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'Coronary Sinus Filling Time'- For Diagnosis of Microvascular Disease in Patients with Chronic Stable Angina

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ABSTRACT

Background: Patients having angina with normal epicardial coronary arteries are often considered to have coronary microvascular dysfunction that may result in coronary slow flow. Delayed Coronary Sinus Filling Time (CSFT) may represent transit time through coronary microcirculation.We evaluated CSFT in patients having angina with normal epicardial coronary arteries and compared it with control population. **Methods:** 31 patients having definite angina or probable angina with positive exercise tolerance test with normal epicardial coronary arteries in coronary angiogram (CAG) were included in the study group. 31 patients having normal epicardial coronary arteries in CAG during preoperative evaluation before surgical treatment for valvular and congenital heart diseases were in control group. CSFT, TIMI (Thrombolysis In Myocardial Infarction) frame count, cTIMI (Corrected TIMI) frame count and TMP (TIMI Myocardial Perfusion) score were assessed in CAG of both group and compared between groups. **Results:** Patients' Mean±SD of age in study and control group were 48.84±9.50years and 46.71±5.53years respectively with no significant difference (p=0.569) and there was female preponderance (55% and 65%) in both groups. CSFT was significantly prolonged in study group (4.22±0.71sec vs. 3.65±0.25sec, P value 0.001) but TIMI frame count, cTIMI and TMP showed no significant difference between two groups (25.71±5.74 vs. 26.74±3.81, p= 0.552; 14.76±3.6 vs. 15.4±2.56, p=0.449; 2.54±0.5 vs. 2.61±0.49, p=0.326; respectively). **Conclusion:** We concluded that CSFT was significantly prolonged in patients having angina with normal epicardial coronary arteries which might be a marker for diagnosis of coronary microvascular disease.

Keywords: Angina, Normal epicardial coronary artery, Coronary sinus filling time.

INTRODUCTION

Early detection and adequate management of coronary artery disease (CAD) can reduce CAD related morbidity and mortality. Coronary angiogram remains the gold standard for diagnosing CAD. However, normal epicardial coronary arteries are found in 20-30% of cases undergoing coronary angiography for chest pain evaluation.[1,2] Kemp HG3used the term 'Syndrome X' for the condition of having normal epicardial coronaries in coronary angiogram in patients presented with typical angina and positive exercise stress test. Dysfunction of the coronary microcirculation was suspected in such cases.[4,5] These patients have increased risk of development of hypertension[6], significant coronary artery disease and early cardiac death.[6-8]

Various noninvasive as well as invasive modes were tried to assess microcirculation but failed to demonstrate a consistent result and there is hardly any simple method available at present.[9-11] Some studies revealed presence of slow flow in coronary circulation evidenced by slow progression of angiographic dye.[12,13] Higher TIMI frame count in all three coronary arteries and impaired tissue perfusion was demonstrated in patients with Syndrome X.[14,15] On 2008, Sangareddi and Alagesan (cited in Vellani[16]) proposed that the time taken by angiographic dye to cross from left anterior descending artery (LAD) to origin of coronary sinus would indicate the microcirculatory time.

This study evaluated the coronary sinus filling time (CSFT) in patients having angina with normal coronaries to assess transit time through coronary microcirculation. Delayed CSFT can be a diagnostic marker for coronary microvascular disease (CMVD). The result may guide development of a quantitative, easily available & reproducible diagnostic tool for

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coronary microvascular disease. Early diagnosis of CMVD may help treatment modulation to offer angina free living and prevent major adverse cardiac events.

MATERIALS AND METHODS

The study was done in Department of Cardiology, University Cardiac Center, BSMMU, Dhaka From January 2013 to July 2014. It was a cross-sectional observational study. Patients undergoing CAG in University cardiac center of BSMMU for evaluation of angina pectoris were screened for the study and those having normal epicardial coronary arteries formed the study group. Patients with myocardial infarction were excluded from the study. A normal coronary artery at angiography was defined as epicardial coronary artery without any wall irregularities, ectasia or stenosis. The reference group was constructed from the patients with valvular or congenital heart disease undergoing CAG for pre-operative evaluation before surgical treatment. Among them patients having diseased or abnormal coronaries and pulmonary artery mean pressure ≥25mm Hg were excluded. Sample size was calculated with the formula to calculate sample size to test difference between two means[17] and it was 31. 31 patients were taken in each of study & reference group. Ethical clearance was taken from the Institutional Review Board of BSMMU. Informed written consent was taken from every patient and appropriate safety measures were ensured in every steps of the study. Only research personnel were allowed to access the data. The presentation of data and information related to patient were done anonymously. Patients underwent coronary angiogram according to their clinical need and it carried usual risk. No additional intervention, risk or costing was imparted for the study purpose. There was no potential conflict of interest in this study and it was an entirely an academic research.

Coronary angiogram was done with Siemens Axiom Artis Angiostar-Plus system and recorded at a rate of 15frames/second and viewed by Viewerlite software. Left coronary artery angiogram was taken with manual dye injection. Coronary sinus was evaluated in at least two views, left anterior oblique (LAO) with appropriate cranial angulation and right anterior oblique (RAO) with caudal tilt. In these views, the tract and effluent of coronary sinus are well visualized draining into the right atrium after about six to eight cycles. Coronary sinus origin was defined as the point where great cardiac vein joins the posterolateral vein (that is marked by the joining of oblique vein of Marshall to coronary sinus). Thrombolysis In Myocardial Infarction (TIMI) frame count, Coronary sinus filling frame count and TIMI myocardial perfusion score were obtained offline. The values were taken from average result of findings of two independent experts who were blinded to each other. CSFT was defined as the time (in seconds) taken by the contrast agent to traverse the coronary artery & its microvascular bed and reach the coronary sinus origin. Frame count at the maximum opacification of LAD at D1 or S1, which one was earlier, was noted as first frame count. A column of fully concentrated dye must extend across the entire width of LAD at D1/S1 and move forwards. The frame count at which dye was first seen at the origin of coronary sinus was taken as the last frame. The CSFT was calculated as:

CSFT in seconds= (last frame count- first frame count)/15

TIMI Frame Count was defined as the number of angiographic frames elapsed when the contrast dye crossed the length of artery. For LAD, TIMI frame count = Frame count at distal bifurcation – frame count at D1/S1. The frame rate was corrected (to get corrected TIMI or cTIMI) for the length of the LAD by dividing it by 1.7.[18]

TMP scoring was done with the grading system described by Gibson et al,[19] as TMP grade 0 (no myocardial blush), grade 1 (Minimal myocardial blush but no clearance), grade 2 (Moderate myocardial blush, clears slowly, strongly persistent after 3 cardiac cycle) and TMP grade 3 (normal blush and clearance of dye from myocardium).

TIMI frame count, cTIMI frame count, CSFT & TMP grade were calculated by offline analysis of coronary angiograms and were compared between groups.

Continuous variables were expressed as means±SDs and categorical variables were expressed as percentages. The demographic data was analyzed using Chi square test. The impact of risk factors for CMVD viz. DM, HTN, dyslipidemia, smoking, family history of CAD were analyzed by odds ratio. Angina group & control group were compared for differences in means of TIMI, cTIMI, CSF-FC. CSFT and TMP score using unpaired t test. A $p<0.05$ was used to reject the null hypothesis. The statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL, USA).

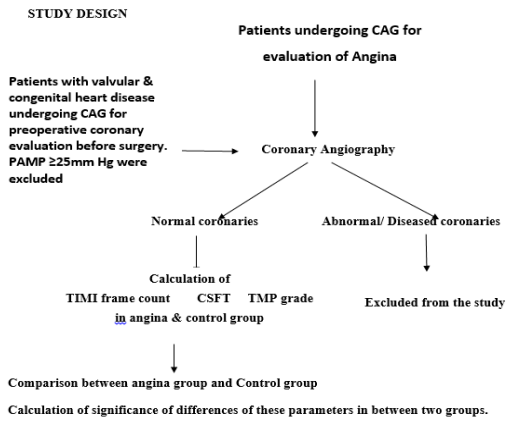


Figure 1: Flow diagram showing the study design

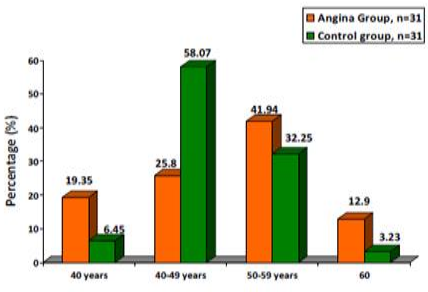
RESULTS

This study assessed coronary slow flow parameters viz. TIMI frame count, TMP score and CSFT in patients having angina with normal epicardial coronary arteries (angina group).These parameters were compared with those in patients undergoing CAG for preoperative evaluation for surgical treatment of congenital or valvular heart diseases (control group). Angina and control groups were constructed with 31 patrients in each. They were studied for demographic and anthropometric variables, presence of traditional CAD risk factors and coronary slow flow parameters.

Table 1: Baseline characteristics of the study populations:

Variables	Angina group (n=31) N(%)	Control group (n=31) N (%)	P value / Odds ratio
Sex			
Male	14 (45)	11 (35.5)	0.437
Female	17 (55)	20 (64.5)	
Age (in Years, mean±SD)	48±9.5	47±5.33	0.565
Diabetes mellitus	16 (51.60)	6 (19.35)	4.44 (OR)
Hypertension	22 (71)	1(32)	73.33 (OR)
Dyslipidemia	26 (84)	5 (16.1)	27 (OR)
BMI	26.24±2.57	22.06±1.183	0.001
Family History	15 (48.4)	2 (6.4)	14.6 (OR)
Smoking	12 (38.7)	9 (29)	1.54 (OR)
RA pressure (mm of Hg)	3 (2)	4 (2)	0.763

It was found that age & sex distribution was similar in both groups. Conventional cardiovascular risk factors like DM, HTN, dyslipidemia, obesity, positive family history & smoking were significantly higher in angina group.



%= Percentage of frequency in each group
Significance of difference was analyzed by unpaired t test.
P value <0.05 was considered as significant
n= Number of subjects

Figure 2: Age distribution of study subjects:

[Figure 2] is showing that most of the patients of angina group are in 50-59years age group and most of the patients of control group belong to 40-49 years age group.

Table 2: Results of CSF FC, CSFT, TIMI FC, cTIMI FC, TMP score , CSF FC and CSFT at Coronary angiography in study population (n=31)

Parameter	Study group (n=31)	Control group (n=31)	P value
	(Mean±SD)	(Mean±SD)	
CSF FC	63.48±10.62	54.68±3.39	0.001
CSFT (second)	4.22±0.71	3.65±0.25	0.001
TIMI FC	25.71±5.74	26.74±3.81	0.552
cTIMI FC	14.76±3.6	15.4±2.56	0.499
TMP (score)	2.58±0.5	2.61±0.49	>0.05

n- number of patients
SD= Standard deviation
CSF FC= Coronary sinus filling frame count
CSFT= Coronary sinus filling time (Seconds)
TIMI FC= Thrombolysis In Myocardial Infarction frame count
cTIMI FC=Corrected TIMI frame count
TMP score= TIMI Myocardial Perfusion Score
P value <0.05 was considered as significant
Analysis was done by unpaired t test.

Mean±SD of CSF frame count & CSFT were significantly higher in angina group. But there was no difference between two groups in regards to TIMI frame count, cTIMI frame count and TMP score.

DISCUSSION

Disease of coronary microcirculation, the underappreciated segment of CAD, is getting emphasis now a days, as it bears a higher risk for further cardiovascular events.[6-8] Epicardial coronary artery disease is evaluated by visual and digital analysis of coronary angiography. But there is no simple method available to assess the status of the coronary microcirculation.

Various invasive or non-invasive tests to explore coronary microcirculation were proposed. Intracoronary Doppler recording during CAG, an invasive evaluation, is a complex and time-consuming procedure and imposes unjustified adjunctive risks to patient.[20] Whereas, a noninvasive tests, Transthoracic echocardiographic Doppler recording (TTE-DR) of coronary blood flow is easy to perform, reproducible, largely available and possibly, inexpensive.[20] But TTE-DR cannot identify mild CMVD and cannot explore coronary territories other than LAD.[20] Contrast stress echocardiography is a promising method to detect CMVD in different myocardial territories. But there is scarcity of studies to support its applicability.[20] Cardiac Magnetic Resonance (CMR) imaging with pharmacological stress tests and gadolinium enhancer (as a flow tracer) is perhaps the most promising method for noninvasive assessment of CMVD. However, at present, CMR seems to be too expensive, complex and time-consuming technique to use it in routine practice.[21,22] Myocardial perfusion imaging by scintigraphic stress test (SPECT, PET) is the most reliable tool, but it is expensive and not easily

available for routine use.[20] Assessment of lipid peroxidation products in the coronary sinus after stress tests seems to be sensitive,[23] but it involves unjustified risk for the patient and impractical for routine use. CMR spectroscopy can detect ischemic abnormalities of phosphorus metabolism under stress tests,[24] however, this technique is expensive, less available and can only explore the anterior cardiac wall.

Digital frame counting of coronary angiograms (CAG) has been used to measure the transit time of dye across the coronary artery. The transit time between the coronary artery to the coronary sinus (CS) would indicate the time to traverse microcirculation. According to Sangareddi and Alagesan, 2008 (cited in Vellani[16]) the time taken by the angiographic dye to cross from left anterior descending artery (LAD) to origin of coronary sinus would represent this time, which was termed as coronary sinus filling time (CSFT). Coronary sinus exhibits dynamic motion.[25] Exaggeration of this motion may result in slow coronary flow.[26] Rouleau & White,[27] demonstrated that modulation of coronary sinus outflow pressure could impede coronary flow. Thus, full opacification of the coronary sinus depend on multiple factors other than the condition of microcirculation. So, filling at the origin of coronary sinus was used as the distal landmark in the current study. This study tried to determine coronary sinus filling time by coronary angiogram in patients having angina with normal epicardial coronary arteries and compared it with normal controls.

In the current study, angina group was formed by the patients with angina and positive stress test or typical angina having high likelihood of presence of CAD. The control group was formed by the patients, aged >35years, with valvular or congenital heart disease without symptom for CAD and having normal coronary artery at CAG. There is guideline directed indication for CAG in such patients for evaluation of coronaries before scheduled cardiac surgery.[28] In other studies control group was formed with patient having chest pain with negative stress test or patients with mitral stenosis undergoing PTMC.[15,16,29]

Negative ETT cannot exclude microvascular disease as those studies found significant slow flow in some of the control population. So, patient with angina cannot be control subject. There is an ethical bar against CAG in patients with mitral stenosis before PTMC as it is not indicated according to guideline.[28] In these respects the control group formulation in the current study is more representative and more ethically sound.

In the current study the mean age of patients was 48.84±9.5 years in angina group and 46.71±5.53 years in control group which are similar to that in Indian study,[16] where the values were 50.4±7.6years and 47.4±9.6 years respectively. This study showed that most of the patients of angina group were in 50-59 years of age which agreed with the result of Framingham cohort study which discovered increased risk of CAD after 50 years of age.[30] Frequency of patients in control group was more in 40-49 years age. This correlates with natural history of those congenital and chronic rheumatic valvular heart diseases found in control group. Patients with secondum type of ASD, restrictive type of VSD become symptomatic in 2nd and 3rd decades but mostly present after 40years of age.[31] In countries with high prevalence of rheumatic fever, as in Bangladesh, severe chronic rheumatic valvular disease may present in 2nd decade, but usually after 3rd or 4th decade.[32]

This study showed 55% and 64.5% female in angina and control group respectively, where as similar Indian study found 68.3% and 81.2% female.[16] Nihat et al[29] studied coronary slow flow in patients with 48% and 52% female in angina and control group respectively. Our findings are consistence with the prevalence of the Microvascular disease, as it is more prevalent in female.[33] In the current study, 12 out of 17 female (70%) in angina group were menopausal. This finding agreed with the suggested pathogenic factor of estrogen deficiency in menopausal women.[34]

David & Willium,[35] found that about half of the patients with Syndrome X have typical angina and others present with various forms of atypical angina. Typical angina was present in 71% of angina group and remaining had atypical angina or non-specific chest pain in this current study. This inconsistency may be due to subjective expression of chest pain with a different educational and social status. The conventional risk factors viz. family history of CAD, dyslipidemia, hypertension, smoking and DM were significantly higher in angina group with odds ratio >1 for each. These findings are consistent with the study of Vellani et al.[16] DM, HTN, dyslipidemia and smoking insult the vascular endothelium and microcirculation resulting in reduced microvascular vasodilator flow reserve.[36,37]

Regarding coronary angiography, TIMI frame count was 25.71±5.74 in angina group and 26.74±3.81 in control group and cTIMI frame count was 14.76±3.6 and 15.4±2.56 respectively. TMP score was 2.54±0.5 and 2.61±0.49 respectively in angina and control groups. These three parameters did not show significant difference between two groups (p value >0.05 for each).

CSF frame count was significantly higher in angina group (63.48±10.62) than control group (54.68±3.39). CSFT was also higher in angina group than control group which was 4.22±0.71vs. 3.65±0.25 respectively (P value<0.05).These findings correlate with a similar study on Indian population where Vellani et al,[15] found that CSFT was significantly higher in angina group but TIMI, cTIMI and TMP did not show statistically significant difference between two groups.

Several studies found un-uniform result of TIMI frame count and TMP grade in patients with diagnosed Syndrome X or coronary microvascular disease.

Nihat et al,[28] studied epicardial coronary blood flow in patients with Syndrome X in Turkish population by TIMI frame count and TMP grade. Diagnosis of cardiac Syndrome X was made based on complaint of typical angina with ischemic findings on either myocardial perfusion scintigraphy or a treadmill exercise test and normal coronary angiograms. There were no significant difference between the groups in terms of mean TIMI frame count and TMP grade. TIMI frame count for LAD was 36.2±15.3 vs. 31.4±13.7 and mean TIMI frame count (mean of three coronary arteries) was 26.2±9.3 vs. 24.5±12.1 in study and control groups respectively. They also found abnormal myocardial blush grade in 34.7% patients in the control group. The values of TIMI FC of the current study do not agree with Nihat et al.[28] TIMI frame count found in control group of Nihat et al,[28] (31.4±13.7) is higher than that found in the current study (26.74±3.81). This may be due to ethnic variation of patients of the two studies.

In another study by Yusuf et al,[15] TMP score was found significantly lower in patients with Syndrome X than control subjects. They defined cardiac Syndrome X with presence of typical exercise-induced angina pectoris, transient ischemic ST-segment depression (>1 mm) during exercise, and angiographically normal coronary arteries. The control group was formed by the patients having chest pain with negative stress test or patients undergoing CAG for coronary evaluation before valve surgery. The current study does not support the result of Yusuf et al.[14] This may be due to inter-observer variation observed in TMP score analysis.

Chen et al,[14] studied on TIMI frame count in patients with Syndrome X in Korean population and found it to be significantly higher than control group. They defined Syndrome X as patients with angina & positive stress test. And patients undergoing electrophysiological studies or invasive procedures for valvular heart disease other than angina were taken as controls. The current study differs with the findings of Chen et al.[14]

In the current study, coronary angiograms were done by manual dye injection by different performers. So, it may affect flow velocity and thus make impact on observation results. Use of automated dye injector may overcome this.

In this study, TMP was observed during LCA injection only, but there are variations in dominancy pattern of coronary arteries which may affect the myocardial perfusion during individual coronary artery injection. So, TMP should be assessed by total myocardial blush score with injection in all three coronary arteries.

In this study, coronary flow was assessed in LAD to coronary sinus. But there is significant variation in types of LAD which leads to variations in TIMI and cTIMI frame count, i.e. higher frame count for type-IV and lower frame count for type-II LAD.

Further refining of this concept with more study on CSFT and comparison of three coronary arteries in respect of CSFT is required to use CSFT in clinical practice for evaluation of coronary microvascular disease.

CONCLUSION

We concluded that CSFT was significantly prolonged in patients having angina with normal epicardial coronary arteries which might be a marker for diagnosis of coronary microvascular disease.

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