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C-reactive protein and fibrin clot strength measured by thrombelastography after coronary stenting

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Abstract

Inflammation is implicated in the progression of coronary artery disease and the molecular processes of inflammation and thrombosis are closely intertwined. Elevated levels of C-reactive protein (CRP) have been associated with an elevated risk of adverse ischaemic events after coronary stenting and hypercoagulability. Heightened whole blood clot strength measured by thrombelastography (TEG) has been associated with adverse ischaemic events after stenting. We intended to examine the relationship of CRP to plasma fibrin clot strength in patients after coronary stenting. Plasma fibrin clot strength was measured by TEG in 54 patients 16–24 h after undergoing elective percutaneous coronary intervention (PCI). Coagulation was induced in citrated plasma by addition of kaolin and CaCl₂. Plasma levels of CRP and fibrinogen were measured by enzyme-linked immunoassay. Increasing quartiles of CRP were associated with increasing levels of maximal plasma fibrin clot strength measured by TEG ($P < 0.001$) and increasing BMI ($P = 0.04$). Patients in the highest quartile of CRP had significantly higher maximal fibrin clot strength (G: 3438 ± 623 vs. 2184 ± 576 dyn/cm², $P < 0.0001$). Fibrinogen concentration was not significantly different across quartiles of CRP ($P = 0.97$). Patients with established coronary artery disease undergoing coronary stenting who have elevated CRP after PCI exhibit heightened maximal plasma fibrin clot strength as compared with those with low CRP. Thrombotic risk associated with elevated CRP may be linked to procoagulant changes and high tensile fibrin clot strength independent of fibrinogen concentration.

Keywords

clot strength; coronary artery disease; C-reactive protein; fibrin; thrombelastography

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Conflicts of interest

The authors have no conflicts of interest to declare.

Introduction

Platelet activation and aggregation are important in the genesis of coronary thrombosis, and dual antiplatelet therapy with aspirin and clopidogrel is the standard of care in the prevention of stent thrombosis after coronary stenting [1]. Although procoagulant changes in patients with coronary artery disease have been associated with adverse outcomes, oral anticoagulation with warfarin has not been associated with significant reductions in stent thrombosis rate when used in combination with aspirin alone [2–4]. Recently, results from the ATLAS ACS 2-TIMI 51 trial showing improved ischaemic outcomes in patients with recent acute coronary syndromes (ACS) treated with the factor Xa inhibitor rivaroxaban have revived interest in the role of coagulation in long-term outcomes after percutaneous coronary intervention (PCI) in patients with coronary artery disease [5].

Thrombelastography (TEG) has been well established in the clinical analysis of coagulation and fibrinolysis [6]. Previous results have suggested the predictive utility of measuring whole blood maximal clot strength in assessing risk for ischaemic events after coronary stenting, with significantly increased risk observed in patients within the highest quartiles of whole blood clot strength [2,7]. Although no direct comparison has been published between the positive predictive value of whole blood TEG and platelet reactivity testing, which has been well established in the identification of clopidogrel nonresponse after coronary stenting, the data available suggest similar utility [2,7–9]. Whole blood TEG-maximal clot strength comprises simultaneous contribution of plasma fibrin generation and platelet aggregation in the generation of a stable thrombus. The risk associated with the ex-vivo finding of elevated TEG-maximal clot strength in whole blood has been attributed to persistence of high platelet reactivity and generation of thrombin on the surface of activated platelets in patients on dual antiplatelet therapy [2,7].

Inflammation has been extensively studied in the pathogenesis and risk assessment of patients with suspected or known coronary artery disease, and elevated levels of C-reactive protein (CRP) have been consistently associated with an elevated risk for coronary artery disease as well as worse outcomes in patients with coronary stenting [10–15]. On the basis of these previous findings, we hypothesized that elevated CRP is associated with heightened plasma clot strength measured by TEG in individuals undergoing coronary stenting on dual anti-platelet therapy.

Materials and methods

Patients

The study protocol was approved by the Indiana University institutional review board for research. Informed consent was obtained from all individuals.

Inclusion criteria for the study included the presence of obstructive coronary artery disease, defined by at least 70% diameter stenosis in any epicardial coronary artery on coronary angiography and ad hoc PCI with planned coronary stent implantation. All enrolled individuals received a 600 mg clopidogrel loading dose and aspirin 325 mg at the time of PCI. Exclusion criteria included acute myocardial infarction within the last 30 days, a history of drug or alcohol abuse, bleeding disorder (per clinical history), chronic liver

disease (defined as known hepatic cirrhosis by biopsy or clinical cirrhosis with Child–Pugh score B or C, or abnormal hepatic function tests with aspartate aminotransferase/alanine aminotransferase/total bilirubin above upper limit of normal), myelodysplastic or myeloproliferative disorders, warfarin use, a platelet count less than 150 000 cells/ μ l, as well as if there was planned glyco-protein IIb/IIIa antagonist use during PCI.

Blood samples

A baseline blood sample was obtained from the arterial access sheath prior to coronary stenting. Peripheral venous blood samples were drawn 16–24 h after PCI and administration of the clopidogrel loading dose. All blood samples were directly transferred into vacutainer tubes containing sodium citrate 3.2% or heparin. Citrate and heparin plasma was obtained by centrifugation at 2000 $\times$ g for 15 min and stored at –80°C until analysis.

Thrombelastography

Thrombelastography was performed using citrate plasma samples obtained 16–24 h after PCI according to the manufacturer's instructions (TEG 5000 Thrombelastograph Hemostasis Analyzer System; Haemonetics, Brain-tree, Massachusetts, USA). Citrate plasma was mixed with kaolin, inverted five times, and then loaded in a heparinise-coated cup containing 20 μ l of CaCl₂. Thrombelastography was stopped after maximal fibrin clot strength was recorded. Time to fibrin formation (R), angle constant (K), angle (α) and maximal clot strength (MA, mm and G, dyn/cm²) were recorded. TEG-G was calculated from thrombelastography–maximal clot strength by use of the following formula:

$$G=(5000 \times MA)/(100-MA)$$

Platelet aggregation studies

Ex-vivo platelet function was assessed by light transmittance aggregometry (LTA) at 37°C with an Optical Lumi-Aggregometer (Model 700 with AggroLink 8 software; Chrono-Log Corporation, Havertown, Pennsylvania, USA). Platelet-rich plasma (PRP) and platelet poor plasma (PPP) were obtained by differential centrifugation of citrate blood obtained 16–24 h after clopidogrel loading dose as previously described [16,17]. Platelet aggregation in PRP was induced with ADP at 5 and 20 μ mol/l.

C-reactive protein

Serum obtained at baseline prior to coronary intervention was analysed by ELISA according to manufacturer's instructions [CRP (human) ELISA kit; Abnova, Walnut, California, USA]. The minimum detectable concentration of the CRP ELISA is estimated to be 0.1 mg/l with a functional sensitivity of 0.1 mg/l (as determined with inter-assay % C.V. < 20%).

Fibrinogen

Citrated plasma obtained at 16–24 h after PCI was analysed by ELISA according to manufacturer's instructions after appropriate dilution [Fibrinogen (human) ELISA kit; Alpcos Diagnostics, Salem, New Hampshire, USA].

Statistical analysis

Statistical significance was defined as a P value less than 0.05. Tests were conducted two-sided and values are represented as mean $\pm$ SD, except as otherwise stated. Categorical variables were compared using the χ^2 test. Normal distribution of continuous data was assessed by the Kolmogorov–Smirnov test. Unpaired, two-sided Student's t -test was used to compare normally distributed continuous data between two groups and for multiple groups with the one-way analysis of variance test. Bonferroni correction was used after one-way analysis of variance test to adjust for multiple comparisons. Spearman's rho was used to calculate correlation between CRP and other continuous variables.

Results

Baseline characteristics of the study participants are described in Table 1. Among the 54 patients included in this study, 43 (80%) were men and 11 (20%) women. The majority were of European descent (87%) and a minority African-American (13%). Prevalence of preexisting coronary artery disease (67%) and preexisting multivessel disease (46%) with prior coronary artery bypass grafting (CABG) was high. There was a high prevalence of diabetes mellitus (44%) and hypertension (98%) among the recruited participants. Clinical variables and comorbidities were further analysed by grouping according to quartiles of CRP (Table 1). In general, no significant differences were found in the distribution of variables across quartiles with few notable exceptions. In specific, increasing BMI was associated with increasing quartiles of CRP ($P = 0.042$).

In addition, there was a lower prevalence of family history of coronary artery disease in individuals in the lowest quartile of CRP ($P = 0.023$). However, the prevalence of diabetes mellitus was not significantly different across quartiles ($P = 0.67$).

Levels of CRP demonstrated a wide variation across quartiles (Table 2). The median value of CRP was 4.1 mg/l. TEG measurements are reported according to quartiles of CRP (Table 2).

The time to thrombus formation (R), time of clot formation (K) and angle (α) were not significantly different across quartiles ($P = 0.26$, $P = 0.17$ and $P = 0.85$). In contrast, there was a significant association of increasing quartiles of CRP and maximal clot strength (G) (Table 2). There was a graded increase in plasma TEG-G and TEG-maximal clot strength with increases in CRP, with highest maximal clot strength measured in individuals in the highest quartile of CRP (Table 2). Patients in the highest quartile of CRP had significantly higher TEG-G than the patients in the lowest quartile (TEG-G: 3438 ± 623 vs. 2184 ± 576 dyn/cm², $P < 0.0001$). CRP correlated strongly with maximal clot strength (TEG-G) ($\rho = 0.585$, $P < 0.00001$, Fig. 1) and modestly with BMI ($\rho = 0.3$, $P = 0.028$). However, BMI did not correlate significantly with TEG-G ($r = 0.21$, $P = 0.14$).

Maximal clot strength (G) was not significantly different between smokers and nonsmokers (3008 ± 818 vs. 2704 ± 790 dyn/cm², $P = 0.2$)

There was no significant correlation between CRP and other TEG measures (Fig. 1.).

Maximal percentage of platelet aggregation (MPA) induced by ADP is reported according to quartiles of CRP (Table 2). There was no significant difference in posttreatment platelet aggregation among quartiles of CRP (Table 2), and no significant correlation between CRP and measurements of platelet aggregation (data not shown).

Discussion

In addition to procedural factors such as extent of coronary disease, complex bifurcation stenting and stent length, other clinical risk factors such as diabetes mellitus or smoking have been associated with worse outcomes after coronary stenting [1,18,19]. In addition, patients with elevated biomarkers of inflammation have been found to have more ischaemic events and worse prognosis after ACS and coronary stenting [7–15]. In specific, a large Korean study [14] of 2691 patients demonstrated a significantly increased risk of coronary stent thrombosis in patients with an elevated CRP (hazard ratio 3.86, 95% confidence interval, 1.82–8.18; $P < 0.0001$). High maximum tensile clot strength measured by TEG, induced either by kaolin or ADP in whole blood, has been associated with an increased risk for recurrent ischaemic events after coronary stenting [2,7,20]. Elevated whole blood TEG clot strength, elevated levels of CRP, fibrinogen and various other inflammatory biomarkers were documented in patients with unstable angina as compared with stable, asymptomatic patients [21]. When analysed in quartiles, whole blood TEG clot strength showed a distinct association with elevated CRP and fibrinogen, and a more modest association with interleukin (IL)-8 and von Willebrand factor [22].

Similarly, elevated whole blood TEG clot strength has been associated with increased incidence of postoperative myocardial infarction, stroke and death at 30 days in patients undergoing CABG as well as postoperative myocardial infarction in patients with non-cardiac surgery [23,24].

In the current study, maximal clot strength measured in plasma showed modest variability among patients and was roughly half of maximal clot strength measured in whole blood, reflecting the relative contribution of fibrin and platelet-aggregation to the mechanoelastic properties of whole blood thrombus. Previous studies have shown that clopidogrel nonresponse with high on treatment platelet aggregation induced by ADP is associated with shortened time to thrombus formation (R) and higher maximal clot strength in whole blood TEG assays. Thrombin is generated on the surface of activated platelets, which may further accelerate cleavage of fibrinogen. As in our study, plasma was used instead of whole blood for TEG assays, our findings demonstrate that the correlation of inflammation with maximal plasma fibrin clot strength by TEG is not related to generation of thrombin by activated platelets. In our current study, on treatment, ADP platelet reactivity measured by LTA was not significantly different among quartiles of CRP, as previously described by Park *et al.* [15] who could not demonstrate an association between CRP and residual platelet reactivity in a large cohort of patients on dual antiplatelet therapy.

The results of our study document a relationship between plasma levels of CRP and TEG-G, with increasing plasma fibrin clot strength observed with increasing levels of CRP. These findings are consistent with findings of previous studies examining whole blood TEG-

maximal clot strength and CRP in patients with coronary artery disease [21–23]. Obesity is known to be associated with heightened CRP, and we similarly observed increasing BMI across quartiles of CRP [25]. However, BMI did not correlate significantly with TEG-maximal clot strength ($r = 0.22$, $P = 0.12$).

Fibrinogen is a precursor to fibrin and fibrinogen concentration is a major determinant of whole blood clot strength [6,26]. Fibrinogen and CRP are both acute phase proteins, and in patients with symptomatic coronary disease may be upregulated concomitantly. However, in our study, fibrinogen concentration did not correlate with CRP concentration ($\rho = 0.1$, $P = 0.48$) and thus is unlikely to be the primary mediator of high clot strength phenotype observed in individuals with elevated CRP after coronary stenting in our study.

Once fibrinogen is cleaved to fibrin, additional cross-linking of fibrin occurs by factor XIII [26]. Factor XIII deficiency has been documented to affect plasma clot strength [26], and we cannot exclude the possibility that variability in factor XIII activity could have contributed to the increased plasma clot strength in patients with high CRP after PCI. Nevertheless, the previously documented association of CRP and stent thrombosis after PCI and the presence of high plasma clot strength in these patients suggest a possible contribution of stable fibrin mesh in the pathogenesis of stent thrombosis, irrespective of the extent of concomitant P2Y₁₂ receptor inhibition. Other factors altering fibrinogen sensitivity to cleavage by thrombin, such as carbon monoxide mediated changes as shown by Nielsen *et al.* [27–29], could also contribute to the findings. The contribution of plasma hypercoagulability to coronary stent thrombosis is also supported by findings by Undas *et al.* [30] who documented altered fibrin clot permeability and fibrinolysis in a case–control study of patients with coronary stent thrombosis.

In conclusion, patients with elevated CRP at the time of PCI exhibit a concomitant increase in fibrin clot strength as measured by TEG in plasma. This association could in part explain higher rates of stent thrombosis and recurrent ischaemic events in patients after coronary stenting with high levels of CRP. Future studies are required to evaluate the predictive utility of plasma TEG and measurements of fibrin clot kinetics in larger cohorts of patients with coronary stenting.

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Fig. 1. Correlation of C-reactive protein and Thrombelastography: C-reactive protein vs. TEG-G (a), C-reactive protein vs. TEG-R (b), C-reactive protein vs. TEG-K (c), and C-reactive protein vs. fibrinogen concentration (d). Spearman's (ρ) correlation coefficient. CRP, C-reactive protein; TEG, thrombelastography.

Table 1
Demographics and clinical variables according to quartiles of C-reactive protein in patients with coronary stenting

Characteristics	Total study population	Quartiles of C-reactive protein				P
		First quartile (n = 14)	Second quartile (n = 13)	Third quartile (n = 14)	Fourth quartile (n = 13)	
Age (years)	61.6 ± 9	62.4 ± 8	57.8 ± 9	62.3 ± 11	64 ± 8	0.35 [‡]
BMI (kg/m ²)	31.5 ± 8	27.9 ± 8	30.3 ± 3	32.3 ± 8	35.8 ± 8	0.042 [‡]
Male sex (%)	43/54 (80)	13/14 (93)	11/13 (85)	10/14 (71)	9/13 (69)	0.37 [‡]
African-American (%)	7/54 (13)	1/14 (7)	2/13 (15)	0/14 (0)	4/13 (31)	0.1 [‡]
Prior coronary artery disease (%)	36/54 (67)	8/14 (57)	9/13 (69)	10/14 (71)	9/13 (69)	0.85 [‡]
Prior CABG (%)	25/54 (46)	6/14 (43)	6/13 (46)	8/14 (57)	5/13 (38)	0.79 [‡]
Prior PCI (%)	11/54 (20)	2/14 (14)	4/13 (31)	2/14 (14)	3/13 (23)	0.67 [‡]
Congestive heart failure (%)	8/54 (15)	3/14 (21)	0/13 (0)	3/14 (21)	2/13 (15)	0.36 [‡]
Left ventricular ejection fraction (%)	47.3 ± 19	38.6 ± 23	51.6 ± 17	43.5 ± 22	56.5 ± 7	0.06 [‡]
Diabetes mellitus (%)	24/54 (44)	5/14 (36)	6/13 (46)	8/14 (57)	5/13 (38)	0.67 [‡]
Hypertension (%)	53/54 (98)	14/14 (100)	12/13 (92)	14/14 (100)	13/13 (100)	0.36 [‡]
Hyperlipidemia (%)	49/54 (91)	13/14 (93)	11/13 (85)	14/14 (100)	11/13 (85)	0.45 [‡]
Current smoking (%)	17/54 (31)	4/14 (29)	5/13 (38)	6/14 (43)	2/13 (15)	0.43 [‡]
Family history of coronary artery disease (%)	31/54 (57)	4/14 (29)	8/13 (62)	12/14 (86)	7/13 (54)	0.023 [‡]
Proton pump inhibitor use (%)	22/54 (41)	4/14 (29)	4/13 (31)	6/14 (43)	8/13 (62)	0.29 [‡]
Baseline clopidogrel use (%)	13/54 (24)	2/14 (14)	2/13 (15)	6/14 (43)	3/13 (23)	0.26 [‡]

Values represent mean ± SD. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

[‡] χ^2 test.

[‡] One-way analysis of variance test.

Table 2

Platelet aggregation, plasma thrombelastography measurements and fibrinogen concentration stratified according to quartiles of C-reactive protein

	Quartiles of C-reactive protein				
	First quartile (n = 14)	Second quartile (n = 13)	Third quartile (n = 14)	Fourth quartile (n = 13)	P [‡]
C-reactive protein (mg/l); median (range)	1.1 (0.1–2)	3 (2.1–3.7)	7.5 (4.5–12)	42.2 (15–220)	
Fibrinogen (mg/ml)	4.9 ± 2.1	5.2 ± 2.3	5.2 ± 1.9	5.3 ± 1.9	0.97
MPA ADP 5 μmol/l (%)	31.2 ± 16	25.6 ± 15	22.6 ± 11	33.5 ± 20	0.27
MPA ADP 20 μmol/l (%)	42.1 ± 17	37.6 ± 18	33.9 ± 14	44.3 ± 18	0.38
TEG-R (min)	7.1 ± 2	6 ± 2.5	7.8 ± 2	7.8 ± 3.4	0.26
TEG-angle (α)	71.1 ± 8	71 ± 12	71 ± 6	67.5 ± 17	0.83
TEG-K (min)	1.6 ± 0.9	1.1 ± 0.3	1.2 ± 0.4	1.3 ± 0.8	0.17
TEG-MA (mm)	30 ± 5.5	33.9 ± 6.4	36 ± 4.6	40.4 ± 4.7	<0.0001
TEG-G (dyn/cm ²)	2184 ± 576	2629 ± 806	2850 ± 618	3438 ± 623	<0.001

Values represent mean ± SD. TEG-G, maximal fibrin clot strength (dyn/cm²); TEG-MA, maximal fibrin clot strength (mm); TEG-R, time to clot formation; TEG-K, time of clot formation. MPA, maximal platelet aggregation; TEG, thrombelastography.

[‡] One-way analysis of variance test.