Relation of Angiographic Thrombus Burden with Severity of Coronary Artery Disease in Patients with ST Segment Elevation Myocardial Infarction

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Background: We planned to investigate the relationship of thrombus burden with SYNTAX score in patients with ST elevation myocardial infarction (STEMI).

Material/Methods: We retrospectively enrolled 780 patients who underwent PPCI in our clinic due to STEMI. Clinical, laboratory, and demographic properties of the patients were recorded. Angiographic coronary thrombus burden was classified using thrombolysis in myocardial infarction (TIMI) thrombus grades.

Results: Patients with high thrombus burden were older, with higher diabetes prevalence longer pain to balloon time, higher leukocyte count, higher admission troponin, and admission CK-MB concentrations. SYNTAX score was higher and myocardial perfusion grades were lower in patients with high thrombus burden. Multivariate logistic regression analysis revealed SYNTAX score as the strongest predictor of thrombus burden. ROC analysis demonstrated a sensitivity of 75.5%, specificity of 61.2%, and cut-off value of >14 (area under the curve (AUC): 0.702; 95% confidence interval [CI]: 0.773–0.874;P<0.001) for high thrombus burden.

Conclusions: SYNTAX score may have additional value in predicting higher thrombus burden besides being a marker of coronary artery disease severity and complexity.

MeSH Keywords: **Myocardial Infarction • Percutaneous Coronary Intervention • Thrombosis**

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Background

ST segment elevation myocardial infarction (STEMI) is still an important cause of cardiovascular mortality, and morbidity. Without doubt, coronary thrombosis is the main physiopathologic mechanism of STEMI. Moreover, higher thrombotic burden in infarct related artery (IRA) is related to stent thrombosis, distal embolization, no-reflow phenomenon, and long-term mortality [1–4].

No-reflow phenomenon poses as a major problem in patients with STEMI undergoing primary percutaneous coronary intervention (primary PCI, PPCI). Although the thrombotic lesion in IRA is successfully stented, tissue level perfusion remains low with increased cardiovascular morbidity, and mortality [5,6]. Thus, identification of factors that could increase no-reflow and potential remedies of this phenomenon is clinically significant.

SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score is an angiographic scoring system, which grades coronary artery disease severity and complexity [7]. Even though SYNTAX score is primary utilized for selection of elective revascularization strategies, there is growing data implicating additional clinical value in STEMI. Recent studies revealed that pre-PPCI SYNTAX score is associated with no-reflow phenomenon and long-term mortality in STEMI [8–11]. Moreover, SYNTAX score independently predicted angiographically visible distal embolization in patients undergoing PPCI [12]. These results implicate an association between pre-PPCI thrombus burden and SYNTAX score. Therefore, we planned to investigate this relationship in patients with STEMI.

Material and Methods

Study population

We retrospectively enrolled 780 patients who underwent PPCI in our clinic due to STEMI between April 2009 and February 2015. Our study was approved by the local ethics board.

Our study included patients who had the diagnosis of STEMI according to recent STEMI guideline, and underwent PPCI [13]. The clinical, demographic, and laboratory data of the patients were obtained using patient records and registries. Heart rate, Killip class, previous medications, pain to balloon time and door to balloon time, serum creatinine, lipid panel, and hematological indices of all patients were recorded during hospital admission. Data regarding coronary angiography were gathered through re-evaluation of stored media. The patients were treated according to relevant guidelines [13,14]. Tirofiban was used at a dose of 10 mg/kg bolus and 0.15 mg/kg/min intravenous infusion if preferred by the physician. Experienced operators performed all PPCI procedures.

We excluded cases that underwent fibrinolytic therapy (n=15), emergent cardiovascular bypass surgery (n=18), and patients with end stage renal failure (n=11), malignancy (n=3), culprit left main coronary lesion (n=3), and spontaneous coronary dissection (n=1).

SYNTAX score was calculated using SYNTAX Score Calculator 2.11 software downloaded from http://www.syntaxscore.com [7,15].

Clinical definitions

Hypertension was defined as systemic blood pressure >140/90 mmHg or the use of antihypertensive medication. Hypercholesterolemia was accepted if a serum total cholesterol level >200 mg/dL, or with the use of a cholesterol lowering agent. Diabetes mellitus was acknowledged as an HbA1c >6.5%, a plasma glucose level ≥126 mg/dL (7.0 mmol/L) after an overnight fast, or the use of antidiabetic medications. Positive family history of coronary artery disease was defined as documented evidence of premature coronary artery disease in a first degree relative (men <55 and women <65 years of age).

Killip Classification was noted as follows: Class I: No evidence of heart failure. Class II: Findings of mild to moderate heart failure (S3 gallop, rales < half-way up lung fields or elevated jugular venous pressure). Class III: Pulmonary edema. Class IV: Cardiogenic shock defined as systolic blood pressure <90 and signs of hypoperfusion such as oliguria, cyanosis, and sweating.

Angiographic definitions

Three experienced investigators who were blinded to clinical parameters of the patients' carefully reviewed coronary angiograms. The TIMI flow grades were determined by the consensus of the three investigators. Angiographic thrombus burden was classified as follows: Grade 0: no thrombus, Grade 1: Possible thrombus, Grade 2: the thrombus' greatest dimension is <1/2 vessel diameter, Grade 3: Greatest dimension >1/2 to <2 vessel diameters, Grade 4: Greatest dimension >2 vessel diameters, Grade 5: total vessel occlusion due to thrombus [3]. The patients were stratified into low thrombus burden (Grades 1, 2 and 3) and high thrombus burden groups (4 and 5) according to final thrombus score.

Postprocedural final thrombolysis in myocardial infarction (TIMI) flow grade, TIMI myocardial perfusion grade (TMPG), corrected TIMI frame count (cTFC), and TMPG were noted as previously defined. [16–18]. TIMI flow grade <3, and final myocardial blush grade <2 were described as angiographic no-reflow.[19].

Table 1. Baseline clinical and laboratory characteristics according to thrombus burden.

Variable	Low thrombus burden (n=299)	High thrombus burden (n=481)	P value
Age, years	55.4±10.8	57.1±11	**.033**
Sex, male%	43.5	49.5	.105
Diabetes,%	23.7	30.4	.049
Hypertension,%	42.5	43.2	.882
Smoking,%	42.1	44.9	.459
Dyslipidemia,%	43.5	48	.237
Previous history of CAD,%	11	14	.297
Family history of CAD	37.4	43.2	.116
Pain-balloon time, min	220±121	280±502	**.042**
Door-balloon time, min	30.8±10.9	30.4±10.2	.623
Killip status (≥II)	9	13.3	**.085**
Heart rate, /min	76.5±16	74.7±16	.145
Hemoglobin, g/dL	13.3±1.4	13.9±1.3	.732
White blood cell count ×10³/µL	9.2±2.5	9.7±2.5	.013
Platelet count, ×10³/µL	216±76	218±78	.734
Baseline troponin I, mg/L	2.1±1.5	2.3±1.5	.047
Baseline CK-MB, IU/L	35±13.7	37.1±15.1	.048
LDL cholesterol, mg/dL	150±32	155±26	.188
HDL cholesterol, mg/dL	29±14	28±11	.913
Triglyceride, mg/dL	188±91	201±102	.061
EF,%	48±9.8	47.7±8.1	.595
Previous medications,%			
Aspirin	14.7	13.1	.523
Statin	16.7	17.0	.922
ACE inhibitors/ARB	26.8	29.7	.415
β-blocker	8.7	6.0	.195
Clopidogrel	1	2.7	.124
CCB	16.7	17.9	.699
Antidiabetic medications	9.6	7.8	.104

CAD – coronary artery disease; LDL – low-density lipoprotein; HDL – high-density lipoprotein; ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; CCB – calcium channel blocker; OAD – oral antidiabetic drug. The normal cut-off value of troponin in our laboratory <0.04 mg/L.

Table 2. Baseline angiographic and postprocedural characteristics according to final thrombus grade.

Variables	Low thrombus burden (n=299)	High thrombus burden (n=481)	P Value
Infarct-related artery,%			
LAD	49.5	42.4	
LCx	18.4	24.5	.070
RCA	29.8	31.8	
Tirofiban administration,%	68.6	42.8	<.001
Procedure,%			
Direct stenting	12.4	8.9	
PTCA + stenting	86	85.2	.008
Only PTCA	1.7	5.8	
Postprocedural TIMI flow (≥III)%	82.1	72.9	.003
IRA-cTFC	22.1±6.2	25.2±21	.013
TMPG (≥II),%	75.3	58	<.001
No reflow%	5.5	14.4	<.001

LAD – left anterior descending; LCx – left circumflex; RCA – right coronary artery; LMCA – left main coronary artery; IRA – infarct related artery; PTCA – percutaneous transluminal coronary angioplasty; TIMI – thrombolysis in myocardial infarction; cTFC – corrected TIMI frame count; TMPG – TIMI myocardial perfusion grade; ECG – electrocardiography.
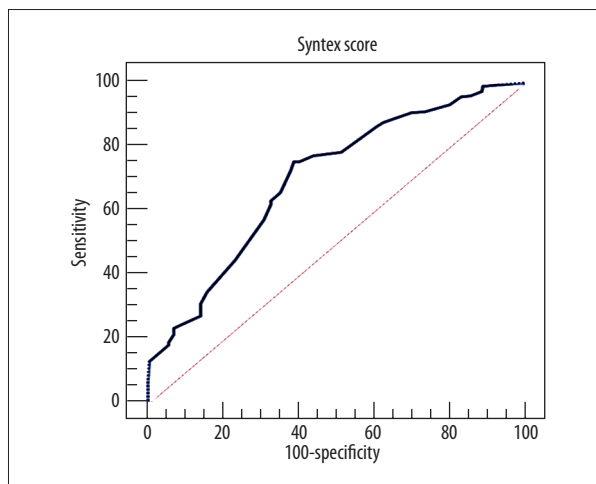

Figure 1. The discriminatory value of Syntax score for high thrombus burden was assessed by ROC analysis.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation, whereas categorical variables are expressed as percentage. Comparison between groups was made using the Student t test, Mann-Whitney U test or chi-square tests, as appropriate. Multiple logistic regression analysis was performed to identify the independent predictors of high thrombus burden using variables. Two-tailed P values <.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS, version 18.0 for Windows. In order to predict cutoff value of SYNTAX score, receiver operating characteristics (ROC) curve analysis was performed by MedCalc statistic software (version 13.2.0, Mariakerke, Belgium).

Results

The study population consisted of 780 patients with STEMI (mean age 56±11, 52.8% male). The mean SYNTAX score was 18±9.5. We formed two groups according to the final TIMI thrombus grade; 299 (%38.3) patients had low thrombus burden whereas 481 subjects (%61.7) had high thrombus burden. The comparisons of basic clinical and laboratory findings between groups thrombus burden were presented in Table 1. Patients with high thrombus burden were older (57.1 *vs.* 55.4 p=0.033), with higher diabetes prevalence (30.4% *vs.* 23.7% p=0.049), longer pain to balloon time (280±502 min *vs.* 220±121 min p=0.042), higher leukocyte count (9.7±2.5×10^3/μL *vs.* 9.2±2.5×10^3/μL p=0.013), higher baseline troponin (2.3±1.5 mg/L *vs.* 2.1±1.5 mg/L P=0.047), and baseline CK-MB concentrations (37.1±15.1 IU/L *vs.* 35±13.7 IU/L p=0.048). Comparison of the baseline angiographic characteristics and postprocedural findings of the groups based on thrombus burden were detailed in Table 2. Tirofiban administration (42.8% *vs.* %68.6%, p<.001), and direct stenting (8.9% *vs.* 12.4%, P=0.008) were less frequent, and SYNTAX score was higher (20.7± 9.1 *vs.* 13.8±8.6) in patients with high thrombus burden. Although epicardial

Table 3. Multivariate logistic regression analyses to detect the independent predictors of high TIMI thrombus burden.

Variables	Multivariate OR, 95% CI	Multivariate P value
Age	1.01 (1.00–1.03)	0.019
Diabetes	0.58 (0.58–0.40)	0.004
Pain-balloon time	1.00 (1.00–1.00)	0.102
White blood cell count	1.11 (1.04–1.18)	0.001
Baseline troponin	1.16 (1.05–1.29)	0.004
Baseline CK-MB	1.00 (0.99–1.02)	0.104
Syntax score	2.45 (1.36–4.39)	<0.001

OR – odds ratio; CI – confidence interval; CK-MB – creatine kinase-MB. Boldface values indicate the variables entered to multivariate model.

perfusion parameters were better (82.1% *vs.* 72.9% for TIMI flow III, p=.003 and 25.2±21 *vs.* 22.1±6.2 for cTFC, p=.013), myocardial perfusion grades were lower (58% *vs.* 75.3%, p<0.001) in patients with high thrombus burden.

The discriminatory value of SYNTAX score for high thrombus burden was assessed by ROC analysis and revealed a sensitivity of 75.5%, specificity of 61.2%, and cut-off value of >14 (area under the curve (AUC): 0.702; 95% confidence interval [CI]: 0.773–0.874; P<0.001) (Figure 1).

Multivariate logistic regression analysis was performed in order to determine the independent predictors of high thrombus burden. SYNTAX score (odds ratio: 2.45,95% confidence interval: 1.36–4.39, P <0.001), age (odds ratio: 1.01,95% confidence interval: 1.00–1.03, P <0.01), DM (odds ratio: 0.58, 95% confidence interval: 0.58–0.40, P <0.004), WBC (odds ratio: 1.11,95% confidence interval: 1.04–1.18, P<0.001), baseline troponin levels (odds ratio: 1.16, 95% confidence interval: 1.05–1.29, P<0.004) were found as significant independent predictors for HTB in patients with STEMI (Table 3).

Discussion

We revealed that SYNTAX is independently related to TIMI thrombus burden in addition to presence of DM, baseline leukocytes and troponin concentration, and age. Our study is the first to show the higher thrombus burden with increasing SYNTAX scores.

The basic pathophysiologic event that initiates atherosclerotic myocardial infarction is plaque rupture, ensued by intracoronary thrombus generation [20]. Following thrombus generation several mechanisms, one of which is nitric oxide (NO) secretion from endothelial cells counteracts in order to limit thrombus propagation. Endothelial dysfunction is closely related to decreased NO secretion and predisposition to vasoconstriction [21]. A recent study documented that coronary artery disease severity and complexity documented by SYNTAX score is associated with worsening grades of endothelial dysfunction [22]. Therefore, increased SYNTAX score with higher endothelial dysfunction may cause decreased NO secretion and result in higher thrombus burden. We think that the same mechanism may also apply in diabetes mellitus and advanced age.

Inflammatory reaction due to atherosclerosis may be another possible mechanism. Atherosclerosis is a chronic inflammatory disease of the vessel wall [23]. Inflammation has both local and systemic effects, which results in plaque rupture or erosion, and thrombocyte activation [24,25]. It is well known that the thrombogenicity of the ruptured material increase with higher inflammatory mediator and cell content [24–26]. Systemic inflammatory response may have additional influence on thrombogenesis [27]. Barron et al. documented that higher leukocyte count was an independent predictor of thrombus burden in patients with STEMI [28], highlighting the importance of systemic inflammation in intracoronary thrombogenesis. We think that higher SYNTAX scores reflect higher atherosclerotic burden and increased systemic inflammation, proved by elevated leukocyte counts, may cause higher thrombus burden in our patients with STEMI. Both increased inflammation and endothelial dysfunction may justify the link between SYNTAX score and thrombus burden in our study.

A recent study by Tanboğa and co-workers identified red cell distribution width as the only independent predictor of thrombus burden in STEMI [29]. Interestingly, DM and advanced age were not predictors in this study. This study and ours share similar results, one of which is that increased troponin concentrations were related to higher thrombus burden. Similarly, angiographic no-reflow was more frequent in patients with high thrombus burden and pre-procedural tirofiban infusion lowered thrombus burden in both studies. Although pain-balloon

time was longer in high thrombus burden group, this was not an independent predictor.

DM is an important cardiovascular risk factor. Several mechanisms are responsible for cardiovascular morbidity and mortality in DM, one of which is increased thrombogenicity [30]. We found DM as an independent prognosticator of initial thrombus burden in patients undergoing PPCI. Similar to our study, Wang et al. demonstrated that admission glucose concentration was independently related to no-reflow phenomenon [31].

Several studies identified that SYNTAX score has important prognostic value. Higher SYNTAX values indicate high thrombus burden, no-reflow risk and higher mortality. Although there is not any definitive proof in the current medical literature, higher SYNTAX scores may warrant additional treatment options like glycoprotein IIb-IIIa inhibitors, thrombus aspiration [32–34]. High SYNTAX scores help the interventionalist additionally by identifying patients with more complex coronary anatomy, larger ischemic territory, and possibility of peripheral arterial disease. High SYNTAX score following PPCI is associated with increased long-term morbidity and mortality [35,36].

Limitations

The main limitation of our study is the retrospective design. We could not assess inflammation by using additional markers such as high-sensitive C reactive protein. Even though we utilized the TIMI thrombus grade, a well-known and widely used classification, this grading may not be the perfect and ideal. Lastly, we did not utilize thrombus aspiration in our study.

Conclusions

Age, diabetes mellitus, admission troponin and leukocyte concentrations, and SYNTAX score are independently associated with TIMI thrombus burden in patients undergoing PPCI for STEMI. Angiographic no-reflow is more frequent in patients with high thrombus burden. SYNTAX score may have additional value in predicting higher thrombus burden besides being a marker of coronary artery disease severity and complexity.

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