and CCS classification demonstrate clinically meaningful symptom burden and functional limitation, emphasizing the need for comprehensive functional assessment and individualized therapeutic strategies in this patient population.

Table 22. Comparison of the results from the five SAQ categories between the present study and trials involving non-obstructive and obstructive coronary artery disease.

Variable	Present study	ISCHEMIA	ORBITA	CorMicA
Physical limitation	61.85 ± 15.08	78.5 ± 23.7 (invasive arm), 80.2 ± 23.4 (conservative arm)	71.3 ± 22.5 (PCI arm), 69.1 ± 24.7 (placebo arm)	52.1 ± 24.4
Angina frequency	74.11 ± 13.96	80.8 ± 20.0 (invasive arm), 82.1 ± 19.3 (conservative arm)	63.2 ± 20.4 (PCI arm), 60.0 ± 25.1 (placebo arm)	59.3 ± 23.5
Angina stability	25.74 ± 19.09	Not specified	64.7 ± 25.5 (PCI), 68.5 ± 24.3 (плацебо)	44.7 ± 24.4
Treatment satisfaction	85.4 ± 12.28	60.9 ± 26.5 (invasive arm), 62.7 ± 26.3 (conservative arm)	Not specified	81.9 ± 19.5
Disease perception	34.15 ± 19.14	Not specified	Not specified	40.9 ± 21.7

Assessing the the time for contrast to pass through the myocardium (TCPM) and the indexed time for contrast to pass through the myocardium (iTCPM)

To date, no published data are available in the literature regarding the time for contrast to pass through the myocardium (TCPM) determined in the manner described by us. The present study provides the first quantitative characterization of this parameter. The mean TCPM value in the investigated cohort was 4.96 seconds, with a standard deviation of ±1.12 seconds. Graphical

representation of the data demonstrated an approximately normal distribution, with a slight rightward shift of the mean relative to the median. The clustering of data within the 4.0–5.5 second interval and the smooth KDE curve indicate a stable central tendency with moderate dispersion. This distribution may hold potential value for future patient stratification based on microvascular function.

After indexing for mean arterial pressure (MAP), heart rate (HR), and myocardial mass, the mean iTCPM value was 4.97 seconds, with a standard deviation of ±1.02 seconds. The range of ±1 SD (3.95–5.99 seconds) encompassed the majority of observations, further supporting the normal distribution visualized by the histogram with KDE curve (Figure 9). The Shapiro–Wilk test confirmed the absence of a statistically significant deviation from normality ($p = 0.390$; $W = 0.9865$), while the Q-Q plot (Figure 10) showed good agreement between empirical and theoretical values. Notably, the distribution pattern of iTCPM closely mirrored that of the non-indexed TCPM – the indexing process achieved the intended physiological adjustment without introducing data distortion, while enhancing interindividual comparability and analytical applicability.

Correlation analysis between the indexed time for contrast to pass through the myocardium (iTCPM), CCS functional class, and Seattle Angina Questionnaire (SAQ)

To assess the clinical validity of the iTCPM, its relationships with two independent indicators of angina severity were analyzed: the Canadian Cardiovascular Society (CCS) functional class and the five domains of the Seattle Angina Questionnaire (SAQ). The correlation between iTCPM and CCS class showed a statistically significant moderate positive association ($r_s = 0.443$; $p < 0.0001$) in the full sample ($n = 102$), which strengthened to a moderate-to-strong correlation ($r_s = 0.545$; $p < 0.0001$) after excluding 13 patients with anatomical variations. The excluded cases included myocardial bridges and coronary–cameral microfistulae ("Wearn's vessels"), in which alternative mechanisms of ischemia may exist independently of microcirculatory perfusion.

In patients with a myocardial bridge, the characteristic intramural course of a segment of the LAD leads to dynamic systolic compression, which especially during tachycardia or increased inotropy can extend into early diastole, critically impairing diastolic flow. Evidence suggests that this may cause myocardial ischemia even in the absence of endothelial or microvascular structural abnormalities (Samuels et al. 2023; Forsdahl et al. 2017; Tsujita et al. 2009). Coronary–cameral microfistulae, on the other hand, represent congenital vascular connections between the terminal branches of the coronary arteries and the ventricular cavity, creating a low-resistance shunt with potential for a "coronary steal" phenomenon – the diversion of blood flow from the arterial to the ventricular circulation at the expense of capillary perfusion. Moreover, in patients with microfistulae, accelerated venous drainage may be expected, reducing the effective myocardial oxygen exchange

time, although this remains unproven and requires further study. In these anatomical variations, anginal symptoms can be clinically significant but stem from hemodynamic and anatomical mechanisms distinct from the typical delay in myocardial contrast transit captured by iTCPM (Snodgrass and Chilakala 2020; Hussain and Roberts 2015; Angelini 2005; Agarwal et al. 2014). Therefore, excluding such patients from the analysis likely improves the precision of the relationship between iTCPM and the severity of angina symptoms as measured by CCS and SAQ, by eliminating the influence of alternative ischemic mechanisms.

A similar pattern was observed when examining the associations between iTCPM and the SAQ scales. In the full cohort, statistically significant negative correlations were found with "Physical Limitation" ($r_s = –0.317$; $p = 0.001$), "Angina Frequency" ($r_s = –0.460$; $p < 0.00001$), and "Disease Perception" ($r_s = –0.206$; $p = 0.038$). After excluding patients with anatomical variations, these correlations became stronger – most notably for "Angina Frequency" ($r_s = –0.533$; $p < 0.00001$), followed by "Physical Limitation" ($r_s = –0.378$; $p = 0.0003$) and "Disease Perception" ($r_s = –0.289$; $p = 0.006$). These findings further support that iTCPM reflects the degree of symptomatic burden in ANOCA patients more accurately when cases with distinct pathophysiological mechanisms are excluded. The lack of significant associations with the "Angina Stability" and "Treatment Satisfaction" domains likely reflects their greater subjectivity and susceptibility to non-perfusion-related influences.

In summary, the results demonstrate that iTCPM shows good concordance with both the objective physician-assessed functional classification (CCS) and the subjective patient-reported symptom burden (SAQ), and its diagnostic performance improves after adjusting for possible confounding anatomical factors.

Group analysis of the results

To enable a more in-depth interpretation of the clinical significance of iTCPM, patients were stratified into two groups – "fast" and "slow", based on the mean iTCPM value for the entire cohort (4.97 s). The comparative analysis between these groups revealed a statistically significant difference in CCS functional class, with patients exhibiting iTCPM values above the mean (i.e., slower contrast transit) having a mean CCS class of 2.10 compared to 1.48 among those with iTCPM below 4.97 s ($p < 0.0001$). Although the correlation between iTCPM and symptom severity had already been established, this additional analysis provides important clinical confirmation of a discrete threshold beyond which time for contrast to pass through the myocardium is associated with a pronounced worsening of anginal symptoms. Thus, the group-based approach complements the correlation analysis by demonstrating the applicability of iTCPM not only as a continuous variable but also as a

potential cutoff for clinical stratification. This highlights the index's potential utility for identifying ANOCA subgroups with greater symptom burden and possibly higher risk, thereby supporting individualized diagnostic and therapeutic strategies.

Similar relationships were observed in the analysis of SAQ data. The strongest difference between groups was found in the "Angina Frequency" domain, where patients in the "slow" group reported significantly more frequent angina episodes (67.7 vs. 79.8; $p < 0.0001$). Unfavorable differences for the slow group were also observed in the "Physical Limitation" and "Disease Perception" categories. The absence of significant differences in the "Angina Stability" and "Treatment Satisfaction" domains is consistent with the previous analyses and likely reflects the lower sensitivity of these metrics in the context of microvascular ischemia.

In summary, the between-group differences complement and expand the previously established correlations between iTCPM and angina severity, demonstrating that even when applying a simple threshold value, it is possible to achieve statistically and clinically meaningful discrimination between patients with differing symptom profiles. This finding adds practical value to iTCPM not only as a continuous physiological measure but also as a potential clinical marker for symptom severity confirmation in ANOCA patients. The observation that patients with more pronounced symptoms exhibit longer myocardial contrast transit times supports the hypothesis of underlying microcirculatory dysfunction and may open opportunities for improved phenotyping and individualized treatment in the future.

Analysis of the relationship between classical cardiovascular risk factors, anatomical features, and the indexed time for contrast to pass through the myocardium (iTCPM)

To identify the factors influencing iTCPM values, a multiple linear regression analysis was performed, including classical cardiovascular risk factors and anatomical characteristics of the coronary circulation. The applied model enabled simultaneous evaluation of the independent contribution of each predictor while controlling for the others. Only the variable "presence of coronary–cameral microfistulae" showed a tendency toward an inverse association ($\beta = –0.91$; $p = 0.025$), which, however, lost statistical significance after model reduction ($p = 0.095$). Although this association did not retain definitive statistical strength, the observed direction of the effect is consistent with previously proposed pathophysiological hypotheses, suggesting that such vascular anomalies may facilitate accelerated venous drainage through the shunt, leading to shorter contrast transit time, independently of microcirculatory function. Given the limited number of patients with this anatomical feature in the present study, validation of these findings in larger, specifically targeted cohorts is warranted.

The explanatory power of the model, as indicated by the coefficient of determination (R^2 = 0.028) and the adjusted R^2 (0.018), highlights that only about 2.8% of the variance in iTCPM values can be explained by the included predictors. Graphical evaluation of the residuals revealed no systematic deviations, and the VIF values for all independent variables were below 2, excluding substantial multicollinearity. These results indicate that the measured contrast transit time is only minimally influenced by classical cardiovascular risk factors, even though such factors play a key role in the disease's pathophysiology. A plausible explanation is that iTCPM captures the immediate hemodynamic characteristics of the microcirculation such as endothelial reactivity, local vascular tone, and vasomotor dynamics that are not directly determined by chronic conditions like arterial hypertension or diabetes mellitus. Moreover, the sample size of the present study may limit the statistical power to detect weaker effects, particularly in a multivariate model.

An additional comparative analysis between patients stratified according to the mean iTCPM value ("fast" and "slow" groups) confirmed the absence of significant differences between groups with respect to classical cardiovascular risk factors and anatomical variations. None of the categorical variables including sex, hypertension, diabetes mellitus, dyslipidemia, smoking status, or the presence of coronary anomalies showed a statistically significant association with group assignment (all $p > 0.2$). Similarly, among continuous variables (age, BMI, eGFR, LDL), no substantial differences were found, except for age, which showed a borderline tendency toward higher values in the "slow" group ($p = 0.0828$), without reaching statistical significance.

It is noteworthy that this weak relationship with traditional risk factors is consistent with findings from large-scale studies in ANOCA populations, where the prevalence of hypertension, dyslipidemia, and diabetes is systematically lower than in patients with obstructive coronary artery disease (Thomas J. Ford et al. 2018; Mygind et al. 2016; Pepine 2025). This highlights the distinct clinical and pathophysiological profile of this population, in which microvascular dysfunction often represents the predominant mechanism, independent of classical atherosclerotic burden. Nevertheless, long-term data, including those from the WISE study, demonstrate that conventional cardiovascular risk factors retain prognostic value for adverse clinical outcomes among women with ANOCA. Over a median follow-up of 9.5 years, WISE reported an all-cause mortality of 20%, with 31% of cardiovascular deaths occurring in women without obstructive coronary lesions. Multivariate analysis identified higher age, elevated systolic blood pressure, diabetes mellitus, smoking history, increased triglycerides, and reduced renal clearance (eGFR) as independent predictors of mortality among patients with non-obstructive disease (Kenkre et al. 2017).

In summary, the present findings suggest that iTCPM is relatively autonomous and independent of traditional clinical and anatomical predictors. This reinforces its value as a functional

parameter capable of capturing specific features of coronary microcirculation that often remain undetected by standard angiographic assessment or risk factor profiling alone.

Relationship between pharmacological therapy and the indexed time for contrast to pass through the myocardium (iTCPM)

Analysis of the pharmacological therapy administered among patients in the studied cohort revealed a high prevalence of outpatient prescriptions of standard antianginal and concomitant cardiovascular medications. The most frequently prescribed antianginal agents were β-blockers, followed by calcium channel blockers. ACE inhibitors or ARBs were used in 70.6% of patients, and statins in 58.8%. Trimetazidine and nitrates were prescribed less frequently, while ranolazine was not used in any case. Almost all participants (91.2%) were receiving pharmacological therapy, with 22.6% taking five or more medications concurrently, reflecting a substantial therapeutic burden in part of the cohort.

To assess whether symptom severity was associated with more intensive pharmacological treatment, the number of medications taken was analyzed according to CCS class. The mean number of drugs increased with higher CCS class from 2.20 in patients with CCS 0–I to 3.43 in those with CCS II–III, although this trend did not reach statistical significance ($H = 5.786$, $p = 0.3276$). The absence of a significant association between symptom burden and therapeutic intensity suggests that, in routine clinical practice, there is no consistent relationship between these parameters.

A plausible explanation for this discrepancy is that the assessment of symptom severity reflects a state already modified by therapy – that is, patients with initially more severe angina may have received more aggressive treatment and, as a result, presented with a lower CCS class at the time of evaluation. Thus, in a cross-sectional analysis of data collected after treatment initiation, the true relationship between symptom load and treatment intensity may be obscured by the therapeutic effect itself. This highlights the limitations of single-timepoint functional scales such as the CCS classification, especially in populations with long-standing and dynamically adjusted medical therapy, such as ANOCA.

Furthermore, variability in therapeutic approaches among physicians and individualized treatment decisions based on patient characteristics likely contribute to heterogeneity in prescribed regimens. These factors combined complicate the use of medication count as a marker of clinical severity and underscore the need for objective indices to guide patient stratification and treatment optimization.

Consistent with these findings, results from the multiple regression analysis demonstrated that none of the investigated medications, including ASA, clopidogrel, trimetazidine, β-blockers, calcium

channel blockers, ACE inhibitors/ARBs, statins, nitrates, or the total number of medications showed a statistically significant relationship with iTCPM. All p-values exceeded 0.05, and the explanatory power of the model remained low ($R^2 = 0.034$, adjusted $R^2 = –0.049$), indicating that ongoing therapy at the time of assessment did not meaningfully influence myocardial contrast transit dynamics.

Comparison with published results from CorMicA, iPOWER, and WARRIOR revealed several notable parallels and contrasts. In CorMicA, the intensity of pharmacological treatment was comparable to that in the present cohort – 66.9% of patients were receiving β-blockers, 83.4% statins, and 45% ACE inhibitors/ARBs, indicating that the studied population was already under active medical management but remained symptomatic. In iPOWER, the frequency of medication use was lower – 29.5% β-blockers, 49.8% statins, and 32.9% ACEi/ARB, likely reflecting differences in participant selection or local therapeutic strategies. In WARRIOR, one of the largest and most contemporary randomized trials in this population, 62.4% of patients were receiving statins, 36.8% β-blockers, and 48.2% ACEi/ARB at baseline.

These data demonstrate that, as in our study, patients included in the major international ANOCA trials were characterized by significant anginal symptoms requiring initiation or continuation of intensive pharmacological therapy even before coronary anatomy was known (Thomas J. Ford et al. 2018; Michelsen et al. 2017; Pepine 2025). The high prevalence of β-blocker, statin, ACEi/ARB, and other antianginal medication use at baseline reflects the clinical need for active management in patients with persistent angina. Collectively, these observations highlight a similar clinical phenotype across studies – patients with inadequately controlled angina despite ongoing medical therapy, underscoring the need for additional diagnostic evaluation.

A particularly notable finding is the markedly lower frequency of acetylsalicylic acid (ASA) use in our study (22.5%) compared with CorMicA (86.8%) and WARRIOR (52.1%). This likely reflects a different therapeutic philosophy regarding antiplatelet therapy in patients without prior imaging of coronary anatomy. Interestingly, 7.8% of our patients were receiving clopidogrel at baseline, while none of the comparative studies reported the use of $P2Y_{12}$ inhibitors (Pepine 2025; Thomas J. Ford et al. 2018). The lower aspirin use in our cohort aligns with current guideline recommendations, which discourage routine aspirin use for primary prevention.

The role of antiplatelet therapy in ANOCA remains incompletely understood. The pathophysiological rationale for its use in this population is debated. One small study involving 31 ANOCA patients found shorter resting platelet aggregation times compared with patients with obstructive CAD and healthy controls, suggesting potential platelet hyperreactivity in this group (Lanza 2001). However, the underlying mechanisms remain unclear. Although aspirin may improve endothelial function in atherosclerosis, observational data indicate that low-dose aspirin use may be associated with a higher incidence of coronary spasm (Hokimoto et al. 2023). This raises the

hypothesis that in certain ANOCA subtypes, antiplatelet therapy might not only lack benefit but could even be potentially detrimental.

In the CorMicA trial, aspirin use exceeded 70% of participants, regardless of whether microvascular dysfunction or vasospasm was the identified mechanism (Thomas J. Ford et al. 2018). Given the established bleeding risks associated with aspirin and the absence of prospective randomized evidence of benefit in ANOCA, the question of when and for whom antiplatelet therapy is justified remains open. This underscores the need for future studies evaluating the risks and benefits of antiplatelet therapy in well-defined ANOCA subgroups, including those with microvascular angina and epicardial vasospasm.

A distinct finding in the present study is the relatively low frequency of use of certain antianginal agents traditionally regarded as symptomatically effective but with less well-established roles in microvascular angina. Nitrates were prescribed in only 16.7% of patients, and ranolazine was not used at all. This likely reflects both the absence of clear recommendations for their use in the absence of angiographically confirmed ischemia and the high cost of ranolazine on the Bulgarian market. Literature data support this cautious approach: long-acting nitrates have only modest effects on symptoms, and results from trials with ranolazine are inconsistent—ranging from no benefit to improvement in subgroups with severe microvascular dysfunction (CFR < 2.5) (Bairey Merz et al. 2016; Koh et al. 2020; Mehta et al. 2011; Villano et al. 2013).

In CorMicA, nitrates were used in 47% of participants, likely reflecting a more liberal and empiric approach to antianginal therapy in patients with uncertain symptom etiology (Thomas J. Ford et al. 2018). Calcium channel blockers (CCBs), on the other hand, remain one of the mainstays of symptom-oriented angina management and represent a logical therapeutic choice in patients with yet-unclarified coronary anatomy such as those in our cohort. They are often preferred alongside β-blockers, especially in cases with concomitant arterial hypertension – one of the most prevalent comorbidities in this study population. In our cohort, calcium channel blockers were prescribed to 44.1% of patients, a considerably higher proportion than in iPOWER (21.5%) and WARRIOR (25.1%) (Michelsen et al. 2017; Pepine 2025). This broader therapeutic use likely reflects individualized physician judgment based on clinical presentation and comorbid conditions. However, it should be emphasized that the efficacy of CCBs in isolated microvascular angina remains uncertain. Available studies provide mixed evidence, supporting their benefit primarily in patients with concomitant epicardial vasospasm, whereas their effect in pure microvascular dysfunction appears less consistent and often modest (Pepine et al. 1981; Chahine et al. 1993).

β-blockers, ACE inhibitors, and statins were the most commonly used medications both in our cohort and in other ANOCA studies. A comparative summary of baseline medication use between the present study and leading ANOCA trials is presented in Table 23.

In summary, our findings highlight the considerable therapeutic heterogeneity among patients presenting with angina. In routine practice, treatment is often guided by symptoms and comorbidities rather than by a clear understanding of the underlying mechanism. Even after excluding obstructive coronary disease via angiography, many of these patients remain symptomatic, underscoring the need for additional, easily applicable methods to evaluate coronary microcirculation. Such tools could help identify microvascular dysfunction as a potential mechanism of ischemia or ANOCA. In this context, iTCPM may represent a promising and practical functional index to identify these patients, guide individualized therapy, and signal the need for further diagnostic assessment of coronary microvascular function.

Table 23. Comparison of the administered pharmacological therapy between our group and leading trials in patients with angina and non-obstructive coronary artery disease.

Medication	**Present study (%)**	**CorMicA (%)**	**iPOWER (%)**	**WARRIOR (%)**
Aspirin	22.5	86.8	44.3	52.1
Clopidogrel	7.8			
Trimetazidine	20.6			
Statins	58.8	83.4	49.8	62.4
Beta-blockers	59.8	66.9	29.5	36.8
Calcium channel blockers	44.1	34.4	21.5	25.1
ACEi/ARB	70.6	45.0	32.9	48.2
Nitrates	16.7	47.0		21.2
Ranolazine	0.0			
Nicorandil		17.2		

Limitations

Absence of functional evidence of ischemia

In the present study, no standardized functional imaging tests for myocardial ischemia were documented, although some patients had undergone such assessments earlier in their diagnostic course. This limits the ability to analyze the relationship between iTCPM and the presence or extent of objectively verified ischemia. It should be noted that in the ANOCA population, only about 25% of patients demonstrate ischemia on functional testing (Vrints et al. 2024); thus, performing these

studies in all participants would not have provided universal confirmation that symptoms were due to microvascular disease. Nevertheless, the lack of standardized ischemia assessment precludes direct interpretation of iTCPM as a marker of ischemic burden.

Methodological limitations related to iTCPM measurement

Contrast injection during iTCPM measurement could not be synchronized with cardiac cycle phases via ECG, potentially leading to minor variations depending on whether the injection occurred during systole or diastole. Although the starting frame, defined as the first appearance of contrast at the catheter tip was clearly identifiable and a strict measurement protocol was followed, some degree of variability remains possible. The iTCPM was independently measured by two investigators, and if the difference exceeded two frames (equivalent to ±0.2 seconds), a joint reassessment was performed to reach consensus. Despite this, minimal subjective variability in determining start and end points is inherent to any angiographic method relying on visual assessment.

Lack of validation against established functional methods

The study did not include parallel assessment using invasive physiological techniques for coronary circulation evaluation. Such methods include Coronary Flow Reserve (CFR), which reflects the global capacity to augment coronary blood flow but does not distinguish between epicardial and microvascular mechanisms, and the Index of Microcirculatory Resistance (IMR), regarded as the gold standard for microvascular function assessment. The absence of direct comparison with validated methods, particularly IMR, prevents direct validation of iTCPM as a marker of microvascular dysfunction and precludes determination of whether abnormal iTCPM values correspond to pathological CFR or IMR thresholds.

Potential influence of pharmacotherapy on iTCPM

Although ongoing therapy was documented and incorporated into regression models, all patients were studied under active antianginal treatment that was not discontinued prior to angiography. Consequently, coronary hemodynamics and iTCPM values could have been influenced by medications such as β-blockers, calcium channel blockers, or nitrates. Furthermore, as treatment was likely titrated according to symptom severity, some patients may have been partially stabilized at the time of measurement. This may blur the true relationship between medication use, symptom burden, and iTCPM, complicating precise interpretation of pharmacological effects.

Low explanatory power of regression models

Despite the presence of statistically significant correlations between iTCPM and angina severity indices, multivariable regression failed to identify independent, stable predictors of iTCPM. The explanatory power of the models remained low, limiting the construction of predictive equations and suggesting the influence of additional, unmeasured determinants of myocardial contrast dynamics.

Lack of longitudinal follow-up

The study employed a cross-sectional design without longitudinal follow-up. Therefore, no conclusions can be drawn regarding the prognostic value of iTCPM or its responsiveness to treatment and changes in microvascular function over time.

Future perspectives

The results of the present study provide an important foundation for further research aimed at developing and validating iTCPM as both a diagnostic and potentially prognostic index in patients with angina and non-obstructive coronary anatomy.

First, prospective studies involving larger cohorts are needed to enable more precise statistical estimates and improve the generalizability of the findings. Longitudinal follow-up assessing clinical evolution, treatment response, and cardiovascular event occurrence would allow evaluation of the prognostic value of iTCPM and its potential for risk stratification.

Furthermore, validation of iTCPM against established invasive functional methods, including CFR and IMR is essential to determine its ability to reflect pathological values associated with microvascular dysfunction. Such comparison would define the diagnostic accuracy, sensitivity, and specificity of iTCPM across different ANOCA subtypes.

Another key direction for future work is isolating the pharmacological influence on iTCPM. Studies involving temporary withdrawal of antianginal therapy or controlled medication interventions would clarify the effects of specific drug classes (e.g., β-blockers, calcium channel blockers, nitrates) on coronary flow velocity and, consequently, on iTCPM values.

To directly assess the clinical utility of incorporating functional angiographic data into patient management, an interventional randomized controlled trial can be performed, in which iTCPM is used as a diagnostic tool for stratification and for guiding individualized therapy. Potentially, iTCPM could serve as an accessible and routinely applicable method for identifying patients with microvascular angina who might benefit from targeted therapeutic strategies.

In summary, future studies should focus on validating the method, assessing risk stratification potential, integrating iTCPM into functional diagnostic workflows, and evaluating the clinical benefit

of therapy guided by this index. Such research would establish iTCPM as a reliable tool for diagnosis and personalized management of patients with angina and non-obstructive coronary artery disease.

VI. KEY FINDINGS

1. The methodology for measuring the time for contrast to pass through the myocardium (TCPM) can be standardized and applied in clinical practice. The study demonstrates that TCPM measurement is technically feasible, quantitatively reproducible, and amenable to standardization. Implementing a unified protocol, including fixed parameters of the automatic injection system, recording speed, angiographic projections, and strictly defined criteria for identifying the first and last frame ensures high reliability of the measurement.

2. The mean indexed time for contrast to pass through the myocardium (iTCPM) in the studied cohort was 4.97 ± 1.02 seconds. The distribution of values showed a clear central tendency, with minimum and maximum values of 2.44 s and 7.69 s, respectively. This is the first study to describe this parameter in patients with angina and non-obstructive coronary anatomy.

3. The severity of anginal symptoms in the cohort was clinically significant despite the absence of anatomically proven obstruction. The mean CCS functional class and Seattle Angina Questionnaire (SAQ) scores demonstrated clinically relevant symptom burden, comparable to or even greater than that observed in patients with obstructive coronary artery disease. This emphasizes that the absence of angiographic stenoses should not lead to underestimation of symptoms.

4. TCPM is influenced by certain physiological and anatomical variables. Correlation analysis revealed a weak but statistically significant positive relationship between TCPM and myocardial mass, and a negative association with mean arterial pressure. The relationship with heart rate was weak and statistically non-significant, yet heart rate was included in the indexation process for physiological reasons, given its well-established effect on myocardial perfusion. The combined indexation against these three parameters aimed to eliminate physiological variability and improve comparability between patients.

5. There is a statistically significant relationship between indexed TCPM and the severity of anginal symptoms assessed by CCS and SAQ. Patients with higher iTCPM values exhibited higher CCS class and lower SAQ scores – particularly for physical limitation and angina frequency, supporting the applicability of iTCPM as an objective marker of symptom burden.

6. No classical cardiovascular risk factors or pharmacological therapies predicted iTCPM values. Despite including sex, age, traditional risk factors (hypertension, diabetes, dyslipidemia), and medication use in the regression model, none demonstrated a statistically significant predictive effect on iTCPM.

VII. CONCLUSION

This dissertation addresses a relevant and clinically significant issue – the assessment of myocardial microcirculation in patients with angina and no obstructive coronary artery disease (ANOCA) through the development and application of a novel method: the indexed time for contrast to pass through the myocardium (iTCPM). In the context of the growing prevalence of ANOCA, the limited diagnostic options for precise evaluation of coronary microcirculation, and the need for a personalized approach in this population, the development of a new, accessible, and safe method holds substantial potential for contribution to both clinical practice and cardiovascular science.

By implementing a standardized angiographic protocol and automated contrast injection system, the study demonstrates that the measurement of TCPM is technically feasible, quantitatively reproducible, and applicable in real clinical settings. The developed index – iTCPM integrates physiologically relevant parameters such as heart rate, arterial pressure, and left ventricular mass, thereby eliminating individual hemodynamic variability and improving objectivity and inter-patient comparability.

The main findings indicate that higher iTCPM values are significantly associated with more severe anginal symptoms, both according to the validated Seattle Angina Questionnaire (SAQ) and the Canadian Cardiovascular Society (CCS) functional class. This association was confirmed in a stratified analysis dividing patients according to the mean iTCPM value, where the group with higher values (slower contrast transit) exhibited markedly more severe symptoms. Furthermore, the relationship remained consistent after excluding patients with anatomical variants that could cause angina and/or ischemia through alternative mechanisms. These results support the hypothesis that prolonged iTCPM reflects the severity of underlying microvascular dysfunction – a key pathophysiological mechanism in patients with ANOCA.

It is noteworthy that neither classical cardiovascular risk factors nor pharmacological therapy showed a statistically significant relationship with iTCPM values in the regression analysis. This finding is consistent with published data indicating that traditional atherosclerotic risk factors are less prevalent and less predictive in ANOCA populations. Regarding pharmacotherapy, it must be considered that symptom assessment reflects a treatment-modified state – patients with more severe initial symptoms likely received more intensive therapy, which at the time of investigation could have reduced symptom burden.

Unlike established invasive methods for coronary microcirculatory assessment such as CFR and IMR, the iTCPM method does not require additional catheters or guidewires, does not prolong the procedure or increase radiation exposure, and entails no additional costs. This makes 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 arteries, guiding further diagnostic and therapeutic decisions.

In conclusion, iTCPM provides a novel opportunity for assessment of coronary microcirculatory function in patients with ANOCA. The method is simple, quantitative, reproducible, and safe, requiring no additional equipment or cost. iTCPM has the potential to become an integral component of the diagnostic algorithm for patients with angina and non-obstructive coronary arteries, contributing to more accurate stratification, personalized treatment, and improved quality of life for this often under-recognized population.

VIII. CONTRIBUTIONS

Fundamental contributions:

1. A novel angiographic index has been developed and theoretically substantiated – the indexed time for contrast to pass through the myocardium (iTCPM). The index integrates three key physiological parameters: myocardial mass, mean arterial pressure, and heart rate. This method aims to eliminate individual hemodynamic variability and offers a quantitative, standardized, and potentially reproducible approach for assessing myocardial contrast dynamics, with potential applications in the diagnosis and management 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.

Confirmatory contributions:

1. The absence of a clear association between classical cardiovascular risk factors (age, sex, arterial hypertension, type 2 diabetes, dyslipidemia) and the severity of symptoms in patients with ANOCA has been confirmed, consistent with published data from large studies in patients with angina and no obstructive coronary artery disease.
2. It has been confirmed that patients with ANOCA frequently present with pronounced symptoms and often need to be treated with intensive pharmacological therapy despite the absence of angiographically significant obstruction.

List of publications related to the dissertation topic:

1. Grigorov R, Yambolov S, Tsvetkov D, Borisov I, Georgiev S. Association between the time for contrast to pass through the myocardium, risk profile and hemodynamic parameters. *Folia Med, 2025;67(4)*
2. Grigorov R, Jordanov R, Zhelev C, Hristov D, Yambolov S. Myocardial infarction with non-obstructive coronary arteries (MINOCA) – a case report. *Heart-Lung (Varna)*. 2024;28(1):59–67.
3. Grigorov R, Zhelev C, Hristov D, Yambolov S. Angiographic assessment of microvascular perfusion after ST-elevation myocardial infarction with myocardial blush – literature review. *Sardechno-sadovi Zabolyavaniya / Cardiovascular Diseases*. 2023;54(2):12–20.

Participation in scientific forums and conferences:

1. Presentation: “Diagnosis and treatment in ANOCA/INOCA,” presented at the scientific conference Varna Cardiology Days – Hotel International, Golden Sands, February 7–9, 2025.
2. Presentation: “Optimal pharmacological therapy in chronic coronary syndrome,” presented at the scientific conference Coronary Physiology and the Physiology of Non-Coronary Vessels – Rila Hotel, Borovets, June 21–23, 2024.
3. Presentation: “Treatment with ranolazine in a patient with chronic coronary syndrome,” presented at the scientific conference Varna Cardiology Days – International Hotel, Golden Sands Resort, February 2–4, 2024.
4. Poster Presentation: “A series of three clinical cases of myocardial infarction with non-obstructive coronary arteries (MINOCA),” presented at the 11th Congress of Interventional Cardiology – Sofia, November 9–12, 2023.