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Original Article

Diagnostic performance of thrombin generation assay in patients with acute myocardial infarction

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Abstract

Background: Thrombin generation (TG) assays have been developed to assess the overall coagulability of blood, as thrombin plays a pivotal role in hemostasis and thrombosis. Although increased TG has been associated with acute myocardial infarction (MI) in some previous reports, the results have been inconsistent. This study aimed to evaluate TG in platelet-poor plasma specimens from patients with confirmed acute MI.

Methods: In this case-control study, we enrolled a total of 50 patients diagnosed with acute MI using convenience sampling, along with 50 healthy individuals. TG assays were performed in both groups, and the calculated TG indices were compared.

Results: Forty-one patients with confirmed acute MI (24 males, 17 females; mean age 62.7±14.9 years) and 50 healthy controls (40 males, 10 females; mean age 57.5±12.9) were included in the analysis. TG assay indices were not significantly different in acute MI patients compared to healthy subjects ($p > 0.05$). In terms of the diagnostic utility of TG assays, a five-variable panel yielded an AUC of 0.659 [95% CI: 0.547-0.770, P=0.010], with a sensitivity of 65.9% and specificity of 62% for identifying acute MI.

Conclusion: All TG parameters taken together appear to have a predictive value in detecting acute MI. However, further studies with larger sample sizes are needed to confirm this finding.

Keywords: Myocardial infarction, Thrombin generation, Endogenous Thrombin Potential, Atherothrombosis, Coagulation.

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Acute myocardial infarction (MI), the most severe manifestation of coronary artery disease (CAD), is characterized by myocardial necrosis resulting from an unstable ischemic syndrome (1). This condition imposes a substantial global health burden, affecting over 7 million individuals annually (2). It is noteworthy that more than 80% of the global burden of cardiovascular disease and acute MI is borne by low- and middle-income countries (3, 4). The diagnosis of MI traditionally involves clinical assessment, electrocardiography, laboratory data, invasive and noninvasive imaging, and pathological examination (1). In many cases of acute MI, the underlying mechanism involves the rupture of a vulnerable, lipid-laden atherosclerotic coronary plaque or endothelial erosion in the coronary artery, triggering a cascade of events. These events manifest as elevated cardiac biomarkers in peripheral blood (5). Among these biomarkers, cardiac troponin isoforms I and T have emerged as highly sensitive and specific indicators of myocardial injury, detectable within 2-3 hours and peaking at 24-28 hours (6). The adoption of cardiac troponin T in clinical practice has resulted in a 20% increase in NSTEMI (non-ST segment elevation myocardial infarction) diagnoses, accompanied by a decrease in unstable angina diagnoses (7). Interestingly, several novel biomarkers have surfaced for identifying or predicting acute MI outcomes.

These include combinations such as Heart-type Fatty Acid Binding Protein + copeptin + cardiac troponin, N-Terminal Pro-B-type Natriuretic Peptide, growth differentiation factor-15 + high-sensitivity C-reactive protein (CRP), pregnancy-associated plasma protein A levels with chest pain, myeloperoxidase, and high-sensitivity CRP (8). However, currently, only cardiac troponin sees routine clinical use, recent research has emphasized thrombin, a key enzyme in the clotting system, as having a central role in ischemic heart disease (IHD), particularly in acute coronary syndrome (ACS) (9, 10).

Thrombin generation (TG), a laboratory tool introduced by Hemker et al. in 2000, has enabled the monitoring of thrombin activity in plasma-based systems through continuous measurements of the fluorescent split-product of a fluorogenic substrate (11). This method capitalizes on thrombin's critical regulatory role in hemostasis and thrombosis, as it governs pro- and anti-coagulant reactions by interacting with other coagulation proteins and cellular receptors (12, 13). Consequently, over the last two decades, TG has captured the attention of numerous researchers as a laboratory tool for investigating hypo- and hyper-coagulability, surpassing the capabilities of conventional global coagulation tests. A scrutiny of the literature reveals that. TG has been applied in five categories: elucidating mechanisms of thrombogenesis, diagnosing hemostatic disorders, monitoring treatment with pro-hemostatic agents, monitoring treatment with antithrombotic drugs, and predicting the risk of recurrent venous thromboembolism (14). In patients with ACS, several TG values have shown associations with coronary stenosis, although this trend is not consistently reproducible. TG values do not reliably predict coronary stenosis severity in patients without myocardial injury evidence but may hold predictive value in patients with established IHD and ACS. Moreover, TG may correlate with troponin peak levels (9).

While various studies have reported significant associations between different coagulation proteins and atherosclerosis, as well as atherothrombotic complications, the results, particularly in clinical studies, have not always been consistent (15). For instance, studies by Loeffen's team emphasized that "hypercoagulability may be an important contributor to the pathophysiology of atherosclerosis and atherothrombosis." In 2014, they demonstrated that a delayed and decreased TG assay was a strong and independent predictor of stroke in elderly individuals at an increased risk of vascular disease. However, no consistent association was found between TG assay and incident CAD (16). Nonetheless, their 2016 study showed a significant increase in TG assay values in ACS compared to non-ACS patients (17). In 2020, Elad B et al. confirmed that TG may possess the ability to predict the severity of coronary disease in ACS patients (9). Additionally, more evidence has emerged concerning the mechanisms of hypercoagulability and clinically relevant outcomes, affirming that certain TG parameters are independently associated with overall mortality (14). Previous studies have focused less on the diagnostic value of the TG assay, so in this study, we aimed to compare TG assays in platelet-poor plasma (PPP) specimens from patients with confirmed acute MI with those from healthy subjects and investigate the diagnostic potential of TG assays for acute MI.

Methods

Subjects and setting: In this case-control study, we included all newly confirmed acute myocardial infarction (MI) patients admitted from March 2018 to March 2020 at two hospitals: Zahra Expert Cardiac Hospital affiliated with Shiraz University of Medical Sciences and Peymaniyeh Hospital affiliated with Jahrom University of Medical Sciences. Patients who agreed to participate in the study and were eligible for testing were enrolled (n=50). The control group consisted of 50 healthy age-matched individuals with no previous medical history of cardiovascular disease, coagulopathy, or chronic diseases. These control subjects were recruited from individuals receiving family physician health services in outpatient clinics at the same medical centers. Nine patients' coagulation assessment samples did not pass quality control and were excluded from further analysis, resulting in a final case group of 41 patients. We determined the sample size based on Loeffen R, van Oerle R, Leers MP, Kragten JA, Crijns H, Spronk HM, et al.(17), considering a peak height of 148±53 nM in patients with ACS versus 122±42 nM in individuals without ACS, with a confidence level of 95% (1-α) and a power of 70% (β), resulting in a required sample size of 42.

Inclusion Criteria:

Case group: Confirmed acute myocardial infarction. No medical history of chronic or acute diseases affecting the coagulation system, such as diabetes, chronic liver diseases, chronic or acute infectious disease, collagen vascular disease. Not using any medication that interferes with the coagulation system.

Control group: Age-matched healthy participants referred to the same centers for family physician health services. No past medical history of cardiac or coagulation problems.

Exclusion criteria (case group): Medical history of chronic or acute diseases affecting the coagulation system, such as diabetes, chronic liver diseases, chronic or acute

infectious disease, and collagen vascular disease. Use of medications interfering with the coagulation system, such as anticoagulants (i.e., heparin, warfarin, enoxaparin, etc.) or platelet activity-interfering drugs (i.e., aspirin).

Assessments: The coagulability state of acute MI patients was assessed using the thrombin generation (TG) assay. This assay employed the thrombin scope system, its software (Thermo Fisher Scientific Company, MA, USA), and domestic kits to compare thrombograms of acute MI patients with controls. To minimize the influence of anticoagulants such as LMWH on the TG assay, blood sampling was performed upon arrival for suspicious subjects.

The sampling procedure ensured a smooth and relaxed environment. Nine milliliters of blood were collected in citrate tubes, and plasma was promptly extracted. Thrombin generation analysis was carried out on platelet-poor plasma (PPP) to exclude the effects of platelets. PPP was prepared by centrifuging the samples at 2000 g for 20 minutes at room temperature. The extracted plasma was snap-frozen with liquid nitrogen and stored at -80°C until confirmation of acute MI diagnosis based on ECG changes and positive serum troponin levels. The extent of generated thrombin was plotted against time by introducing a reagent to PPP, constructing a thrombin-generation curve (thrombogram). This was accomplished using the Fluoroskan Ascent Microplate Fluorometer (Thermo Scientific, Vantaa, Finland) and Thrombinoscope software (Thrombinoscope BV, Maastricht, the Netherlands). Thrombin levels were quantified using a fluorometer. The analytical program computed various parameters from the thrombogram and expressed the results as the nanomolar amount of thrombin per time unit (table 1). Troponin level of confirmed acute MI patients were evaluated by VIDAS® based on the Enzyme- Linked Fluorescent Assay (ELFA) technology, bioMérieux, France.

Statistical analysis: Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) (IBM Corp. Released 2013, IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY: IBM Corp.). Quantitative and qualitative variables were described using mean ± standard deviation (SD) or median [interquartile range (IQR)], and frequency (percent), respectively. Data normality was assessed using the Kolmogorov-Smirnov test. Quantitative variables were compared between the two groups using the student's t-test or Mann-Whitney U test, as appropriate.

The chi-square test was used to compare qualitative variables between the two groups. The Spearman correlation coefficient was calculated to determine the correlation between TG assay indices, age, and troponin levels. Additionally, we assessed the sensitivity and specificity of each TG assay parameter at the optimal cut-off value for discriminating cases from controls. The area under the curve (AUC) of each index and the combination variable (derived from five parameters) were reported through receiver operating characteristic (ROC) analysis. The "combination variable" was defined as the predicted probability obtained through logistic regression. A p- value <0.05 was considered statistically significant.

Table 1. TG assay-derived parameters

Parameter	Definition
ETP	Area under the thrombin generation curve: In vitro capacity of plasma to generate thrombin over time (or the total amount of substrate that could potentially be converted by thrombin if enough substrate is available)
Lag time	Equivalent to the clotting time
Peak	Maximum velocity of net thrombin production
TT Peak	Time elapsing to get the maximal thrombin production
Start tail	Time at which thrombin generation has come to an end

ETP: endogenous thrombin potential, TT: thrombin time.

Results

Forty-one patients with confirmed acute MI and 50 healthy controls (24 males and 17 females in patients vs 40 males and 10 females in controls (P=0.037), mean age 62.7±14.9 years in patients and 57.5±12.9 in controls, P=0.079) were included in the analysis (table 2). The values of all thrombin generation (TG) parameters were insignificantly higher in patients compared to healthy controls (p>0.05) (table 3). Troponin levels were found to be negatively correlated with Peak (rs = -0.632, P = 0.004) and positively correlated with ttPeak (rs = 0.549, P = 0.015). (Troponin level data was available for only 19 patients).

Additionally, only the Start tail showed a positive correlation with the age of acute MI patients (rs = 0.335, P = 0.032). Importantly, none of the TG indices showed a significant association with sex (p > 0.05) (table 4). In terms of predictive value of TG assay parameters for identifying acute MI patients, no single TG parameter yielded a significant AUC. However, a five-variable panel of TG assay parameters exhibited a significant AUC as a diagnostic tool for identifying acute MI, with an AUC 0.659 (95% CI:0.547-0.770), sensitivity 65.9%, specificity 62%, and cut-off value 0.417 for combined variable (figure 1 and table 5).

Table 2. Demographic and clinical variables of acute MI patients and healthy controls

Variable	Acute MI (n=41)	Controls (n=50)
Sex (Male)	24 (58.5%) †	40 (80%)
Age	62.7±14.9 ‡	57.5±12.9
Positive past medical history	28 (68.3%)	----
Positive family history of cardiovascular diseases	15 (36.6%)	----
Positive drug history (cardiovascular/anti-glycemic)	23 (56.1%)	----
Mortality	3 (7.3%)	----

† Frequency (percent); ‡ Mean ± standard deviation; Abbreviations: MI = myocardial infarction.

Table 3. Comparison of TG indices in patients and healthy controls

Parameters	Controls (n=50)	Acute MI (n=41)	P value
Lag time (*min*)	3.34 [1.36]†	3.68 [1.23]	0.281
ETP *(nmol/L)*	1818±475	1975±557	0.151
Peak (*nmol/L*)	304±88	325±69	0.221
ttPeak (*min*)	6.58 [2.19]	6.67 [2.21]	0.854
Start tail (*min*)	22.9 [6.24]	25.1 [3.67]	0. 221

† Median [IQR] or Mean ± standard deviation; Abbreviations: TG = thrombin generation assay, ETP = endogenous thrombin potential, ttPeak = time to peak, MI = myocardial infarction, IQR = inter quartile range

Table 4. TG indices correlation with demographic variables and troponin level amongst acute MI patients

Parameters	Troponin *rs* (n = 19)	Age *rs* (n = 41)	Sex (female vs. male) (n = 41, 17 vs. 24)
Lag time *(min)*	0.360, 0.130†	0.197, 0.216†	3.68 [1.34]vs.3.83 [1.33],0.605 ‡
ETP *(nmol/L)*	-0.333, 0.164	-0.048, 0.764	1951±586 vs.1992±548, 0.822
Peak *(nmol/L)*	-0.632, 0.004*	-0.253, 0.111	319±74 vs.329±66, 0.624
TT Peak *(min)*	0.549, 0.015*	0.185, 0.248	7 [1.56]vs.6.5 [2.61],0.442
Start tail *(min)*	0.252, 0.299	0.335, 0.032*	25.3 [3.37]vs,24.1 [4.14], 0.569

† Correlation coefficient, *P* value; ‡ Median [IQR] or Mean ± standard deviation, *P* value; * Statistically significant; Abbreviations: TG = thrombin generation assay, ETP = endogenous thrombin potential, TT Peak = time to peak, MI = myocardial infarction, IQR = inter quartile range; *rs* = Spearman correlation coefficient.

Table 5. Sensitivity and specificity of TG assay parameters in identifying acute MI patients

Parameters	AUC [95% CI]	P-value	Cut-off value	Sensitivity %	Specificity %
Lag time *(min)*	0.566 [0.446-0.685]	0.282	3.62	58	58
ETP *(nmol/L)*	0.572 [0.454-0.691]	0.238	1797.33	63.4	56
Peak *(nmol/L)*	0.555 [0.437-0.673]	0.367	324.79	51.2	56
TT Peak *(min)*	0.511 [0.391-0.631]	0.854	6.58	53.7	50
Start tail *(min)*	0.575 [0.456-0.694]	0.221	22.97	78	50
Panel †	0.659 [0.547-0.770]	0.010*	0.417	65.9	62

† Using predicted probability obtained from logistic regression as the test variable; * Statistically significant; Abbreviations: TG = thrombin generation assay, ETP = endogenous thrombin potential, TT Peak = time to peak, 95% CI = 95% confidence interval, AUC = area under curve

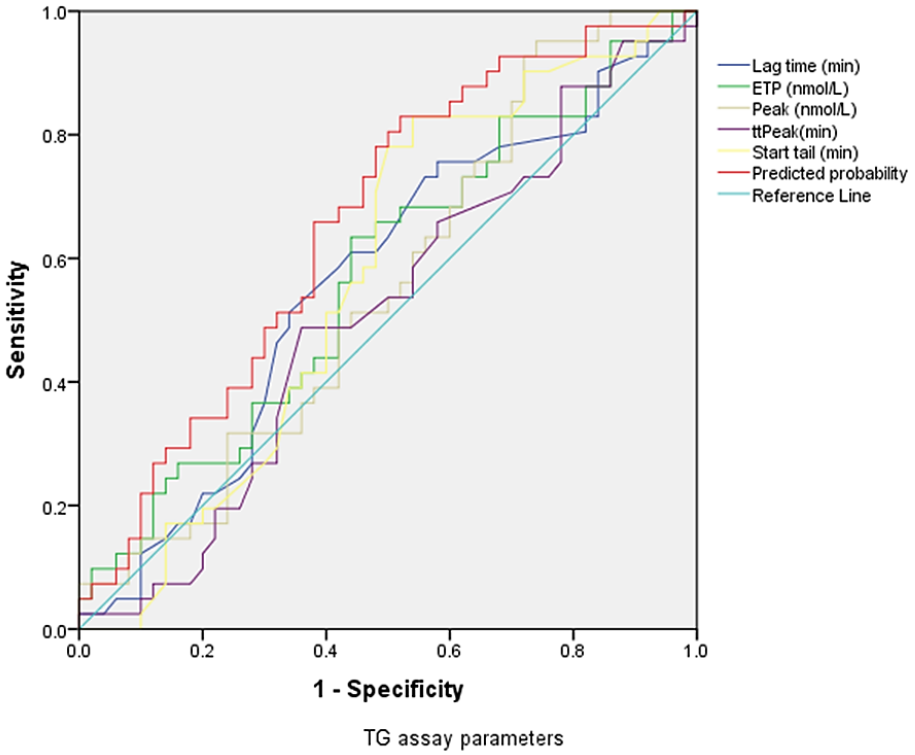

Figure 1. Area under the curve (AUC) of TG assay parameters according to receiver operating characteristic (ROC) analysis for predicting acute MI

Discussion

The blood coagulation cascade is known to be activated in the acute phase of MI and unstable angina pectoris. Both cellular and plasmatic coagulation have been identified as major contributors to cardiac damage and outcome in the setting of myocardial infarction (18). Thrombin and thrombin generation potentials are the key elements of this cascade, which are upregulated during STEMI (or ACS), activate the coagulation pathway and suppress the protein C anticoagulant function (17). According to Hemker's first law, a low level of thrombin produced in a clotting blood accompanies with bleeding risk, whereas a high level accompanies with risk of venous thrombosis (11, 19, 20). Therefore, thrombus formation system normally reduces blood loss, by maintaining a limited vascular occlusion (13). Based on the ex-vivo capacity of plasma to generate thrombin as a test of the clotting system function, we designed a case-control, double center study to evaluate the predictive value of TG parameters in identifying acute MI. Based on the results of our study, although none of the individual TG assay parameters were significantly associated with acute MI, the five-variable panel of the TG assay showed moderate diagnostic power. It exhibited a sensitivity of 66% and a specificity of 62% for identifying

acute MI patients. Furthermore, the TG assay was not associated with sex and age, except for the start tail parameter, which demonstrated a significant positive correlation with age. Additionally, troponin levels exhibited a significant positive correlation with time to peak (ttpeak) and a significant negative correlation with peak. The foundation of the hemostatic markers of thrombin activity is based on TAT (thrombin-antithrombin) and F1+2 (prothrombin fragment) complexes. It is learned from the pioneer studies that the elevated plasma levels of TAT and F1+2 promote to the activation of the end steps of the coagulation process. While the nature of TG assay is ex-vivo and developed by a distinct technology, worth noting, these studies have been shown that thrombin activity alters in acute MI, and associated with prognosis as well. Granger et al. (21) reported that baseline and 12-hour F1+2 values might be associated with an increased risk of mortality or re-infarction during 30 days after incident MI. Ardissino et al. (22), added that both high and low F1+2 levels might carry predictive value for 24 hours post-MI. Moreover, authors showed that elevated baseline TAT levels could predict mortality or re-percutaneous coronary intervention amongst ST-segment elevation MI patients. Furthermore, several studies have shown that TAT or F1+2 levels are increased in symptomatic CAD (23-28) and unstable angina (29, 30) patients. Elad B et al. found a correlation between peak height and troponin levels in the entirety of the patient's population. Seemingly, the greater severity of myocardial injury may correlate with a greater ability to generate thrombin (9). Our findings revealed a significant negative correlation between peak height and troponin levels, which is in contrast to this result. It is important to mention that our study was limited due to the small subgroup of patients of whom we were able to assess troponin levels.

Generally, we found that TG assay indices were mostly uncorrelated with age or sex. In this regard, while unrecognized confounding factors are plausible, it appears that BMI and the use of medication like aspirin and statins may not affect the TG assay indices in PPP specimen, significantly (31-33). Similarly, in a study by Orbe et al., age was not associated with TG assay indices (31). Perhaps the first study on TG assay in acute MI was carried out by Orbe et al. (31). They showed that TG indices were higher in patients with acute MI compared to patients with stable CAD or healthy controls. Smid et al. (32) showed that baseline peak height, ETP and lag time were significantly higher in the acute phase of MI compared to the control population. In Glasgow Myocardial Infarction Study, the same research group reported that 3-9 months after the incident MI, plasma thrombin generation had been significantly increased compared to healthy controls (33). In addition, Elad B et al., confirmed the ability of TG to predict the severity of coronary disease in ACS patient (9). Furthermore, Loeffen et al. (17), showed that ACS patients had altered TG assay indices compared to non-ACS patients. Also, more evidence has been found on the mechanisms of hypercoagulability and clinically relevant outcomes that confirmed some TG parameters were independently associated with overall mortality (14). By and large, it appears that TG assay reflected acute hypercoagulability in plasma during acute MI. Similar to these results, all TG parameters in our study were higher in MI patients than in healthy individuals, although the difference was not statistically significant. A larger sample size may be needed to achieve statistical significance.

The TG assay is not a complicated tool for assessing the coagulation system. It is a simple, compact piece of equipment that requires only one skilled technician to operate and provides quick results. Given its durability and efficiency, the TG assay should be considered a future diagnostic tool for various coagulation-related diseases, including acute MI. On the other hand, the five-variable panel of TG assay yielded a sensitivity and specificity of 66% and 62% in diagnosing acute MI, respectively. It suggests the possible efficiency of TG assay as a future diagnostic tool for MI. However, previous studies implied that the diagnostic performance of TG assay in PPP spacemen might be limited, due to the noticeable overlap with control values (29, 30). TG assay of whole blood and simultaneously in vivo TG assessment would be a topic for further research, since platelets pose a noticeable role in TG and arterial thrombosis.

Our study had several limitations. Case-control design and selection bias were the most important limitations of this study. Another limitation of our study was the small number of available MI cases. To more accurately determine the value of TG as a biomarker of MI, larger patient populations will need to be studied. Hence, storing serum in proper condition might lead to lose of some eligible samples. In addition, we need to transport stored samples from the medical sites to test site that also made it complicated as the samples were stored in liquid Nitrogen.

In conclusion, our study demonstrates that while the TG assay is a fast and easy-to-perform test that can be quickly analyzed, the indices are not significantly different in patients with acute myocardial infarction (MI) compared to healthy individuals. However, analyzing TG assay as a five-panel variable yielded a moderate predictive value in detecting acute MI patients. These findings suggest the

potential utility of TG assays during the acute phase of MI for diagnostic and prognostic purposes. However, further comprehensive investigations are warranted to elucidate the precise role of TG assay parameters in the clinical management of acute MI and to establish their relevance as valuable biomarkers in this context.

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Authors' contribution: Omid Reza Zekavat: concept, design and editing. Mohammad Shojaie: drafting the manuscript. Hoda Sezavarian: drafting and data collection. Sonia Rostami Ghorbani: data collection. Seyed Javad Dehghani: Laboratory analysis. Javad Gerdabi: laboratory analysis. Peyman lzadpanah: data collection and editing. Shirin Parand: data collection. Sezaneh Haghpanah: design, statistical analysis and editing.

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Availability of data and materials: Data will be shared on request to the corresponding author with permission of third party.

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