Mechanisms of ST Elevation Myocardial Infarction in Patients Hospitalized for Noncardiac Conditions

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ST elevation myocardial infarction (STEMI) occurring in patients hospitalized for a noncardiac condition is associated with a high mortality rate and thus we sought to determine the mechanisms underlying STEMI in this patient population. This is a single center retrospective study of 70 patients who had STEMI while hospitalized on a noncardiac service and underwent coronary angiography. Thrombotic in-hospital STEMI was defined by angiographic or intravascular imaging evidence of intracoronary thrombus, plaque rupture, or stent thrombosis. Thirty-six (51%) inpatient STEMIs developed in the operating room or various postoperative stages and 6 (9%) after endoscopy or a percutaneous procedure. Thrombotic etiologies were found in 39 (56%) patients. Nonthrombotic etiologies included vasospasm, supply-demand mismatch, and takotsubo cardiomyopathy. Patients in the thrombotic group were more likely to have antiplatelet medications discontinued on admission, had higher peak troponin levels and were more likely to undergo percutaneous coronary intervention than patients in the nonthrombotic group. Exposure to vasopressors, time from ECG to angiography, post-STEMI ejection fraction, length of stay, and in-hospital mortality were similar in both groups. There was no difference in the use of percutaneous coronary intervention in patients but longer ECG to coronary angiography times and fivefold higher in-hospital mortality in thrombotic inpatient STEMI compared with 643 patients who presented with an out-of-hospital STEMI during the same time period. In conclusion, thrombotic and nonthrombotic mechanisms cause STEMI in hospitalized patients and are associated with a high mortality. **(Am J Cardiol 2019;123:1393−1398)**

ST-segment elevation myocardial infarction (STEMI) that occurs in hospitalized patients is a unique disease entity with distinct epidemiology and outcomes compared with STEMI occurring out of the hospital. Patients with in-hospital onset of STEMI tend to be older, are more often women, have more co-morbid conditions and are less likely to undergo revascularization than outpatient onset STEMI.[1−6] These patients experience longer delays in recognition, less utilization of standard therapies, longer lengths of stay, and more resource utilization than outpatient STEMI.[1−6] The in-hospital mortality for inpatient STEMI is 4—10-fold higher than out-of-hospital STEMI.[3] The mechanisms underlying out-of-hospital STEMI have been well defined with the vast majority of cases being caused by atherosclerotic plaque rupture, ulceration, erosion, or fissure resulting in intraluminal coronary artery thrombosis and occlusion of blood supply.[7] In contrast, the mechanisms underlying in-hospital STEMI have not been characterized and thus the purpose of the present study was to define the etiology of in-hospital STEMI in a retrospective analysis of 70 cases from a large, tertiary care hospital.

Methods

This is a single center retrospective study performed at the University of North Carolina Hospitals, an academic tertiary health care facility. After approval by the Institutional Review Board, we identified 70 patients who met the inclusion criteria. All of these patients were admitted to a noncardiac service, had ST elevations meeting STEMI criteria on ECG[8] and underwent coronary angiography for further evaluation. Patients were excluded if initial presentation and reason for hospitalization was cardiac in nature or if they had cardiac surgery or coronary angiography with percutaneous coronary intervention (PCI) immediately before the ST elevations noted on ECG.

Information on demographics, co-morbidities, procedural and hospitalization details, angiographic characteristics, hemodynamic status, use of vasopressors and mechanical circulatory support, transfusion or prothrombotic agents, and discontinuation of antiplatelet agents were independently reviewed by 2 cardiologists. Angiographic and intravascular imaging (if available) findings were used to characterize each patient as thrombotic versus nonthrombotic. If the findings were equivocal or if there was a disagreement, the chart, angiography, and intracoronary images were reviewed by a third cardiologist. Thrombotic in-hospital STEMI was defined as occurring if there was angiographic or intravascular imaging evidence of

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.01.039

intracoronary thrombus, plaque rupture, or stent thrombosis. Data elements for outpatient STEMIs that underwent coronary angiography were obtained from the hospital NCDR CathPCI Registry.

History of cerebrovascular accident or transient ischemia attack was obtained from the medical record. Sleep apnea, hypertension, diabetes mellitus, and/or chronic obstructive pulmonary disease were considered present if the patient was receiving treatment. Known coronary artery disease was present if the patient had previous angiographic evidence of >70% stenosis in a major epicardial coronary artery or branch, previous history of coronary revascularization or previous myocardial infarction (MI). Chronic kidney disease was considered present as a binary variable if the patient had been diagnosed with stage 3, 4, or 5 chronic kidney disease.

Continuous variables are presented as mean ± standard deviation if normally distributed and median [25%, 75%] if non-normally distributed. Differences in continuous variables were compared using a Student's *t* test for normally distributed continuous variables and a Wilcoxon rank sum test for non-normally distributed continuous variables. Categorical variables were compared using chi-square test or a Fisher's exact test when appropriate. Data are presented in graphical form using box-and-whisker plots with boxes representing medians with 25th and 75th quartiles, whiskers representing 10th and 90th percentiles and dots representing data points that fall outside the 10th and 90th percentiles.

Results

We identified 99 patients who had STEMI while hospitalized on a noncardiac service from January 1, 2007 to December 31, 2017 including 70 (71%) who underwent coronary angiography. Reasons patients were deemed unsuitable for coronary angiography included active or excessive risk of bleeding, acute neurological symptoms and/or altered mental status, family and/or patient wishes, or excessive co-morbidities. Of the patients who underwent coronary angiography, 5 (7%) inpatient STEMIs developed in the operating room, 31 (44%) at various postoperative stages (median [25%, 75%] 2.5 [1, 4] days postoperatively) and 6 (9%) developed after endoscopy or a percutaneous vascular, noncardiac procedure. Twenty-eight (40%) patients were in the hospital being treated for a nonsurgical condition. Demographics are shown in Tables 1 and 2.

Based on findings at coronary angiography, patients were classified as having a thrombotic (n = 39; 56%) or nonthrombotic event (n = 31, 44%; Figure 1). Etiologies of nonthrombotic events included vasospasm, presumed supply-demand mismatch, stress-induced (takotsubo) cardiomyopathy and other (e.g., pulmonary embolism, anterior wall aneurysm, electrolyte abnormality, embolization of a valvular vegetation to an epicardial coronary artery). Patients with supply-demand mismatch had severe coronary artery disease (Figure 2) and an inciting event such as hypotension and tachycardia due to bleeding or sepsis. Five patients (7.1%) were classified as having ST elevations secondary to coronary vasospasm which was demonstrated by coronary angiography. Stress cardiomyopathy was diagnosed in 4 patients (5.5%) using the Mayo Clinic definition.[9] The mean age (SD) was 67 ± 9 years and 3 (75%) of the patients were women. These patients were in the hospital for respiratory failure (2), pancreatitis (1), or failure to thrive in the setting of a malignancy (1).

Patients in the thrombotic group had higher peak troponin levels after the STEMI and were more likely to undergo PCI than patients in the nonthrombotic group (Table 1 and Figure 3). There was no significant difference between thrombotic and nonthrombotic groups in the number of patients with known CAD or the use of aspirin or statin as home medications (Table 2). The use of P2Y12 inhibitors and β blockers prior to admission was more common in the thrombotic group. There was a trend toward thrombotic patients being more likely to be male but there were no statistically significant differences in demographics between patients with and without coronary thrombus. Exposure to vasopressors within 1 hour of development of ST elevation occurred in approximately one-third of patients in both

Table 1
Comparison of in-hospital STEMI and outpatient STEMI. UNC Hospitals switched from using troponin T (TnT) to troponin I (TnI) during the period covered by this study. Echocardiographic ejection fraction (EF) was obtained within 48 hours of STEMI. EF = ejection fraction; FDA = first device activation; PAD = peripheral arterial disease

	Thrombotic in-hospital STEMI (n = 39)	Nonthrombotic in-hospital STEMI (n= 31)	p value Thrombotic vs nonthrombotic in-hospital STEMI	Outpatient STEMI (n = 636)	p value Thrombotic in-hospital STEMI vs outpatient STEMI
Age (years)	64.5 ± 11.2	66.4 ± 12.1	0.51	63.0 ± 13.9	0.37
Women	11 (28%)	15 (48%)	0.08	210 (33%)	0.5
Hypertension	33 (85%)	22 (71%)	0.19	458 (72%)	0.44
Diabetes Mellitus	14 (36%)	8 (26%)	0.37	158 (25%)	0.16
PAD	9 (23%)	6 (19%)	0.47	57 (9%)	0.66
ECG to angiography (minutes)	80 [50, 145]	81 [55, 123]	0.65	52 [36, 66]	<0.0001
ECG to angiography ≤60 minutes	13 (33%)	8 (26%)	0.66	403 (67%)	0.02
ECG to FDA (minutes)	97 [62, 164] n = 37	108 [73, 155] n = 10	0.68	62 [51, 79] N = 598	<0.001
ECG to FDA ≤90 minutes	17 (46%)	4 (40%)	0.80	508 (85%)	.01
Peak TnT (ng/ml)	3.99 [0.91, 6.7] (n = 7)	0.12 [0.03, 4.11] (n = 3)	0.34	2.7 [0.99, 6.27] (n = 106)	0.90
Peak TnI (ng/ml)	50.1 [11.5, 199.5] (n = 32)	0.59 [0.06, 9.63] (n = 28)	<0.001	27.6 [10.5, 65.2] (n = 506)	0.067
Post-STEMI EF (%)	55 [45, 60]	60 [44, 65]	0.22	50 [40,58]	0.24
Length of stay (days)	14.1 ± 13.8	20.4 ± 32.6	0.28	3.9 ± 4.1	<0.0001

Table 2
Comparison of events before in-hospital STEMI and outcomes in patients with and without intracoronary thrombus. CVA/TIA = cerebrovascular accident/transient ischemic attack; previous history of coronary artery disease was present if the patient had previous angiographic evidence of >70% stenosis in a major epicardial coronary artery or branch, previous history of coronary revascularization or previous myocardial infarction

	Thrombotic STEMI (n = 39)	Nonthrombotic STEMI (n = 31)	p value
Post-operative state	22 (56%)	19 (61%)	0.75
Discontinuation of anti-platelet agent during admission	14 (36%)	1 (3%)	0.001
Vasopressors within one hour of STEMI	13 (34%)	12 (39%)	0.69
Chronic kidney disease	9 (23%)	8 (26%)	0.79
Sleep Apnea	1 (3%)	1 (3%)	0.89
Chronic obstructive pulmonary disease	5 (13%)	8 (26%)	0.17
CVA/TIA	7 (23%)	7 (23%)	0.63
Prior history of coronary artery disease	16 (41%)	9 (29%)	0.26
Home medications			
Aspirin	24 (62%)	14 (45%)	0.17
P2Y12 inhibitor	14 (36%)	3 (10%)	0.01
Beta-blocker	22 (56%)	10 (32%)	0.04
Statin	21 (54%)	14 (45%)	0.47

groups (Table 2). The time from ECG to angiography, time from ECG to first device activation, post-STEMI ejection fraction, and length of stay were similar in both groups (Table 1). There was no difference in survival to hospital discharge (69% in thrombotic group and 68% in nonthrombotic group, p = 0.89; Figure 3).

Patients with thrombotic events were more likely to die from cardiogenic shock or arrhythmia (30.5% vs 0%; p = 0.01) and to have antiplatelet medications (aspirin and/or P2Y12 inhibitor) discontinued on admission than the nonthrombotic group (Table 2). There was no significant difference in platelet count on admission versus platelet count preceding the onset of STEMI (252,000 (190,000, 316,750)/ul versus 264,000 [170,000, 316,750]/ul; p = 0.93). Of the 5 patients with stent thrombosis, 4 had antiplatelet drugs held on admission (2 for thrombocytopenia and 2 in preparation for surgery) and the other patient had received intravenous tPA for a stroke (antiplatelet medications were continued).

To compare patients with an in-hospital thrombotic event to those with an out-of-hospital thrombotic event, 643 patients who presented with an out-of-hospital STEMI during the same time period were identified (Table 1). Patients who were transferred from another facility were excluded. Of these patients 636 (99%) underwent coronary angiography. There was no difference in age, gender, or the prevalence of hypertension, or diabetes in patients with thrombotic in-hospital STEMI compared with out-of-hospital STEMI who underwent coronary angiography. The use of PCI was similar (95% vs 94%, p = 1.0; Figure 3) with in-hospital STEMI patients having longer ECG to coronary angiography times and ECG to first device activation times. There was a trend towards higher peak troponin I levels and a fivefold higher in-hospital mortality in patients with thrombotic in-hospital STEMI compared to outpatient STEMI (31% vs 6%, p <0.001; Figure 3).

Discussion

Although, the primary mechanism for outpatient-onset STEMI is thrombotic occlusion of an epicardial coronary artery, the mechanisms of inpatient STEMI are more variable. In our study, 44% of the patients had ST elevations on ECG due to a nonthrombotic mechanism such as supply-demand mismatch or stress-induced cardiomyopathy. The overall mortality rate in patients who developed inpatient-onset STEMI was high and was not affected by the etiology with both thrombotic and nonthrombotic groups having a mortality rate of approximately 32%. The high in-hospital mortality seen in the present study is consistent with previous studies which have reported in-hospital mortality for patients who develop in-hospital STEMI to be in the range of 8% to 66%.[3] In this study, the in-hospital mortality rate for inpatient STEMI was approximately fivefold higher

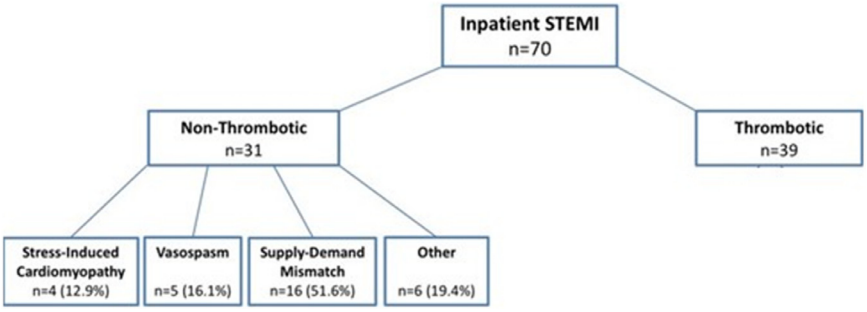

Figure 1. Mechanisms of in-hospital STEMI (central illustration).

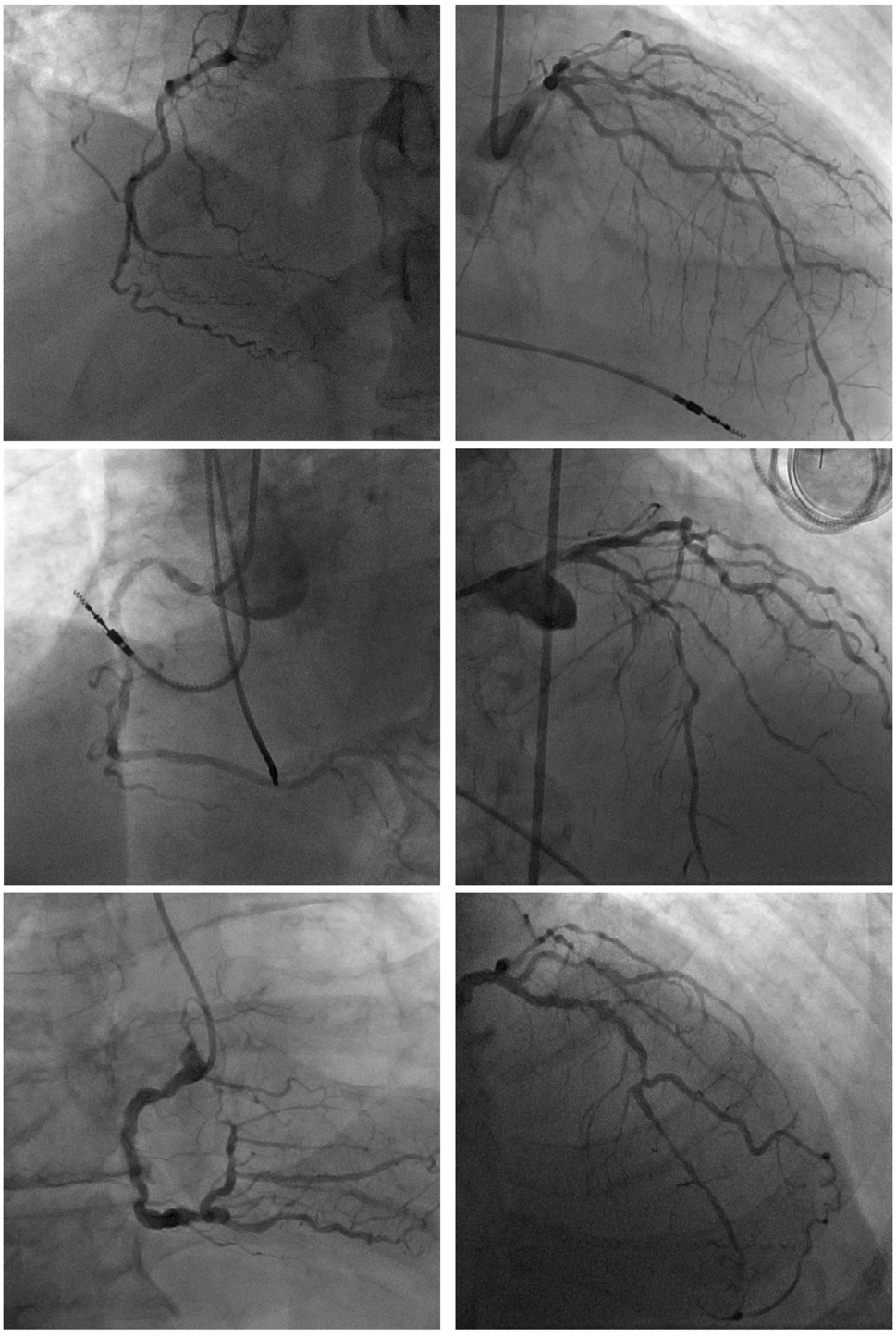

Figure 2. Representative coronary angiograms from 3 patients with supply-demand mismatch causing ST elevation.

than with outpatient STEMI consistent with multiple previous studies showing that in-hospital mortality is much higher when STEMI occurs in hospitalized patients as compared with outpatient onset.[1,5,10–12]

The present study provides insight into previous studies showing that only 22% to 56% of in-hospital STEMI patients undergo PCI, a rate much less than seen with out-of-hospital STEMI.[3] We found that 44% of patients who underwent coronary angiography did not have a thrombotic lesion, and of these only 32% underwent PCI. More surprising was the similar mortality rates observed in patients with thrombotic versus nonthrombotic in-hospital STEMI given the different utilization rates of PCI in the 2 groups (95% vs 29%). We previously showed in a retrospective study that patients who underwent PCI had improved survival irrespective of their pre-STEMI risk profile.[2] Delays in

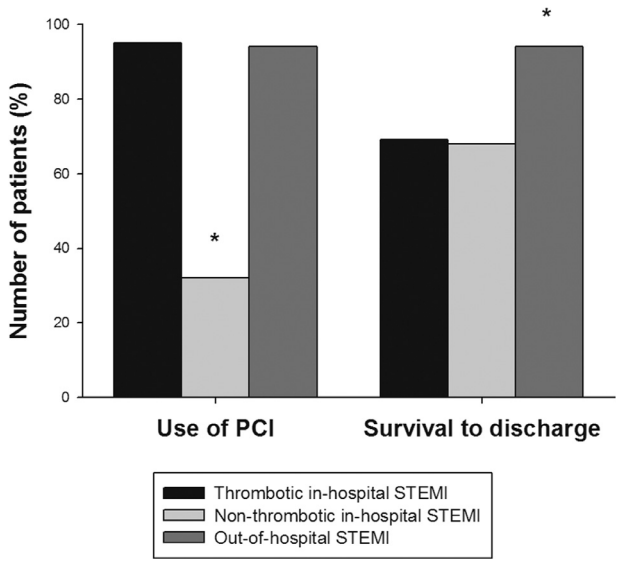

Figure 3. Use of PCI and survival to hospital discharge in patients with in-hospital and out-of-hospital STEMI (*—p <0.05 compared with thrombotic in-hospital STEMI group).

treatment may partially account for the high mortality rate in patients with thrombotic in-hospital STEMI. Patients who developed thrombotic in-hospital STEMI were similar in demographics, co-morbidities, and treatment compared with patients with out-of-hospital STEMI, but there were significant differences in processes of care. ECG to coronary angiography times were 28 minutes longer than observed in outpatient STEMI. Delays in reperfusion are likely much more pronounced as we and others have previously shown delayed recognition of inpatient STEMI and long delays between symptom onset and ECG.[3,11] Previous studies have shown that the time between the onset of coronary ischemia and revascularization in in-hospital STEMI can be improved by programs aimed at increasing inpatient STEMI awareness, encouraging early acquisition and interpretation of ECG, and establishing effective inpatient STEMI alert systems.[13]

Four patients had stent thrombosis as the cause of in-hospital STEMI. Two of these patients had antiplatelet medications discontinued on admission because of thrombocytopenia with stent thrombosis occurring as platelet count increased; for 1 patient the platelet count increased from 26×10^9 per liter on admission to 205×10^9 per liter on the day of in-hospital STEMI and for the other patient the platelet count increased from 18×10^9 per liter to 117×10^9 per liter. ACS has been reported in patients receiving platelet transfusions and in patients with ITP who have rapidly increasing platelet counts after treatment with IgG.[14–16] Cancer patients have also been reported to have a higher incidence of stent thrombosis.[17] Taken together these studies suggest that cancer patients with an intracoronary stent and thrombocytopenia are at risk of stent thrombosis as platelet counts increase.

A significant proportion of nonthrombotic ST elevation patients had severe coronary artery disease without evidence of intracoronary thrombus and thus presumed significant supply demand mismatch in the setting of tachycardia and/or hypotension due to major bleeding, septic shock or other cause of hemodynamic disturbance. These patients would be classified as type 2 MI under the fourth Universal Definition of Myocardial Infarction with myocardial ischemia, not due to plaque rupture but secondary to an imbalance between myocardial oxygen demand and supply due to an underlying cause.[18–20] Previous studies have shown that the frequency of ST elevation in type 2 MIs varies from 3% to 24%.[21] Notably, there are similarities between patients with nonthrombotic in-hospital STEMI and patients who have type 2 MI.[22,23] Although our study was not large enough to provide statistical significance, patients with nonthrombotic in-hospital STEMI were numerically older, more likely to be women and had lower peak troponin levels than patients with thrombotic in-hospital STEMI.

Our study had several limitations. First, it was a single-center, retrospective study. Second, we only included patients that underwent coronary angiography. Third, the number of patients with in-hospital STEMI was relatively small. Fourth, most patients were characterized as thrombotic versus nonthrombotic based solely on angiography as intracoronary imaging was only available in a minority of patients.

The development of a STEMI while hospitalized for a noncardiac condition is associated with a low use of PCI and a high mortality rate. This study provides insight into these findings by demonstrating that 44% of patients had a nonthrombotic etiology. Moreover, mortality was equally high in both thrombotic and nonthrombotic groups suggesting that additional studies are needed to determine the optimal strategy and processes of care for revascularization in patients with in-hospital STEMI.

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