

Original Research Article

Can ischemic time predict the age of thrombus in ST elevation myocardial infarction?: an analysis from tertiary healthcare center in South India

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ABSTRACT

Background: ST Elevation myocardial infarction (STEMI) is characterized by plaque disruption with superimposed thrombus formation. However, studies from western population have suggested a delay between plaque disruption and the onset of symptoms. There is a paucity of Indian data on the relationship between ischemic time and the age of thrombus. Hence, we decided to study the histopathological characteristics of thrombus aspirated during primary percutaneous coronary intervention (PPCI) in patients of STEMI and its relation with the ischemic time.

Methods: 107 consecutive patients of STEMI undergoing PPCI with thrombus aspiration, mostly within 12 hours of symptom onset were included in this study. The aspirated thrombi were fixed in 10% formalin, processed and analysed by light microscopy. The thrombi were categorized as recent or lysed according to the histopathological characteristics.

Results: The mean age of the study population was 54.93 ± 13.19 years. There were males 94 (87.85%) and 13 (12.15%) were females. The culprit vessel was LAD in 36 (32.73%), RCA in 57 (51.82%) and LCX in 13 (11.82%). Left Main, Diagonal and OM were culprit vessels in one case (0.91%) each. Thrombus was identified in 102 (95.3%) out of 107 patients where as in five patients (4.7%) only plaque was seen. Histopathology revealed lysed thrombus in 68 (66.7%) of 102 patients, and recent thrombus in 34 (33.3%) patients.

Conclusions: In patients with STEMI, undergoing PPCI within 12 hours of symptom onset, majority of the thrombi were lysed indicative of a thrombus age of at least 24 hours. This suggests that plaque instability and thrombus formation frequently precedes the onset of symptoms. Hence, ischemic time cannot predict the age of thrombus in STEMI.

Keywords: Old thrombus, Primary PCI, Recent thrombus, STEMI, Thrombus histopathology, Thrombus disruption, Thrombus age

INTRODUCTION

Acute ST-elevation myocardial infarction (STEMI) is characterized by thrombotic total occlusion of a coronary

artery following coronary atherosclerotic plaque disruption.¹ Initial stages of coronary artery stenosis when the plaque disruptions are covered by mural thrombi, mostly remain asymptomatic. Over the time,

continuous inflammation in these lesions with smooth muscle migration and exuberant endothelialisation, lead to the formation of organized mural thrombi. The lesions often heal with incorporation of the mural plaques. Such incorporation restores and maintains the smoothness and integrity of the vessel wall, organized mural thrombi may entirely be incorporated in the atherosclerotic lesion, whereby the integrity of the vessel wall is restored. However, the healed plaque can rupture and lead to thrombosis, total occlusion of vessel, myocardial infarction (MI) and often death.¹⁻³

Alternate pathophysiology is plaque disruption with mural thrombosis leads to a process of repeated or ongoing thrombosis. Ultimately such thrombosis results in an acute coronary syndrome. Thrombus burden in coronary artery and components of the thrombus impose higher risk for long-term adverse cardiovascular events, distal embolization and stent thrombosis. The thrombus burden is larger in STEMI than in non ST elevation (N-STEMI) acute coronary syndromes (ACS). Therefore, STEMI is considered to have relatively worse prognosis and indicators of prognosis are thrombus burden and components of the thrombus.¹⁻⁷

Recent studies have demonstrated that there may be a delay between development and maturation of thrombus and onset of symptoms.¹ Kramer et al. studied aspirated thrombi in a small cohort STEMI patients treated with primary percutaneous coronary intervention within 6 hours of onset of symptoms, for their composition and age. This study demonstrated that thrombi studied were days or even week old in approximately 50% STEMI patients.¹ Studies have demonstrated an association among the histopathological characteristics, angioplasty results, and clinical outcomes of the thrombus.¹⁻⁵ The age of thrombus is also a prognostic indicator in STEMI.¹

In this study we attempted to validate the time delay between plaque disruption (and thrombus formation) and appearance of the symptoms in Indian context as a pilot study. We also revalidated the prognostic value of the age of thrombus in India context.

METHODS

107 consecutive patients of STEMI undergoing PPCI with thrombus aspiration, within 12 hours of symptom onset were included in the present study. The thrombus was aspirated with Xchange thrombus aspiration catheter (MVI Therapeutics India Pvt LTD, Surat, India), immediately fixed in 10% formalin and sent to the histopathology laboratory. After fixation for 24 hours the material was processed, embedded in paraffin and sections of 5 microns were cut using microtome. The hematoxylin and eosin stained sections were examined by 2 pathologists independently who were blinded to the clinical profile of the patients. The thrombi were then categorized as recent or old according to the previously published and histopathologically accepted

definitions.¹ Fresh thrombus (<1 day) is composed of layered patterns of fibrin and intact platelets, erythrocytes and granulocytes. Older thrombus (>1 day) show karyorrhexis, necrosis and proliferation of smooth muscle cells. Thrombus material with a heterogenous composition was graded according to the age of the oldest part.

The histopathology study was performed in the pathology laboratory at MOSC medical college hospital Kolenchery. The study was reviewed and approved by independent ethics committee at MOSC Medical College Hospital Kolenchery.

Data assessment and statistical analysis was performed by Krishnamugdha Institute of Advanced Learning and Research. The statistics for measurement data (age, time etc.) was summarised as central tendency and spread, commonly as Mean and standard deviation. The events and proportions were summarized as frequencies. Significance tests for independent parameters were performed with z-test for means and medians, direct probabilities were taken for frequencies. The data analysis was performed with Minitab software, and MS - Excel.

RESULTS

Demographics and description

We recruited total 107 consecutive STEMI patients at MOSC Medical College Hospital Kolenchery, a tertiary teaching institute from South India. The population was considerably young with an average age of 54.93±13.19 years. Most patients (87.85%) were males. In the cohort, 31.85% subjects were diabetic, 21.50% had hypertension and 15.90% had dyslipidaemia. Family history of CAD was positive in 11 (10.28%) patients and 45.80% patients were currently smoking (Table 1). Demographic pattern of the cohort in the study was typically a "Real World" pattern of the population presenting in the hospital with STEMIⁱⁱ except for smoking, which is otherwise the most prevalent risk factor in STEMI population.

Table 1: Demographics and risk factors.

N	107
Mean Age	54.93 ± 13.19
Males	94 (87.85%)
Risk factors	
Diabetes Mellitus	34 (31.78%)
Hypertension	23 (21.50%)
Current smoking	49 (45.80%)
Dyslipidaemia	17 (15.90%)
Family History	11 (10.28%)

The cohort was a mix of myocardial infarctions of various segments of myocardium and the thrombosis of supplying vessels. In multi vessel disease, the vessel

occluded with thrombus was considered as the culprit vessel for STEMI. The most frequently reported (51.82%) culprit vessel was Right Coronary Artery (RCA). Left anterior descending (LAD) artery and circumflex were occluded in 32.73% and 11.82% cases, respectively (Table 2). Most cases (60.75%) presented with inferior wall myocardial infarction (MI). Most of the subjects had inferior wall MI (60.75%) or anterior walls (37.38%) and very few had posterior wall infarction (3.74%). One subject (0.94%) presented with complete heart block (Table 3).

Table 2: Distribution of lesions by vessels.

Right Coronary Artery	57(51.82%)
Left Main	1 (0.91%)
Circumflex	13 (11.82%)
Left anterior descending	36 (32.73%)
Obtuse marginal	1 (0.91%)
First diagonal	1 (0.91%)
Second diagonal	0 (0%)
Other / ramus	1 (0.91%)

Table 3: Infarcted Myocardial Segments.

Inferior wall	65 (60.75%)
Posterior wall	36 (32.73%)
Anterior wall	6 (6.52%)
Heart block	
Complete heart block	1 (0.94%)

Ischemic time is the duration between onset of symptoms and restoration of the blood supply. In evaluation of the ischemic time, 6 hours is considered the point of great diversity pertaining to start of lysis of thrombus. In this study, most of the patients (80.18%) reported within 6 hours of the symptom onset. Ischemic time forms the basis for evaluation of correlation between onset of symptoms and age of the thrombus. The mean Ischemic time of the cohort was 6.28 ± 14.62 hours and median was 15.48 hours. The skewness of 8.56 was observed in the group due to three outliers. These outliers were three patients who had longer ischemic time more than 24 hours (Table 4).

Table 4: Ischemic time.

Mean (STDEV)	6.28 (14.62)
Median	15.48
Min-max	1.00 - 144.00
Time range (Hours)	
< 6.00 hours	85 (80.18%)
> 6 hours	21 (19.81%)

Histopathological analysis and study outcomes

The collected thrombi were evaluated under light microscope. Among the 107 patients, we could collect

evaluable samples from 102. Five samples were not evaluated as the tissue available was insufficient for analysis (Table 5, Figure 1, 2).

Table 5: Histopathological outcome of thrombi.

Thrombus type	
Non-evaluable	5 (4.67%)
Recent thrombus	34 (32.08%)
Organized or Lysed	68 (64.15%)

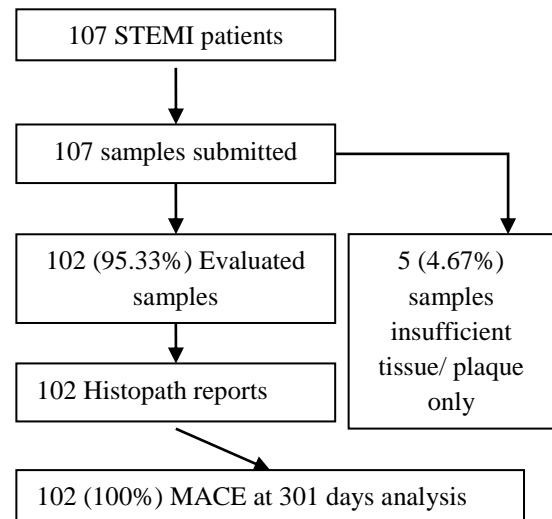


Figure 1: Study Flow chart.

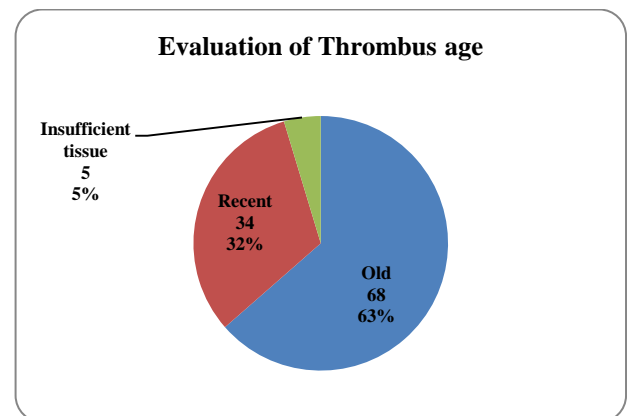


Figure 2: Histopathological classification of thrombi.

Despite majority of patients (80.18%) reporting Ischemic time less than 6 hours which meant that the origin of symptoms was fairly recent, most of the patients had lysed plaque. The histopathology analysis revealed that 32.08% subjects had recent plaque, whereas the majority (64.15%) thrombi were organized or lysed. In the cohort of 83 patients with ischemic time less than 6 hours, 52 patients (62.65% of subset, 49.06% of overall) had organized or lysed thrombus, whereas 31 patients

(37.35% of subset, 29.25% of overall) had recent thrombus. In the cohort with ischemic time more than 6 hours, 16 out of 19 patient (84.21% of subset, 15.09% of overall) had organized or lysed thrombus (Table 6).

Table 6: Relationship of Thrombus type with ischemic time.

	Old [n (%)]		Recent [n (%)]		
< 6 hours	52	49.06	31	29.25	P= 0.001
> 6 hours	16	15.09	3	2.83	p=0.029

Looking towards the 6 hours ischemic time trend, we refined the analysis further. The analysis revealed that the organization and lysis of thrombus rapidly advances between 3 and 12 hours (Table 7).

Table 7: Ischemic time to Thrombus type staged analysis.

	Old	Recent	
In first 3 hours	21	20	p = 0.825
Between 3 and 6 hours	31	11	P < 0.0001
Between 6 and 12 hours	11	2	p = 0.001
Between 12 and 24 hours	4	0	p = 0.029
More than 24 hours	1	1	P = NS

Table 8: ODD's analysis for effect of risk factors on thrombus aging.

	Odds ratio	95% CI upper	95% CI lower	Static Z	
Diabetes	1.42	3.53	0.57	0.75	p = 0.45
Hypertension	2.70	5.89	0.56	1.66	p = 0.009
Smoking	0.66	3.49	0.67	0.98	p = 0.32
Dyslipidaemia	1.61	6.27	0.55	0.77	p = 0.44
Family history	1.38	8.23	0.50	0.45	p = 0.65

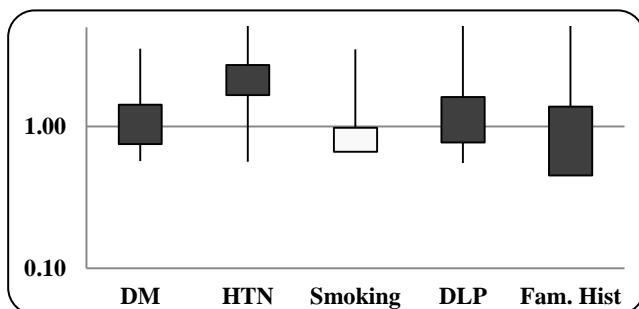


Figure 3: ODD's analysis for effect of risk factors on thrombus aging.

ODD's analysis is a comparison tool for stratified analysis of effect of risk factors on the outcomes. In this case, we considered old thrombus as a positive event and recent thrombus as a negative event. The analysis revealed that hypertension leads to rapid organization / lysis of the thrombus whereas smoking usually delays organization of the thrombus (Table 8, Figure 3).

Prognostic value of thrombus age at 30 days MACE

Age of thrombus has a significant prognostic value. At 30 days, all 102 patients whose thrombus analysis was performed were followed up for MACE. The overall MACE was 2.94%, contributed by target lesion revascularization. In addition to the MACE, there were 1 non-cardiac death and 1 case of renal failure (Table 9).

Table 9: Analysis of MACE and other serious events.

	n	%
Subjects followed up at 30 days	102	96.23
Total MACE	3	2.94
Cardiac deaths	0	0
Myocardial infarction	0	0
TLR - Total	3	2.94
TLR - CABG	3	2.94
TLR - PCI	0	0
Other major events	3	2.83
Deaths- other causes	1	0.94
Deaths- all cause	1	0.94
Renal failure	1	0.94
Congestive heart failure	1	0.94

For analysis of prognostic value of thrombus histopathology, we performed regression analysis of MACE, for MACE-free survival at 30 days (Table 10). The group had 96.57% MACE-free survival and 94.34% event-free survival probabilities. The probabilities of MACE-free survival in case of recent thrombus were marginally higher (97.06%) than when thrombus was organized or lysed (96.32%). However, this difference has limited statistical significance. (p=0.30) (Figure 4).

Table 10: MACE free survival analysis for 30 days.

	Survival P	Exposure N	Survival N
MACE free survival	96.57 %	102	98.5
Organized or lysed thrombus	96.32 %	68	65.5
Recent thrombus	97.06 %	34	33
Event free survival	94.34 %	106	100

P= (0.3); NB: 50% of lost to follow-up considered as survivals in the analysis of regression.

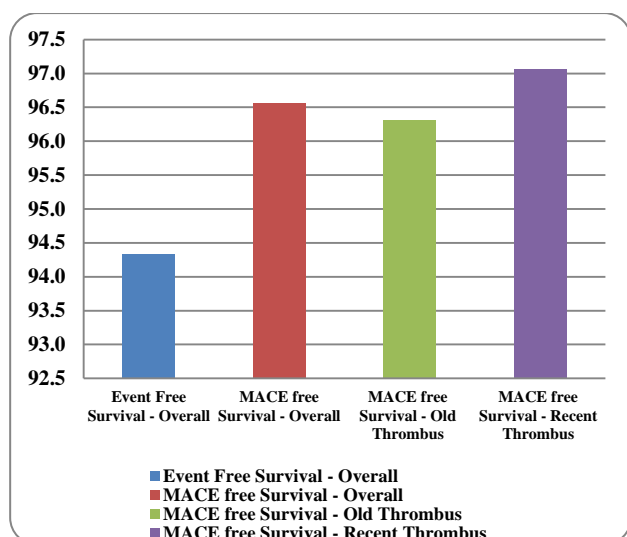


Figure 4: Survival Analysis - probabilities of eventfree and MACE free survival.

DISCUSSION

The present study and other previous studies have reported that the thrombus formation and its subsequent organization or lysis may occur significantly before onset of symptoms in coronary artery disease especially in STEMI.^{3-6,12, 13, 19} Histopathological age of thrombus and its clinical impact was evaluated by many studies in the past.^{12,13,19,25-28} In a study of 959 patients with STEMI undergoing primary PCI, about 60% cases had recent thrombi and 40% cases had organized or lysed thrombi.¹³ Another study with 199 samples of thrombus aspirates, recent thrombus was reported in about half (49%) of the population, whereas 51% cases had organized or lysed thrombi. This study also identified the impact of risk factors namely patient's age, male gender, and the extent of the lesion on the age of the thrombus.¹² In yet another other study Verouden et al. attempted establishing the clinicopathological relationship of the thrombus by electrocardiography and showed that incomplete recovery of the ST-segment and the presence of old thrombi were a strong predictor of long-term mortality, irrespective of the histopathology of the thrombus.¹⁵

In the present study more than three fourth patients had symptoms onset within 6 hours of their treatment. However, the organized or lysed thrombi (aged thrombi) are a significantly ($p = 0.001$) higher in number. For further in detail analysis, we performed staged analysis for ischemic time 3 hours, 3-6 hours, 6-12 hours and more than 12 hours. The staged analysis demonstrated a statistically significant trend that aging pattern of thrombus directly depends upon the ischemic time.

When MACE and event-free survival probabilities of the participating cohort were analysed, 3 patients had repeat revascularization with GABG, accounting for MACE in this study. Hence, MACE analysis by thrombus type,

subsequent time to event analysis and stratification analyses were statistically not possible and significant. The survival analysis and MACE-free survival analysis along with its bifurcation by type of thrombus, revealed that the group with aged thrombus have relatively higher risk of MACE in long term.

In PPCI, long door to balloon time and total ischemic time are critical parameters of patient survival. From this analysis also, the ischemic duration between 3 to 6 hours looks to be critical for rapid aging of the thrombus.

In addition, this and previous studies referred above have established a fact that the risk of MACE is higher with aged thrombus, establishing a stronger rationale for timely management of the ACS patients based upon door-to-balloon time and Ischemic time.

Even though risk stratification in ACS is possible by angiographic grading of thrombus, the most powerful yet simplest method of stratification is based on clinical risk factors. As most of the patients are young adults and males, the comorbidity profile plays an important role. In this study, odds' ratio based risk analysis revealed that hypertension leads to rapid organization/lysis of the thrombus.

Our study is the first study in Indian context, to analyse the clinicopathological correlation of coronary thrombus and has thrown light into several significant facts.

CONCLUSION

Thrombus aspirated during primary PCI for STEMI analyzed and studied under light microscopy reveals that age of thrombus is not predicted by the ischemic time. Even in first 3 hours of ischemic time, almost half of the subjects had organized or lysed thrombus. Clinically, risk of MACE appears to be higher in old thrombus group. However, this will require revalidation with a higher number of subjects where more number of events was reported.

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