Journal of Society Medicine
Research & Review Articles on Diseases
Journal of Society Medicine. 2023; 2(9)

The Relationship between Transient Ischemic Dilation (TID) and Severity of Coronary Artery Disease (CAD) in Patients with Chronic Coronary Syndrome (CCS) in Haji Adam Malik Medan, Indonesia

Ratna Mariana Tamba[1]*, Hilfan Ade Putra Lubis[2], Zulfikri Mukhtar[2], Andika Sitepu[2], Faisal Habib[2], Cut Aryfa Andra[2], T. Bob Haykal[2]

[1] *Cardiology and Vascular Resident, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia / Haji Adam Malik General Hospital, Medan, Indonesia*
[2] *Cardiologist, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia / Haji Adam Malik General Hospital, Medan, Indonesia*

***Corresponding Author**: Ratna Mariana Tamba, E-mail: ratnatamba82@gmail.com

ARTICLE INFO

Article history:
Received
12 July 2023

Revised
17 September 2023

Accepted
30 September 2023

Manuscript ID:
JSOCMED-120723-29-4

Checked for Plagiarism: Yes

Language Editor:
Rebecca

Editor-Chief:
Prof. Aznan Lelo, PhD

ABSTRACT

Introduction: TID ratio derived from ratio of LV volume in stress and rest phase of MPS. It is said that this phenomenon has been a useful marker of severe CAD, that can be present with atypical angina. This occurs due to global myocardial hypoperfusion caused by severe and extensive CAD.

Method: This study was an analytic observational study with a retrospective cohort design in CCS patients who underwent Myocardial Perfusion SPECT at Haji Adam Malik General Hospital from January 2022 to April 2023. All participants underwent MPS with Tc99m sestamibi with pharmacology Adenosine stress test and coronary angiography. The MPS could be performed before or after coronary angiography without any revascularization procedure between the two examination preocedures. An unpaired t-test analysis was performed to find the mean difference in TID values in the mild CAD and moderate-severe CAD groups.

Results: The study subjects totaled 93 people with an average age of 55.87±7.44. It was found that the TID value was significantly different between the two groups of mild and moderate-severe CAD based on Syntax score, 0.906±0.13 vs 1.03±0.11 in the mild vs moderate-severe CAD group ($p<0.001$). Bivariate analysis showed that in this study, the ratio of TID was only associate with LV ESV and LV EDV in stress phase of MPS ($p = 0.001$).

Conclusion: There is a relationship between TID and CAD severity based on Syntax score with higher TID values in patients with moderate-severe CAD compared to patients with mild CAD. TID ratio was only depends on severity od CAD and directly proportional to the volume of LV in the stress phase, suitable to the theory that said TID ratio comes from ratio of LV volume in stress and rest phase of MPS.

Keywords

Chronic coronary syndrome, Coronary artery disease, Severity of CAD, Syntax score, Transient ischemic dilation

How to cite: Tamba RM, Lubis HAP, Mukhtar Z, Sitepu A, Habib F, Andra CA. et al. The Relationship between Transient Ischemic Dilation (TID) and Severity of Coronary Artery Disease (CAD) in Patients with Chronic Coronary Syndrome (CCS) in Haji Adam Malik Medan, Indonesia. *Journal of Society Medicine*. 2023; 2(9): 307-313. **DOI: https://doi.org/10.47353/jsocmed.v2i9.88**

INTRODUCTION

Coronary artery disease (CAD) is considered a major public health problem due to the high mortality rates. It has a long period of stable (chronic coronary syndrome), but can be progressive due to plaque rupture (acute coronary syndrome). In the stable condition, it can present as atypical angina, especially in patients with multivessel disease (MVD), that result in delayed of diagnosis and treatment, and worse prognosis.[1,2]

Coronary angiography is definite procedure giving us information about diagnosis and severity of CAD. But this invasive procedure has conditions that not allowed to be undergo in some patients. Another noninvasive procedure to predict the severity of CAD, especially in extensive lesion is Transient Ischemic Dilation (TID). TID is a phenomenon in which LV volume becomes larger on Myocardial Perfussion SPECT (MPS) imaging after stress than at rest. TID ratio derived from ratio of LV volume in stress and rest phase of MPS. It is said that this phenomenon has been a useful marker of severe CAD. This phenomenon occurs due to global myocardial hypoperfusion caused by severe and extensive CAD. Studies has been shown that the more severe the CAD, the higher TID is.[1-4]

TID as a predictor of severity of CAD has been studied for more than 10 years, but most of them classify the severity od CAD based percentage and location of stenosis of coronary artery, as Mazzanti said in his previous studies. To our knowledge, there is no study about association between TID and severity of CAD in North Sumatera. In this study, we also we want to classify the severity of CAD not only by its location and percentage of stenosis, but also by complexity of the lesions. The Syntax score (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery), is a useful scoring system that has been developed to assess the eseverity and complexity of CAD in order to determine the approprite revascularization strategy.[2-5] The aim of this study was to evaluate the association between TID and severity of CAD based on Syntax score that has not been studied or published before.

METHOD

We reviewed 128 patients with CCS who underwent MPS in Haji Adam Malik Hospital (Medan, Indonesia) from January 2022 to April 2023. A total of 35 patients were excluded from the study. Exclusion criteria were as follows: patient that do not undergo coronary angiography, patients undergoing coronary revascularization before undergo MPS, patients with significant valvular heart disease or cardiomyopathy, patients with malignant arrythmias or malignant hypertension, patient in acute myocardial infarction, and patients with inconclusive data from medical records. Thus, the remaining 93 (73%) patients comprised the study population. The patients were stratified into 2 groups according to Syntax score; mild CAD (Syntax score $<$ 23) and moderate-severe CAD (Syntax score $\geqslant$ 23). All data were conducted from medical records after the study protocol has been approved by University of Sumatera Utara ethical review board.

The procedure of Myocardial perfusion SPECT (MPS) was conducted by following the standart protocol of medical service of Nuclear Medicine Unit in Haji Adam Malik Hospital. All patients were asked to fast for at least 8 hours, not consuming any beta-blocker, nitrate, calcium channel blocker, xanthine, or caffeine for at least 24 hours before the procedure. The procedure was conducted in one day, and started with rest phase. A total of 10 mCI of Technetium-99m (Tc-99m) sestamibi was injected intravenously and the after 30 minutes later, a projection of SPECT imaging was acquired with gamma camera Bright View X-CT Tipe 453560824741 (Phillips Medical System). Scintillation camera with 2 detectors with 64 projection (25 seconds/projection) with 64x64 matrix, orbit 180o and 90o angle will reconstruct the images using AutoSPECT. After resting for 2-3 hours, pharmacological stress test was conducted by injecting adenosin 140 mcg/kg/minutes intravenously for 6 minutes. After 3 minutes from adenosine injection, a total of 20-30 mCI Tc-99m sestamibi was injected intravenously and the images was projected in 30-60 minutes after injection. Data were reconstructed by tomographic section projections of short-axis and long-axis vertical/horizontal views (bullseye plot).6,7 The hemodynamic of the patients during procedure were observed continously. TID, myocardial perfusion data, left ventricular volume measurements and left ventricular ejection fraction were performed using the AutoQuant (QPS, Cedars-Sinai software). If the reconstruction and reorientation of boundaries and axes did not show good results automatically, then it will be done manually.

Syntax score was calculated for all coronary lesion with a diametes stenosis gretaer than 50% in the artery larger than 1.5 mm.2,8 For the calculation, the software on the website (http://syntaxscore.com) was used. The syntax score was evaluated separately by 2 interventional cardiologists based in Haji Adam Malik Hospital blonded to the study protocol and patient characteristics. Low Syntax score (0-22) will be clasifying

as mild CAD intermediate or high Syntax score (>22) will be classifying as moderate-severe CAD, based on ESC Guideline 2018. When disagreement existed, a senior investigator was consented and a final decision was made by consensus. All coronary angiographic procedures were performed by experinced interventional cardiologist using a femoral/radial approach.

Baseline demographic and clinical characteristics, previous history, and medications of patients, were obtained from hospital records or by interviewing the patients on the spot or by contacing the phone number registered in medical record. The hemodynamic were obtained from hospital records. Blood chemistry for glucose, creatinine, and low-density lipoprotein (LDL) and complete blood count were measured in all patients on admission.

Continuous variables are expressed as mean ± standard deviation or median (interquartile range) and categorical variables are expressed as number (percentage). Group means for continuous variables were compared using independent t-test analysis. Categorical variables were compared using chi-square. Correlation between continuous variabels were analyzed using Pearson correlation or Spearman correlation. Significant results were determined at p values <0.05 levels.

RESULT

In this single-center study, 93 patients were divided into two categories according to syntax scores, with 55 patients in moderate-severe group and 38 patients in mild CAD group. Baseline characteristics are shown in Table 1. There are 55 patients having Syntax score 0-22 and clasified to moderate-severe CAD group, and 38 patients having Syntax score > 22 are clasified to mild CAD group. Age, sex, medical history of diabetes mellitus, hypertension, prior AMI, prior PCI/CABG, blood sugar, and hemodynamic were comparable among the groups. There were significant differences among the groups with respect to current smoking, creatinine, and LDL. Additionally, all previous medication were comparable among the groups except for ACE-I/ARB that more commonly consumed in mild CAD groups.

Table 1. Baseline demographic and clinical characteristics of patients and comparisons between moderate-severe and mild CAD

Variables	Total (N=93)	Moderate-Severe CAD (N=55)	Mild CAD (N=38)	P value
Age (years old)	55,87±7,44	54,73±7,93	57,53±6,42	0,75
Male gender	82 (88,2)	49 (59,8)	33 (40,2)	0,741
Diabetes Mellitus	43 (46.2)	25 (45,5)	18 (47,4)	0,856
Hypertension	41 (44,1)	25 (45,5)	16 (42,1)	0,749
Current smoking	83 (89.2)	52 (94,5)	31 (81,6)	0,047
Prior AMI	33 (35.5)	20 (36,4)	13 (34,2)	0,831
Prior PCI/CABG	15 (16.1)	10 (18,2)	5 (13,2)	0,517
SBP, mmHg	113 (100-130)	115 (100-130)	111 (100-130)	0,833
DBP, mmHg	70 (62,5-80)	70 (62-80)	70 (62,5-80)	0,888
Heart rate, bpm	76,82±12,65	75,76±12,86	78,34±12,33	0,337
Creatinine, mg/dl	1,06 (0,9-1,49)	1,17 (0,96-1,6)	1,01 (0,86-1,2)	0,017
LDL, mg/dl	106 (95-123,5)	101 (88-119)	120 (98-132,8)	0,006
Glucose, mg/dl	122 (98,5-174,5)	108 (93-169)	134 (108-179)	0,058
Previous medication				
Aspirin	81 (87.1)	47 (85,5)	34 (89,5)	0,570
Statin	90 (96.8)	53 (96,4)	37 (97,4)	0,787
Beta-blocker	84 (90.3)	48 (87,3)	36 (94,7)	0,231
ACE-I/ARB	77 (82.8)	42 (76,4)	35 (92,1)	0,048
CCB	10 (10.8)	6 (10,9)	4 (10,5)	0,953
Insulin	20 (21.5)	10 (18,2)	10 (26,3)	0,348
Furosemide	69 (74.2)	38 (69,1)	31 (81,6)	0,178

Angiographic and MPS characteristics are shown in Table 2. Moderate-severe CAD group was dominated by 3VD and mild CAD group was dominated by 2VD, followed by 1VD (p <0.001). From the table, we can say that there were increasing rates of culprit lesion and multivessel disease in moderate-severe group. Based on MPS data, moderate-severe CAD group with higher Syntax score has higher TID ratio (1,03±0,11) than TID in mild CAD group (0,906±0,13) (p <0.001). Surprisingly, the value of ischemic burden (p 0.342) and total perfusion defect (p 0.247) between the two group was not significantly different. LV volume in the end phase of systolic and dyastolic, in both stress and rest phase was larger in the moderate-severe group (p <0.001). This finding was appropriate to the lower ejection fraction of the moderate-severe group (p <0.001). In perfusion score, both summed stress score (SSS) and summed rest score (SRS) were significantly higer in the moderate-severe group (p <0.005), but summed difference score (SDS) were comparable between group (p >0.005). We can say that TID is related to severity of CAD based on Syntax score.

Table 2. Angiographic and Myocardial Perfusion SPECT data and comparisons between moderate-severe and mild CAD

Variables	Total (N=93)	Moderate-Severe CAD (N=55)	Mild CAD (N=38)	P value
No. of vessel involved	2,41±0,81	2,82±0,39	1,82±0,90	<0,001
1 VD	10 (10,8%)	0	10 (26,3%)	
2 VD	26 (28%)	10 (18,2%)	16 (42,1%)	
3 VD	54 (58,1%)	45 (81,8%)	9 (23,7%)	
Infarcted-related artery				
LM	21(22,6%)	18 (32,7%)	3 (7,9%)	0,005
LAD	58 (62,4%)	39 (70,9%)	19 (50%)	0,041
LCx	71 (76,3%)	49 (89,1%)	22 (57,9%)	0,001
RCA	71 (76,3%)	53 (96,4%)	18 (47,4%)	<0,001
TID	0,98±0,14	1,03±0,11	0,906±0,13	<0,001
Ischemic Burden (%)	3,0 (2-8)	4 (2-9)	3 (2-6,5)	0,342
LV ESV (stress) (ml)	116 (64,5-180,5)	159 (93-201)	65,5 (41,8-108,5)	<0,001
LV EDV (stress) (ml)	158 (109,5-224,5)	200 (127-248)	119 (85-149,3)	<0,001
LV ESV (rest) (ml)	111 (70,5-188,5)	158 (910206)	77,5 (47,8-111,3)	<0,001
LV EDV (rest) (ml)	183 (117-238)	206,64±72,96	146±77,59	<0,001
Perfusion Score of LV				
SSS (%)	19 (13-28)	23 (15-34)	18 (8-24)	0,019
SRS (%)	17 (10-24,5)	21 (12-29)	14 (5,8-22,3)	0,021
SDS (%)	2 (0,5-5)	2 (0-5)	2,5 (1-4,25)	0,881
LVEF (%)	31 (20-41)	27 (18-36)	39 (24-53)	<0,001
TPD (%)	4,75 (3,25-7)	4,5 (3,25-6,75)	5,25 (3,38-7,78)	0,247
Normal (<5%)	49 (52,7)	31 (56,4)	18 (47,4)	
Ringan (5-9%)	35 (37,6)	21 (38,2)	14 (36,8)	
Sedang (10-14 %)	9 (9,7)	3 (5,5)	6 (15,8)	

Table 3. Spearmen correlation of MPS varibles to TID

Variables	r (Spearman correlation coefficient)	P value
Ischemic Burden	0,10	0,926
LV ESV (stress)	0,335	0,001
LV EDV (stress)	0,353	0,001
LV ESV (rest)	0,147	0,160
LV EDV (rest)	0,163	0,119
LV perfusion score		
SSS	0,187	0,073
SRS	0,128	0,222
SDS	0,006	0,955
TPD	0,120	0,252
EF	-0,106	0,311

Table 2 shows us that severity of CAD will affect the ratio of TID. To identify factors in MPS examination that influence TID ratio besides severity of CAD, Spearmen correlation analysis using TID as the dependent variable was used to statistically analyze the data. Table 3 indicate that ischemic burden, LV volume in the rest phase, EF, and LV perfudion score were not correlated with TID. In contrast, LV volume both in the end phase of systolic and dyastolic in the stress phase were positively correlated with TID (correlation coefficient: 0.335 and 0.353, respectively).

DISCUSSION

TID ratios of the LV have become an important marker of severe and extensive CAD. Previous study had been declared that the higher TID, the more severe CAD. But they clasified the severity based on percentage of stenosis and how many vessels involved.[3,4,9-12] In this study, we established a novel study that investigate the relationship between TID and severity of CAD based on Syntax score. Syntax score not only assess the severity of CAD bassed on percentage of stenosis and how many vessels involved, but also the complexity of the vessel. We choose the Syntax score to define the severity of CAD because many previous studies established in guideline declared that major adverse cardiovascular events were more common in patients with high Syntax score, that will make sense to describe the severity of CAD. In the previous study, it is said that if there is ⩾70% stenosis in the proximal LAD, the lesion will be clasified as severe CAD, but in the Syntax score, if the lesion had 0-22 Syntax score, this lesion will be classified as mild.[10-12]

This study showed that TID has relation to severity of CAD, defined by Syntax score (the more severe the CAD, the higher the TID). The main finding of this study is that severity of CAD affects the TID ratio. TID ratio was depend on the protocol, scanning type, stress type, and software used in the procedure. In this study, the results of TID ratio 1,03±0,11 in moderate-severe group, and 0,906±0,13 in mild CAD group can not be compare because this is the first/ novel study that investigate the relationship of TID with Syntax score. Eventhough the main finding of this study was similar to previous study, that severity of CAD affects the TID ratio.[3,10-13]

TID derives from ratio of LV volume in the stress to rest phase. In this study, we can see that the LV volume in the moderate-severe group was larger than mild group. The rest volume did not affect the TID ratio, but the volume after getting stress. We also found that LV ejection fraction did not correlate to TID ratio, eventhough both 2 group have reduced LV ejection frcation.

MPS imaging plays an important role in the diagnosis and risk stratification of patients with symptoms of or documented CAD, especially in patients with CCS that may be presents with atypical angina. But, balanced 3-vessel CAD prompts a diagnostic dilemma for the cardiologist, because the radiotracer takes the equal portions in all segments of myocardium and the results that we can not see perfusion defect and the myocardial perfusion scintigraphy may be false negative.[3-4,9-11] This condition was also found in this study, that there were no differences in total perfusion defect in the 2 groups, eventhough the severity based on Syntax score and TID was different.

In this study, the ischemic burden between the 2 group was comprable. This finding was similar to the Tanaka et al study, that 11% patients with CAD3VD had <10% ischemic burden/score. This was one of major limitations of MPI in spatial relativity of perfusion defect analysis. But, TID had a feature to detect the LV volume after getting stress may help to identify balance ischemia in severe and extensive CAD and generally signify worse prognosis.[11-15] This postulates how ischemic burden and total perfusion defect in two 2 group were different.

Our study has some limitations. First, this study had a relatively small number participant in mild CAD group. But the study had been met the minimal number of samples. The second is that the we only involved single center. To confirm this hypothesis more effectively, a study with a large sample with attendance of multicentre is required.

CONCLUSION

We have established a novel study and showed that there is a relationship between TID and CAD severity based on Syntax score with higher TID values in patients with moderate-severe CAD compared to patients with mild CAD. TID ratio was only depends on severity of CAD and directly proportional to the volume of LV in the stress phase. TID can be used to predict severe CAD moreover in patients with insignificant perfusion defect and ischemic burden.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

FUNDING

This research has received no external funding

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors significantly contribute to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas. Contribute to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGMENTS

None

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