”CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCUREȘTI

PhD DEPARTMENT

GENERAL MEDICINE

TORTUOSITY OF NON-OBSTRUCTIVE CORONARY ARTERIES AS A MARKER OF VASCULAR REMODELING IN PATIENTS WITH LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

PhD THESIS SUMMARY

Scientific coordinator:

PROF. GHEORGHE ANDREI DAN, MD, PhD

PhD student:

Dumitru Emilian Mihai

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Contents

Published papers

1. **Dumitru Emilian Mihai**, Ioana Lupasteanu, Gheorghe Andrei Dan. Impact of coronary artery tortuosity in ischemic and non-ischemic cardiovascular pathology. Rom. J. Intern. Med.,2021.59, 2, 119-126. https://sciendo.com/article/10.2478/rjim-2021-0003. **IF:1.9**
2. **Dumitru Emilian Mihai**, Caterina Delcea, Buzea Cătălin Adrian, Sabina Balan, Gheorghe Andrei Dan. Coronary artery tortuosity and mid-term all-cause mortality of patients with ischemia and non-obstructive coronary arteries. Volume & Issue: AHEAD OF PRINT. https://doi.org/10.2478/rjim-2023-0019. **IF:1.9**
3. Simona Caraiola, Laura Voicu, Dragoș Cașu, Elena Armășoiu, Claudia Oana Cobilinschi, **Emilian Mihai** and Răzvan Adrian Ionescu. Chronic Complete Distal Aortic Occlusion and Pulmonary Embolism—Atypical Antiphospholipid Syndrome? Diagnostics (Basel). 2023 Apr; 13(7): 1346. doi: 10.3390/diagnostics13071346. **IF: 3.992**

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Presentations:

1. **Dumitru Emilian Mihai** ”Difficult decisions in a STEMI patient with a large amount of thrombus”, EuroPCR, Paris, 24 mai 2018. https://www.pcronline.com/Courses/EuroPCR/Programme/2018/Course-Programme?day=1527112800.

Posters:

1. **Dumitru Mihai** ” To pace or not? A challange in vasospastic angina associated with paroxysmal atrioventricular block” **, Acute Cardiovascular Care 2018.** https://esc365.escardio.org/presentation/168006

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I. General part

1. Coronary artery tortuosity

1.1. History, classification, epidemiology and prognostic

The first known mention of the tortuosity of the vessels belongs to Leonardo daVinci, who in his drawings representing the human anatomy notices that the vessels in the forearm of elderly people are more tortuous compared to those of young people(1). In 1921 Gross L. argued in his research that coronary tortuosity cannot appear earlier than the third decade of life, but Spalteholz W. observed the presence of coronary tortuosity even in newborns, because only a little later, in 1929, Whitten M.B and Barnes A.R. claim that it occurs as a result of the elongation of the arteries between two fixed points, without correlating it with age(2).

In daily practice, coronary artery tortuosity (CAT) is simplistically defined as a series of loops and curves in the course of an epicardial coronary artery greater than 2 mm in diameter, visually estimated. Instead, when we talk about its classification, things change substantially. The classification by qualitative methods is done by visualizing the paths and loops. The classification based on quantitative methods is much more exhaustive.

The most used classification in clinical trials is that of Eleid which established three stages for severity, but also is defining a global tortuosity index. *Mild coronary tortuosity*: ≥3 consecutive curves between 45° and 90° in an epicardial artery larger than 2 millimeters or ≥3 consecutive curves between 90° and 180° in an epicardial artery <2 mm at the end of diastole; *moderate coronary tortuosity:* ≥3 consecutive curves between 90° and 180° in an epicardial artery larger than 2 millimeters; *severe coronary tortuosity*: ≥2 consecutive curves ≥180° in an epicardial artery larger than 2 millimeters. Each grade is classified as: 0-none; 1-mild; 2-moderate; 3-severe. The global tortuosity index (GTI) is defined as the sum of score for each vessel. FIGURE 1-1)(3).

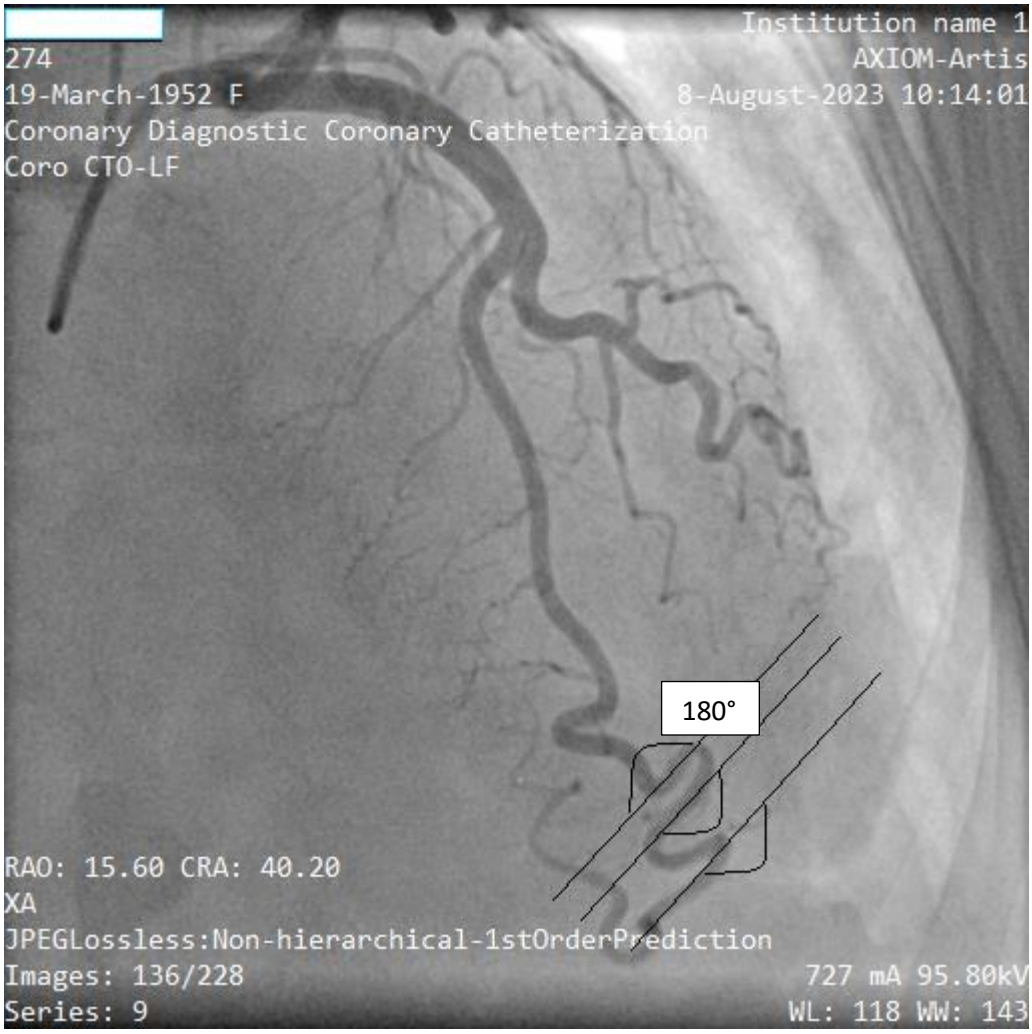


FIGURE 1-1 SEVERE CORONARY TORTUOSITY ACCORDING TO ELEID CLASSIFICATION

Besides the evaluation of the number of buckles and curves, Eleid identified three markers of coronary tortuosity severity (FIGURE 1-2). They are:

1. *intravascular symmetry:* symmetrical buckles with similar angles all over the length of the vessel.
2. *multivascular symmetry*: symmetrical buckles with similar angles all over the length of the vessel, in more than two vessels.
3. *corkscrew sign*: helicoidal appearance of the vessel with an angle ≥360°, perpendicular on the epicardial plane.

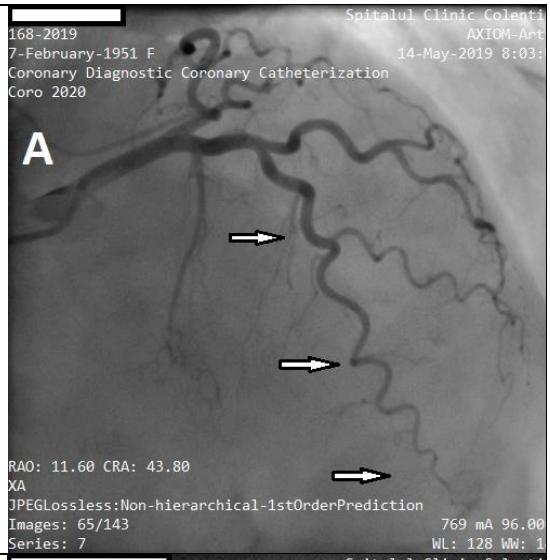
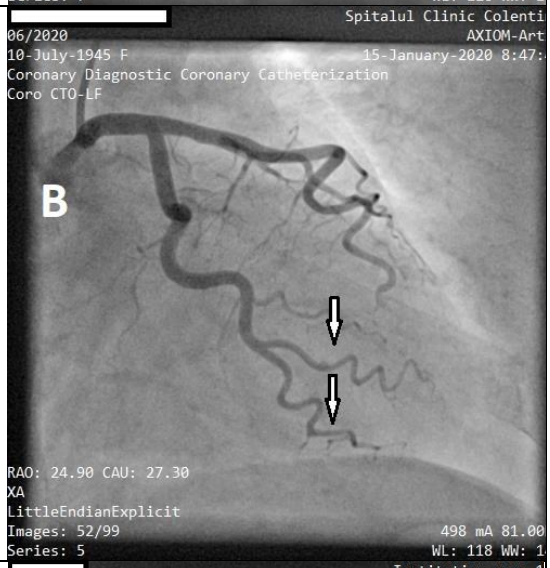
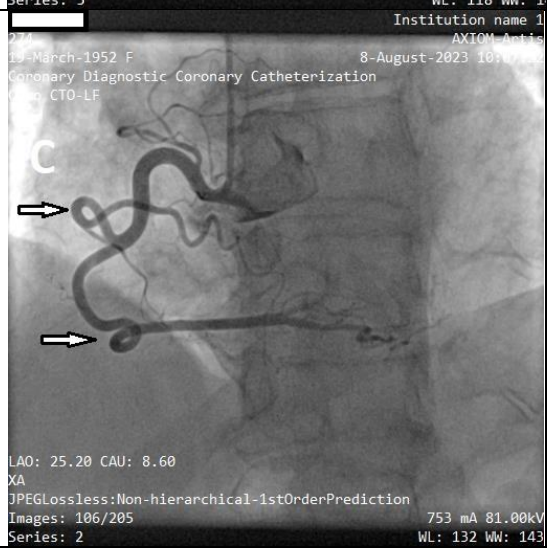
Intravascular symmetry	
Multivascular symmetry	
Corkscrew sign	

FIGURE 1-2 MARKERS OF CORONARY ARTERY TORTUOSITY

The epidemiology of this remodeling of the coronary anatomy is based on invasive coronary angiography reported in literature. The prevalence of coronary artery tortuosity seen in coronarography is between 12% and 40% and more frequent in women than in men(4,5). As well, coronary artery tortuosity is more frequent in patients with no obstructive coronary lesions, almost 60% of these patients being affected by CAT(4). The most affected epicardial vessel is the left circumflex (LCx), then the left anterior descending artery (LAD) and lastly, the right coronary artery (RCA)(6).

Nowadays, the prognosis of these patients is largely debatable giving the fact that we do not definitely know if coronary artery tortuosity is an adaptative process positive influencing major adverse cardiac events (MACE) rate, cardiovascular mortality, or global mortality. Conversely, this coronary feature could be a maladaptive process negatively affecting the endpoints mentioned above. At least for patients with ischemia and non-obstructive coronary artery (INOCA) the existing data reveal that CAT has a positive impact on MACE rate and survival. For our knowledge, there is only one trial investigating this subject, with a follow-up period of 2.4±0.5 years(4).

1.2. Coronary artery tortuosity- practical considerations

Although, infrequently associated with obstructive coronary artery lesions, the presence of CAT in patients with obstructive coronary lesions can seriously affect the outcome of percutaneous coronary interventions (PCI). Another aspect of CAT impact in coronary interventions is regarding the invasive functional measurements. Especially, when we are talking about severe CAT, the registered measurements of fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), coronary flow reserve (CFR) or index of microvascular resistance (IMR) could be significantly altered by the coronary guidewires passing through a tortuous vessel. At contact points, there is crampling of the vessel with possibly total closure, process called" Concertina effect"(7).

1.3 Ischemia and non-obstructive coronary arteries (INOCA)

For the first time, in May 2016, the Committee on Cardiovascular Disease in Women, part of the American College of Cardiology, together with the Heart, Lung and Blood Institute of the United States of America, the American Heart Association and the European Society of

Cardiology constituted the first group working towards the development of a consensus regarding the syndrome of myocardial ischemia with non-obstructive epicardial coronary arteries. Recent data show that most chronic coronary ischemia syndromes occur in patients with non-obstructive or patent coronary arteries(8). In the US, the WISE (Women's Ischemic Syndrome Evaluation) database suggests that approx. 3-4 million women and men with signs and symptoms suggestive of myocardial ischemia do not have obstructive coronary lesions. These patients impose similar costs to health care systems as patients with obstructive coronary artery disease and have a similar rate of disability in both the US and the European Union(9)(10).

2. Diastolic dysfunction

2.1 Definition, classification and prognostic

Diastole is based on the lusitropic function, which is an important component of the cardiac cycle during which the optimal filling of the ventricles determines the stroke volume of the following cardiac cycle. The most important determinants of diastolic function are myocardial relaxation and wall stiffness. The identification and quantification of diastolic dysfunction is done indirectly based on ultrasound parameters or directly, much more expensive, through invasive hemodynamic measurements.

The first generally accepted classification of diastolic dysfunction was developed in 2009 by the American Society of Echocardiography.

2.2 Remodeling of non-obstructive coronary arteries

Data on coronary tortuosity as a component of vascular remodeling are extremely limited. A very important research observed arterial dilatation, elongation with tortuosity, and intimal hyperplasia in response to sequential exposure to low or high pshear stress(11). The low-level proinflammatory status commonly found in patients with HFpEF has been considered central to vascular remodeling and endothelial cell death, thereby inducing decreased arterial elastance and myocardial perfusion. The second mechanism incriminated is the increased sympathetic vasomotor tone that can result from the activation of the sympathetic system secondary to the inflammatory status(12).

3. Coronary artery tortuosity and cardiovascular risk factors

Smoking

There are currently no data investigating the direct correlation between CAT and smoking. Due to the complexity of the toxic compounds it brings to the human body, smoking has been identified as a predictor of any form of manifestation of myocardial ischemia, regardless of the location in the coronary tree(13).

Diabetes melitus

The only study that investigated a direct correlation between diabetes and coronary tortuosity observed a prevalence of 37%, compared to 50% in patients without coronary tortuosity(5).

Dyslipidemia

Several clinical trials that addressed the topic of coronary tortuosity and cardiovascular risk factors observed an approximately equal distribution of dyslipidemia in groups with CAT and in groups without CAT (4,5). There are conflicting data in the literature showing a correlation between elevated LDL-cholesterol levels and CAT in women(14).

Arterial hypertension

Most of the existing data in the literature identified the correlation between CAT and arterial hypertension(4,15,16). Other data in the literature even indicate the association between the degree of arterial hypertension and the severity of CAT or the fact that arterial hypertension is an independent predictor for the development of CAT(17,18).

Advanced age

Risk factors for INOCA are age, postmenopausal status, diabetes, dyslipidemia, hypertension, and left ventricular hypertrophy. Robust data in the literature identify older age as being associated with coronary artery tortuosity(19–22).

Gender differences

It is well known that coronary tortuosity is associated with the female sex(4,23–25). In between are anatomical and hormonal differences that make this conformational remodeling of the coronary tree much more common in women(26).

4. Current knowledge

For the first time, in 2007, Turgut et all. addressed the relationship between coronary tortuosity and diastolic dysfunction. He observed that patients with coronary tortuosity had lower E-wave amplitude, higher A-wave amplitude, therefore a lower E/A ratio. Patients with tortuosity also had longer early-diastolic DT (deceleration time) and IVRT (isovolumetric relaxation time) compared to patients without TAC(27).

In 2021, Elamragy et al. observed that in the CAT group, E-wave velocity and early-diastolic DT were significantly lower, while E/e' ratio, A-wave velocity, and A' were significantly higher. The E/A ratio was <1 in the CAT group and >1 in the non-CAT group(28).

The most recent analysis on this topic is done by Aslan et al. in 2022 who observed no significant difference between A and E wave amplitude, E/A ratio, or early-diastolic DT. The anterior wall E/e' ratio was significantly higher in patients with moderate-severe CAT(29).

Regarding coronary tortuosity and mortality, in the literature we only have the data of the study by Li et al that evaluated the rate of major adverse cardiovascular events and overall mortality in CAT vs non-CAT patients with or without obstructive coronary disease, after a follow-up of 2.4±0.5 years. He observed that in patients without obstructive coronary disease, the presence or absence of CAT did not influence the MACE rate or overall mortality(4).

II. Specific part- Personal contributions

5. General objectives

The overall objective is to assess the tortuosity of non-obstructive coronary arteries and the role of this conformational remodeling with impact on left ventricular relaxation function and long-term overall mortality.

In the two studies of the present work, they will pursue, as main objectives:

1. ***the tortuosity of non-obstructive coronary arteries can be interpreted as a marker of vascular remodeling, against the background of diastolic dysfunction that is very common in patients with INOCA. The study of this non-obstructive epicardial coronary remodeling provides arguments for a better understanding of the progression of INOCA patients to heart failure with preserved ejection fraction;***
2. ***the impact of coronary artery tortuosity as a vascular remodeling factor in INOCA patients on long-term global mortality;***

6. Methods

The present work is based on a retrospective, cross-sectional, unicentric cohort study, which included 328 patients with the diagnosis of INOCA presented consecutively in the cardiology department of the Clinic Colentina Bucharest hospital between January 2014 and December 2020. The diagnosis of INOCA was established based on the symptomatology suggestive of myocardial ischemia, the induction of reversible ischemia in the functional tests - the exercise ECG test and the stress echocardiography with dobutamine - for patients who presented as chronic coronary syndrome and the absence of obstructive coronary lesions at coronary angiography.

All patients signed informed consent for their inclusion in research or educational studies, including consent for coronary angiography.

Inclusion criteria:

1. evidence of inducible ischemia on exercise ECG or dobutamine stress echocardiography

2. the positivity of myocardial cytolysis enzymes without being of any other more probable cause than cardiac

3. preserved systolic function

4. lack of coronary stenoses >50%

Exclusion criteria:

1. the presence of coronary stenoses>50%

2. severe pulmonary hypertension

3. other acute non-cardiac pathology

Patient evaluation protocol

For all patients included in the study, general demographic data, medication at discharge, cardiovascular risk factors, comorbidities, medical history, electrocardiographic recordings, echocardiographic data, procedural and periprocedural data and coronary films were recorded.

For the assessment of global mortality on 31.12.2022, we used the data obtained from the National Health Insurance IT Platform.

Statistical analysis

The database was completed in Office Excel 2017. This was exported to IBM SPSS 19 and EpiInfo 2007 for statistical analysis. Descriptive statistical analyzes were performed, qualitative and quantitative variables were compared, univariate and multivariate regression analyses. For the $p<0.05$ value, statistical significance was considered.

Cohort description

The study group included 328 patients who met the criteria to be declared patients with INOCA.

It is worth mentioning in the description of the group of patients that the average age in the investigated group was 64.14±9.66 years, and the percentage of women was 60.06%. At the level of the entire group, the general mortality on 31.12.2022 was 7.31%.

The doctoral thesis is structured in two studies that evaluate in the first study the correlation between non-obstructive coronary artery tortuosity and diastolic dysfunction, and in the second study the overall mortality in patients with non-obstructive epicardial coronary artery tortuosity is investigated for a period of follow-up of 3.75±1.32 years.

Coronary anatomy assessment

Selective coronary angiography was performed according to the Judkins technique using a Siemens Artis Zee monoplane angiography system. The anterior descending artery, left circumflex artery, and right coronary artery were visualized in both caudal/cranial and right/left oblique incidences.

Classification of coronary tortuosity

The coronary artery tortuosity evaluation was based on the Eleid classification, previously described and which has the highest degree of use in coronary angiography(3).

All patients with an GIT≥3 were labeled as having coronary tortuosity. Severe coronary tortuosity was defined at an GIT≥6 or the presence of severity markers: the "corkscrew" sign, intravascular symmetry and multivascular symmetry.

Transthoracic echocardiography

Cardiac echographs were performed in the Echocardiography Laboratory of the cardiology department in 2D mode, color and pulsed Doppler and "tissue Doppler" with GE Vivid 6 Echograph, Philips. Cardiac ultrasound was performed in all 328 patients. Diastolic dysfunction according to the 2009 classification was measured in all patients.

Since left atrial dilatation is associated with diastolic dysfunction parameters, we evaluated the anteroposterior diameter of the left atrium in the apical 4 chambers, establishing a threshold value of 40 mm.

7. Study I-Coronary artery tortuosity and diastolic dysfunction

7.1 Hypothesis and specific objectives

The working hypothesis *involves the identification of a possible association between coronary tortuosity and diastolic dysfunction in patients with myocardial ischemia and non-obstructive coronary arteries,*

The entire group of 328 patients with non-obstructive epicardial coronary arteries were divided according to the presence/absence of diastolic dysfunction according to the 2009

classification, subsequently the presence of coronary tortuosity was investigated at the level of the two groups.

Specific objectives:

1. The central specific objective is to identify the tortuosity of the coronary arteries in patients with INOCA as a marker of vascular remodeling and the relationship with diastolic dysfunction, with the aim of a better understanding of the evolution of patients with INOCA towards heart failure with preserved ejection fraction;

2. identification of possible common risk indicators for coronary tortuosity and diastolic dysfunction;

3. characterization of patients with tortuous epicardial coronary arteries who, based on clinical data, functional evaluations and coronary angiography, are diagnosed with INOCA, with the aim of identifying the profile of the patient who develops this remodeling of the coronary tree;

7.2 Results

General characteristics of patients with diastolic dysfunction

Analysis of baseline characteristics of patients with diastolic dysfunction (TABLE 7-1) was stratified by coronary tortuosity. Among the 271 patients with diastolic dysfunction, 219 (80.81%) patients had coronary tortuosity, and 52 patients (19.19%) did not have coronary tortuosity. The mean age of patients with tortuous coronary arteries was 66±8.68 years, and of patients with non-tortuous epicardial coronary arteries was 62.34±9.42 years (p=0.007).

In the subgroup of patients with coronary tortuosity, two thirds of the patients were women, i.e. 145 (66.21%) women, respectively 74 (33.79%) men. In the subgroup of patients without coronary tortuosity, the reversal of the female-male ratio was observed, namely, 17 (32.69%) patients were female and 35 (67.31%) patients were male (p<0001).

TABEL 7-1 BASELINE CHARACTERISTICS OF PATIENTS WITH DIASTOLIC DYSFUNCTION

Patients with diastolic dysfunction (271 patients)			
	CAT N = 219	**Non-CAT N = 52**	p value
Age	66±8.68	62.34±9.42	0.007
Women	145 (66.21%)	17 (32.69%)	<0.0001
Men	74 (33.79%)	35 (67.31)	
Cardiovascular risk factors			
Arterial hypertension	192 (87.67%)	44 (84.62%)	0.13
Dyslipidemia	168 (76.71%)	40 (76.92%)	0.56
Prediabetes	18 (8.22%)	3 (5.77%)	0.55
Diabetes melitus	65 (29.68%)	18 (43.62%)	0.50
Active smoking	21 (9.59%)	8 (15.38%)	0.21
High cardiovascular risk	37 (16.89%)	11 (21.15%)	0.54
Coronary artery disease			
Acute coronary syndrome	97 (44.29%)	24 (46.15%)	0.87
Chronic coronary syndrome	104 (47.49%)	25 (48.08%)	0.93
Test de stres pozitiv	67 (30.59%)	14 (26.92%)	0.73
Comorbidities			
Peripheral artery disease	12 (5.48%)	5 (9.62%)	0.33
Heart failure	145 (66.21%)	35 (68.63%)	0.86
Atrial fibrillation	60 (27.52%)	14 (26.92%)	0.93
GFR<60mL/min/1.72m^2	28 (12.84%)	6 (11.54%)	0.79
Thyroid dysfunction	23 (10.50%)	6 (11.54%)	0.80
Hypothyroidism	20 (9.13%)	5 (9.62%)	0.91
Hyperthyroidism	1 (0.46%)	1 (1.92%)	0.63
N-number of patients; NYHA-New York Heart Association; GFR-glomerural filtration rate; CAT-coronary artery tortuosity;			

General characteristics of patients without diastolic dysfunction

For patients without diastolic dysfunction, the analysis of the basic characteristics was done in the same way as in the group of those with diastolic dysfunction, that is, according to coronary tortuosity (TABLE 7-2). The average age in the subgroup of patients with coronary

tortuosity is 60.55±9.72 years, and in the subgroup of patients with non-torturous coronary arteries, it is 57.14±11.47 years (p=0.27).

The distribution by gender shows as follows, 31 (72.09%) patients are women in the group of those with tortuous coronary arteries and respectively, 4 (28.57%) patients are female in the group of those with non-torturous coronary arteries. Regarding the distribution of men, we note that 12 (27.91%) of the patients were men in the group with coronary tortuosity and 10 (71.43%) patients were men in the group with non-torturous coronary arteries (p=0.003).

TABEL 7-2 BASELINE CHARACTERISTICS OF PATIENTS WITHOUT DIASTOLIC DYSFUNCTION

Patients without diastolic dysfunction (57 patients)			
	CAT N = 43	**Non-CAT N = 14**	p value
Age	60.55±9.72	57.14±11.47	0.27
Women	31 (72.09%)	4 (28.57%)	0.003
Men	12 (27.91%)	10 (71.43%)	
Cardiovascular risk factors			
Arterial hypertension	31 (72.09%)	10 (71.43%)	0.96
Hypercholesterolemia	31 (72.09%)	11 (78.57%)	0.73
Prediabetes	3 (6.98%)	5 (35.71%)	0.02
Diabetes melitus	7 (16.28%)	2 (14.29%)	0.86
Active smoking	7 (16.28%)	1 (7.14%)	0.66
High cardiovascular risk	7 (16.28%)	2 (14.29%)	0.86
Coronary artery disease			
Acute coronary syndrome	11 (25.58%)	6 (42.85%)	0.31
Chronic coronary syndrome	30 (69.77%)	8 (57.14%)	0.51
Positive stress test	23 (53.49%)	6 (42.86%)	0.54
Comorbidities			
Peripheral artery disease	5 (11.63%)	0 (0.0%)	0.98
Heart failure	3 (6.98%)	1 (7.14%)	0.86
Atrial fibrillation	2 (4.65%)	2 (14.29%)	0.25
GFR<60mL/min/1.72m^2	4 (9.3%)	0 (0.0%)	0.56
Thyroid dysfunction	7 (16.28%)	0 (0.0%)	0.17
Hypothyroidism	7 (16.28%)	0 (0.0%)	0.17
Hyperthyroidism	0 (0.0%)	0 (0.0%)	1

N-number of patients; NYHA-New York Heart Association; GFR-glomerural filtration rate; CAT-coronary artery tortuosity;

Distribution of severity of coronary tortuosity

For all three main epicardial coronary arteries, the tortuosity score was calculated (TABLE 7-3). Severe tortuosity score was present for LCx in 14% of patients, 8.8% of patients at LAD level and 7.3% of patients at RCA level. It can be concluded that the most tortuous epicardial vessel is LCx, followed by LAD and then RCA.

TABEL 7-3 CORONARY ARTERY TORTUOSITY DISTRIBUTION

Lot-wide tortuosity distribution					
	Score 0	Score 1	Score 2	Score 3	Total
LAD	68(20.73%)	112(34.15%)	119(36.28%)	29(8.84%%)	328 (100%)
LCx	42(12.80%)	98(29.88%)	142 (43.29%)	496(14.02%)	328 (100%)
RCA	72(21.95%)	140(42.68%)	92(28.05%)	24 (7.32%)	328 (100%)

Epicardial coronary artery tortuosity and diastolic dysfunction

The presence of diastolic dysfunction according to the 2009 classification was correlated with the tortuosity of all three coronary arteries calculated individually, as well as with the global tortuosity index. Statistical significance was achieved only for the correlation between LAD, LCx, and global index of tortuosity score (FIGURE 7-1).

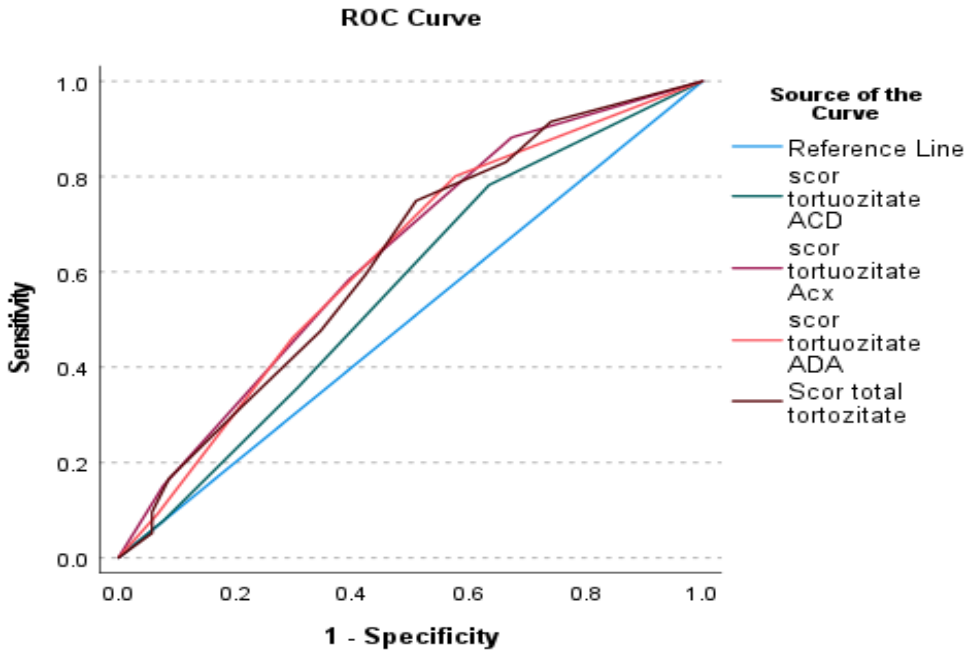


FIGURA 7-1 DIASTOLIC DYSFUNCTION AND CORONARY ARTERY TORTUOSITY

TABEL 7-4 ROC CURVE PARAMETERS FOR CORONARY ARTERY TORTUOSITY AND DIASTOLIC DYSFUNCTION

	AUC	95% CI	p value
LAD tortuosity score	0.624	0.559-0.689	<0.0001
LCx tortuosity score	0.634	0.570-0.699	<0.0001
RCA tortuosity score	0.565	0.498-0.632	0.057
Global tortuosity index	0.625	0.560-0.691	<0.0001

Grade I diastolic dysfunction (delayed relaxation) correlates statistically significantly with LAD tortuosity and global tortuosity index. The lack of statistical association with the tortuosity score of LCx and RCA is noted (FIGURE 7-2).

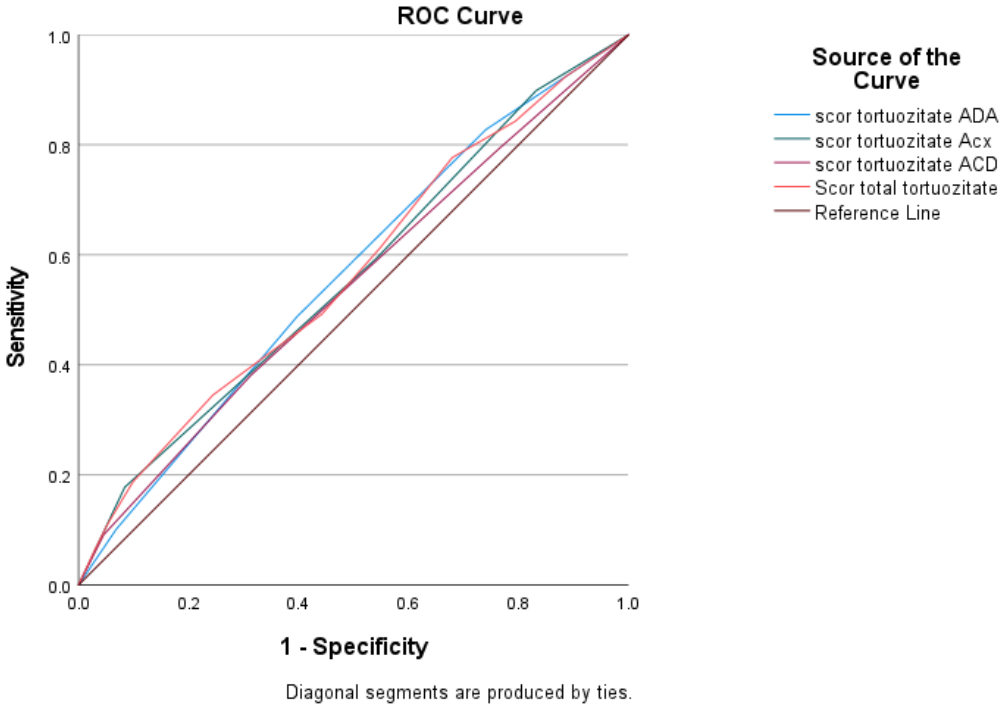


FIGURA 7-2 GRADE I DIASTOLIC DYSFUNCTION AND CORONARY ARTERY TORTUOSITY

TABEL 7-5 ROC CURVE PARAMETERS FOR CORONARY ARTERY TORTUOSITY AND GRADE I DIASTOLIC DYSFUNCTION

	AUC	95% CI	valoare p
LAD tortuosity score	0.563	0.500-0.627	0.05
LCx tortuosity score	0.560	0.497-0.623	0.06
RCA tortuosity score	0.541	0.478-0.604	0.20
Global tortuosity index	0.565	0.502-0.628	0.04

Stress tests and coronary tortuosity

In the subgroup of patients with chronic coronary syndrome, 110 of these patients had positive stress tests (ECG or dobutamine ultrasound). Statistically significant association was observed between positive stress tests and LAD tortuosity, LCx, and global tortuosity index (FIGURE 7-3).

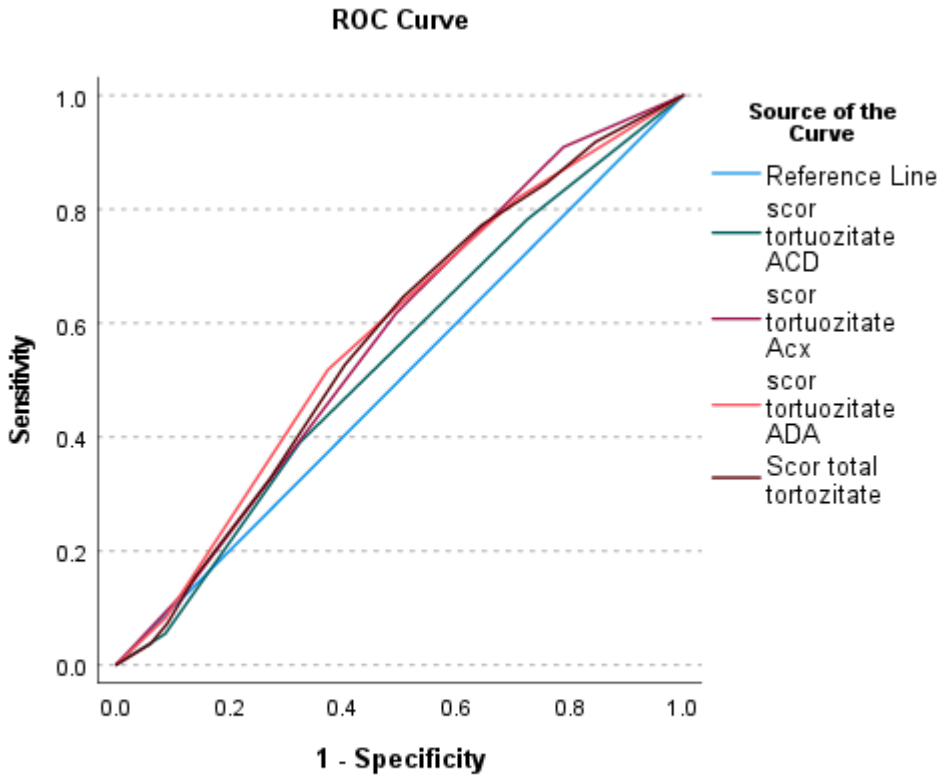


FIGURA 7-3 POSITIVE STRESS TESTS AND CORONARY ARTERY TORTUOSITY

TABEL 7-6 ROC CURVE PARAMETERS FOR POSITIVE STRESS TESTS AND CORONARY ARTERY TORTUOSITY

	AUC	95% CI	valoare p
LAD tortuosity score	0.579	0.517-0.641	0.01
LCx tortuosity score	0.573	0.512-0.634	0.01
RCA tortuosity score	0.535	0.472-0.598	0.27
Global tortuosity index	0.572	0.510-0.633	0.02

Chronic kidney disease and coronary tortuosity

There is a statistically significant association between the tortuosity scores for LCx and the global tortuosity index, with the presence of chronic renal failure (FIGURE 7-4).

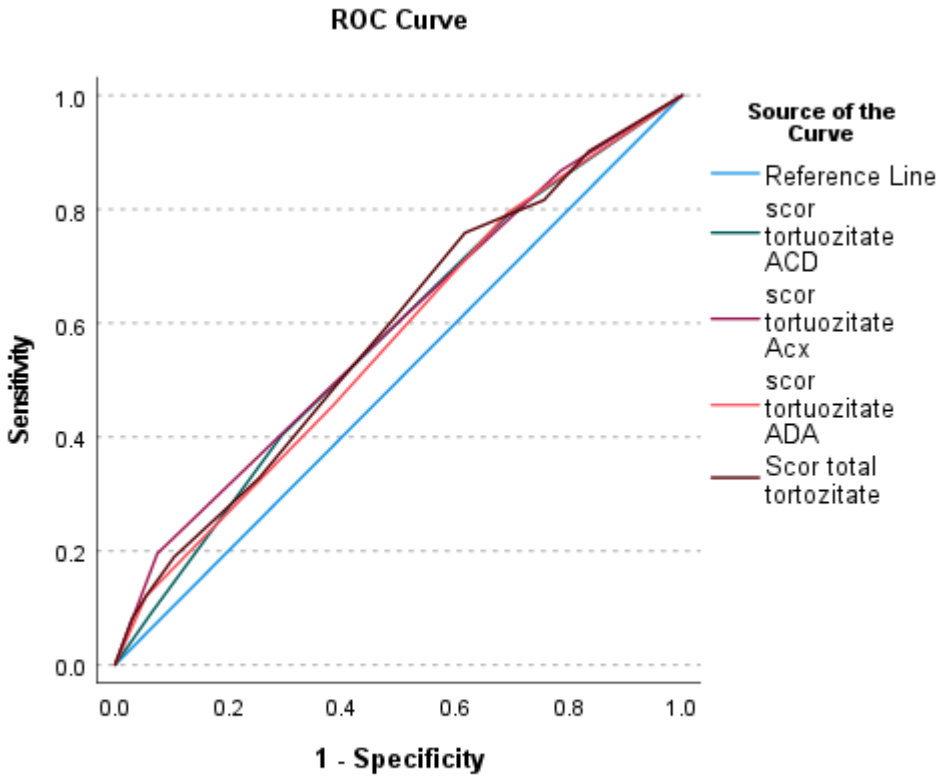


FIGURA 7-4 CHRONIC RENAL DISEASE AND CORONARY ARTERY TORTUOSITY

TABEL 7-7 ROC CURVE PARAMETERS FOR CHRONIC RENAL DISEASE AND CORONARY ARTERY TORTUOSITY

	AUC	95% CI	valoare p
LAD tortuosity score	0.567	0.509-0.625	0.24
LCx tortuosity score	0.587	0.529-0.645	0.03
RCA tortuosity score	0.572	0.515-0.630	0.14
Global tortuosity index	0.581	0.524-0.639	0.006

Hypothyroidism and coronary tortuosity

A statistically significant association is observed between ACx tortuosity and hypothyroidism. There is no association between hypothyroidism and LAD tortuosity, RCA, and global tortuosity index (FIGURE 7-5).

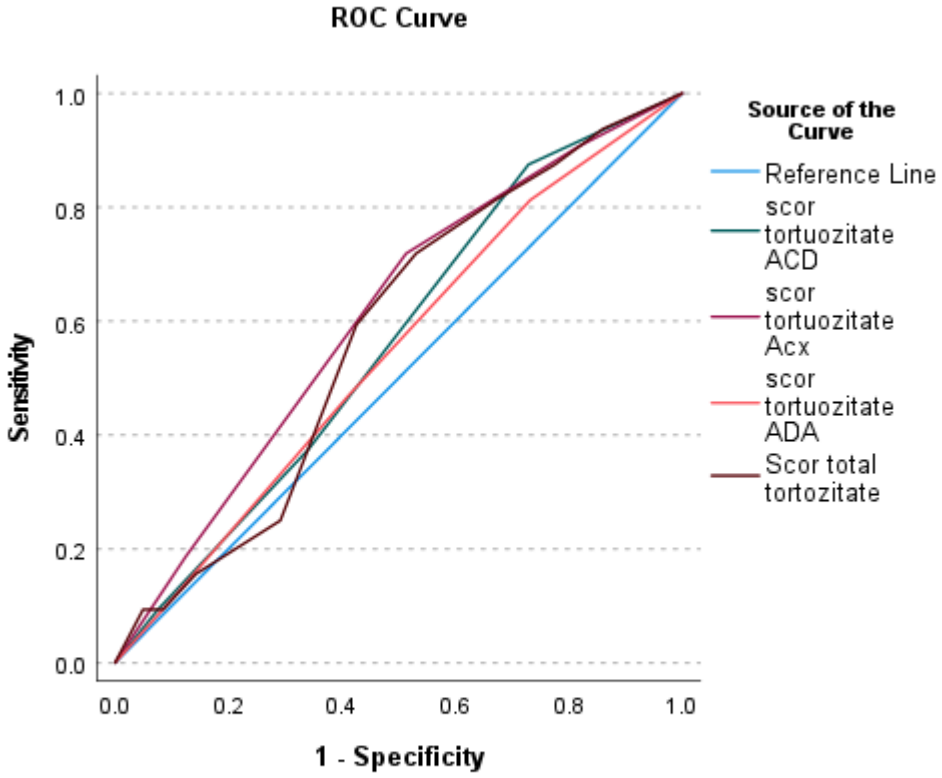


FIGURA 7-5 HYPOTHYROIDISM AND CORONARY ARTERY TORTUOSITY

TABEL 7-8 ROC CURVE PARAMETERS FOR HYPOTHYROIDISM AND CORONARY ARTERY TORTUOSITY

	AUC	95% CI	valoare p
LAD tortuosity score	0.544	0.444-0.645	0.38
LCx tortuosity score	0.609	0.511-0.706	0.02
RCA tortuosity score	0.562	0.467-0.657	0.20
Global tortuosity index	0.576	0.483-0.669	0.10

Arterial hypertension and coronary tortuosity

Statistically significant association is observed for each tortuosity score, including the global tortuosity index and arterial hypertension, except for the correlation with ACD tortuosity where statistical significance was not achieved (FIGURE 7-6).

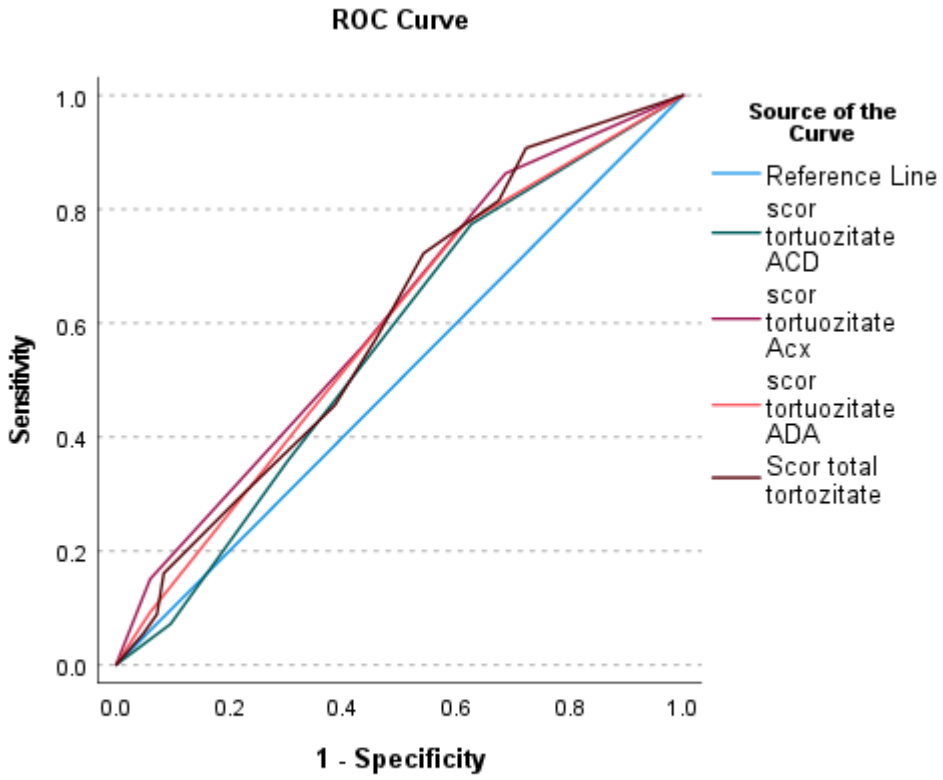


FIGURA 7-6 HYPERTENSION AND CORONARY TORTUOSITY

TABEL 7-9 ROC CURVE PARAMETERS FOR HYPERTENSION AND CORONARY ARTERY TORTUOSITY

	AUC	95% CI	valoare p
LAD tortuosity score	0.586	0.515-0.657	0.017
LCx tortuosity score	0.609	0.539-0.678	0.002
RCA tortuosity score	0.562	0.489-0.636	0.098
Global tortuosity index	0.597	0.524-0.670	0.009

Diastolic dysfunction present/absent

Age

271 patients with diastolic dysfunction and 57 patients with normal diastolic function were identified. An older age of patients with CAT is observed regardless of the presence or absence of diastolic dysfunction (TABLE 7-10).

TABEL 7-10 AGE RELATED TO DIASTOLIC DYSFUNCTION AND CORONARY ARTERY TORTUOSITY

		CAT	Non-CAT	
		N=219 (80.81%)	N=52 (19.19%)	p value
Diastolic dysfunction (271 patients)	Age	66±8.68	62.34±9.42	0.007
		N=43 (75.43%)	N=14 (24.57%)	p value
Normal diastolic function (57 patients)	Age	60.55±9.72	57.14±11.4	0.279

Gender of patients

Among the 271 patients with diastolic dysfunction, 162 (59.77%) are women and 109 (40.23%) are men. ($p<0.0001$). In the group of women with diastolic dysfunction, the results were almost similar to the group without diastolic dysfunction, 31 (88.57%) patients have coronary tortuosity, and in 4 (11.43%) patients, the absence of coronary tortuosity was found (TABLE 7-11).

TABEL 7-11 GENDER RELATED TO DIASTOLIC DYSFUNCTION AND CORONARY ARTERY TORTUOSITY

			CAT	Non-CAT	
			N=219	N=52	p value
Diastolic dysfunction (271 patients)	Gender	Female N= 162	145 (89.51%)	17 (10.49%)	<0.0001
		Male N= 109	74 (67.89%)	35 (32.11%)	
			N=43	N=14	p value
Normal diastolic function (57 patients)	Gender	Female N=35	31 (88.57%)	4 (11.43%)	0.009
		Male N=22	12 (54.55%)	10 (45.45%)	

Hypertension

In the group of hypertensives with diastolic dysfunction it was observed that coronary tortuosity is four times more frequent, thus, 192 (81.36%) of the patients have CAT, compared to 44 (18.64%) hypertensive patients who have non-torturous coronary arteries. In normotensive patients with present diastolic dysfunction, it is found that 27 (77.14%) patients have CAT, and 8 (22.86%) patients do not have CAT (p=0.64).

An approximately similar prevalence of coronary tortuosity is found among hypertensive patients, regardless of the presence or absence of diastolic dysfunction. (TABLE 7-12) (p=0.96).

TABEL 7-12 HYPERTENSION RELATED TO DIASTOLIC DYSFUNCTION AND CORONARY ARTERY TORTUOSITY

			CAT	Non-CAT	
			N=219	N=52	p value
Diastolic dysfunction (271 patients)	Hypertension	Da N= 236	192 (81.36%)	44 (18.64%)	0.64
		Nu N= 35	27 (77.14%)	8 (22.86%)	
			N=43	N=14	p value
Normal diastolic function (57 patients)	Hypertension	Da N=41	31 (75.61%)	10 (24.39%)	0.96
		Nu N=16	12 (75%)	4 (25%)	

8. Study II-Coronary artery tortuosity and general mortality

8.1 Hypothesis and specific objectives

The working hypothesis is that non-obstructive epicardial coronary artery tortuosity can be used as a prognostic marker for long-term overall mortality.

Specific objectives:

1. The primary specific objective is long-term overall mortality in patients with non-obstructive tortuous coronary arteries, with the aim of better understanding from a clinical point of view the role of this conformational remodeling;

2. identification of independent predictors of general mortality in TAC patients;

3. Identification of the clinical profile of the patient with tortuous coronary arteries and its role on general mortality;

8.2 Results

Severity of coronary tortuosity

Coronary tortuosity severity based on GTI≥6, intravascular symmetry, and multivessel symmetry was present in approximately 40% of the 262 patients with tortuous coronary arteries. The "corkscrew" sign was present only in 43 (16.41%) patients out of 262 TAC patients (TABLE 8-1).

TABEL 8-1 CORONARY ARTERY TORTUOSITY SEVERITY

	N=262 patients
Global tortuosity index ≥ 6	100 (38.17%)
Multivascular symmetry	105 (40.08%)
Univascular symmetry	116 (44.27%)
Corkscrew sign	43 (16.41%)

Determinants of overall mortality in TAC patients

The monitoring period spanned a period of 3.75±1.32 years. In the entire group of INOCA patients, CAT was inversely correlated with overall mortality (OR 0.35, 95%CI 0.16 – 0.77, p = 0.01).

TABEL 8-2 UNIVARIATE ANALYZE OF GENERAL MORTALITY PREDICTORS IN PATIENTS WITH CORONARY TORTUOSITY

Cardiovascular risk factors		
	OR (95% CI)	p value
Arterial hypertension	3.33 (0.43 – 25.74)	0.37
Grade III hypertension	1.91 (0.70 – 5.20)	0.29
Left ventricular hypertrophy	1.54 (0.56 – 4.24)	0.57
Hypercholesterolemia	6.16 (0.80 – 47.15)	0.08
Diabetes melitus	5.22 (1.96 – 13.88)	<0.001
Active smoking	1.63 (0.44 – 6.00)	0.71
Quit smoking	0.69 (0.08 – 5.50)	1.00
Clinical presentation		
ACS	1.04 (0.40 – 2.67)	1
Unstable angina	1.02 (0.39 – 2.70)	1
NSTEMI	1.63 (0.19 – 13.77)	1
CCS	0.53 (0.20 – 1.39)	0.29
Positive stress test	0.09 (0.01 – 0.73)	0.01
Comorbidities		
Peripheral artery disease	0.78 (0.09 – 6.28)	1
Heart failure	3.1 (1.004 – 9.61)	0.04
III/IV NYHA class Heart Failure	4.72 (1.37 – 16.24)	0.03
Atrial fibrillation	4.05 (1.56 – 10.51)	0.005
GFR<60 mL/min/1.73m^2	3.83 (1.34 – 10.95)	0.02
Renal chronic disease	1.64 (0.62 – 4.32)	0.43
Thyroid dysfunction	0.41 (0.05 – 3.18)	0.61
Hypothyroidism	0.46 (0.05 – 3.61)	0.71
Correction indicated valvopathy	3.33 (1.001 – 11.09)	0.04

NSTEMI-non-ST elevation myocardial infarction; NYHA-New York Heart Association; GFR-glomerural filtration rate; ACS-acute coronary syndrome; CCS-chronic coronary syndrome;

Analysis of cardiovascular risk factors and their impact on overall mortality in the subgroup of patients with CAT demonstrated that they are associated with an increased risk of mortality. In the case of diabetes, a statistically significant association with overall mortality was observed.

Heart failure of any severity, heart failure class III/IV, chronic kidney disease of any grade but also severe, as well as severe valvulopathy requiring surgical sanction showed an association with increased overall mortality in patients with TAC.

Conversely, for chronic coronary syndromes and positive stress tests (ECG and stress ultrasound), an inverse correlation with overall mortality was observed, with high statistical significance (TABLE 8-2).

Severity of coronary tortuosity and long-term overall mortality

TABEL 8-3 IMPACT OF CORONARY ARTERY TORTUOSITY SEVERITY ON GENERAL MORTALITY

	OR (95% CI)	p value
Corkscrew sign	0.57 (0.12 – 2.60)	0.69
Intravascular symmetry	0.90 (0.35 – 2.33)	1
Multivascular symmetry	1.09 (0.42 – 2.82)	1
GTI≥6	0.94 (0.35 – 2.47)	1
GTI	0.491 (0.365 – 0.617)	0.89

GTI-global tortuosity index ;

Analysis of ROC curves to assess survival by severity of coronary tortuosity showed that GTI≥6, univascular symmetry, and corkscrew sign were associated with increased survival, without reaching statistical significance (TABLE 8-3).

Multivariate analysis of predictors of overall mortality in patients with TAC

The final multivariate analysis showed that NT-proBNP value and diabetes mellitus were the strongest independent predictors of overall mortality in this subgroup of patients, with a statistically significant association for these two predictors. (TABLE 8-4).

TABEL 8-4 INDEPENDENT PREDICTORS FOR GENERAL MORTALITY IN PATIENTS WITH CORONARY ARTERY TORTUOSITY

	HR (95%CI)	P valup
Multivariate regression nr.1 – heart failure		
Log_{10}NT-proBNP	3.96 (1.34 – 11.68)	0.01
Heart failure	0.79 (0.37 – 1.69)	0.54
NYHA class	2.57 (0.33 – 20.01)	0.37
Multivariate regression nr. 2 – Cardiac/non-cardiac comorbidities		
Diabetes melitus	4.76 (1.69 – 13.38)	0.003
Atrial fibrillation	2.68 (0.96 – 7.47)	0.06
Correction indicated valvopathy	0.32 (0.08 – 1.24)	0.09
GFR<60ml/min	2.27 (0.71 – 7.32)	0.17
Multivariate regression nr. 3 – Final independent predictors of overall mortality		
Log_{10}NT-proBNP	3.18 (1.06 – 9.56)	0.04
Diabetes mellitus	7.68 (2.29 – 25.74)	0.001
Atrial fibrillation	1.74 (0.50 – 6.00)	0.38

Log_{10}NT-proBNP -logarithmic transformation in the base of 10 of B-type natriuretic peptide; NYHA-New York Heart Association; GFR-glomerural filtration rate;

9. Conclusion and personal contributions

Study I

Conclusions

- coronary tortuosity was associated with grade I diastolic dysfunction according to the 2009 classification.
- we observed that age, female gender and hypertension have a different predictive value for the association between non-obstructive coronary artery tortuosity and diastolic dysfunction.

- regarding the clinical profile of the INOCA patient with tortuous coronary arteries, we noticed that the tortuosity of the LAD and LCx is associated with the presentation as chronic coronary syndrome.
- there is an inverse correlation between individually assessed coronary tortuosity and peripheral arterial disease.
- we observed that epicardial coronary artery tortuosity assessed separately for each major artery and by the global tortuosity index correlated statistically significantly with hypothyroidism.
- chronic renal disease is statistically significantly associated with LCx tortuosity and global tortuosity.
- we observed that arterial hypertension correlates highly statistically with the tortuosity of each main epicardial coronary artery.
- hypercholesterolemia was statistically significantly associated with LAD and LCx tortuosity.
- positive stress tests (exercise ECG test and dobutamine stress ultrasound) had a positive, highly statistically significant correlation with coronary tortuosity.

Personal contributions

Data from the literature are very limited when we talk about the correlation between epicardial coronary tortuosity and ventricular relaxation function. To our knowledge it is among the very few studies investigating the relationship between diastolic dysfunction and coronary tortuosity.

It is the first analysis to evaluate epicardial coronary tortuosity assessed for each major epicardial artery according to classic cardiovascular risk factors and the most frequently encountered cardiac and non-cardiac comorbidities in daily practice.

The current study identifies age, female sex, and hypertension as possible common risk indicators for coronary tortuosity and diastolic dysfunction, but whether the association of the two in elderly, hypertensive, and female patients is causal or merely coincidental is unknown.

Study II

Conclusions

• the main conclusion is that coronary tortuosity in patients with INOCA was inversely correlated with all-cause mortality.

• the severity of coronary tortuosity had no influence on the prognosis.

• in patients with tortuous coronary arteries, NYHA class III/IV, chronic kidney disease and valvulopathy with indication for surgical correction correlate with increased overall mortality.

• positive stress tests, either ECG or stress echocardiography, had a highly statistically significant inverse correlation with overall mortality.

• NT-proBNP value, diabetes mellitus, NYHA class, severe chronic kidney disease and atrial fibrillation correlate with overall mortality in INOCA patients with coronary artery tortuosity.

• NT-proBNP value and diabetes were statistically significantly associated with long-term overall mortality, being confirmed as independent predictors of overall mortality regardless of coronary tortuosity.

Personal contributions

This is the first national study to investigate overall mortality in INOCA patients with epicardial tortuous coronary arteries and to identify independent predictors for it. In our study the presence of coronary tortuosity in patients with ischemia and non-obstructive epicardial coronary arteries was inversely correlated with overall mortality in a statistically significant manner.

The present study is the first to identify predictors of overall mortality in INOCA patients with coronary tortuosity. The obtained results showed that the value of NT-proBNP and diabetes mellitus are statistically significantly associated with overall mortality in INOCA patients with tortuous epicardial coronary arteries.

Limits of research

• the retrospective nature of the studies does not allow identifying the type of relationship between coronary tortuosity and diastolic dysfunction. The same shortcoming applies to the relationship between coronary tortuosity and overall mortality.

• follow-up of patients over a longer period of time would have been beneficial to identify the type of relationship between coronary artery tortuosity and overall mortality.

• lack of measurement of some ultrasound parameters of diastolic dysfunction that are not influenced by age, may be a bias for the assessment of diastolic function in the elderly.

General conclusions

Epicardial coronary artery tortuosity in patients with INOCA is a common coronary remodeling, but whose role is not clearly established. The typical profile of this patient is represented by elderly women, often hypertensive. In our analysis we observed the association between coronary tortuosity and diastolic dysfunction in patients with INOCA, but the nature of the relationship between the two is not clearly identified, it could be causal or coincidental against a common cause.

In our work we observed statistically significant inverse correlation between coronary tortuosity and long-term overall mortality in patients with INOCA. On the one hand, this relationship may be purely associative, but on the other hand, it may change the perspective on coronary tortuosity as an adaptive phenomenon in the evolution of INOCA patients.

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