Clinical determinants of thrombin generation measured in presence and absence of platelets – results from the Gutenberg Health Study

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Background

Thrombin, a central protease in blood coagulation with both procoagulant and anticoagulant function, regulates the activity of the coagulation cascade.[1] In addition, thrombin is one of the most potent physiological activators of platelets that are critical in cell-mediated thrombin amplification.[2] The tendency of a plasma sample to generate thrombin might be an important indicator of prothrombotic risk linked to cardiovascular disease (CVD), but the presence of platelets may be a critical determinant.

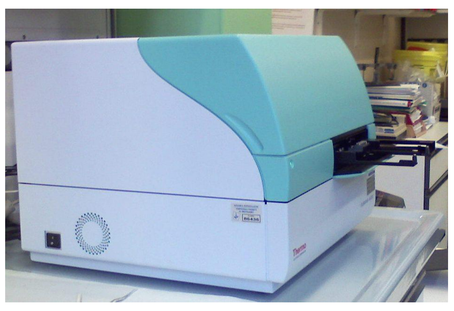
Aim

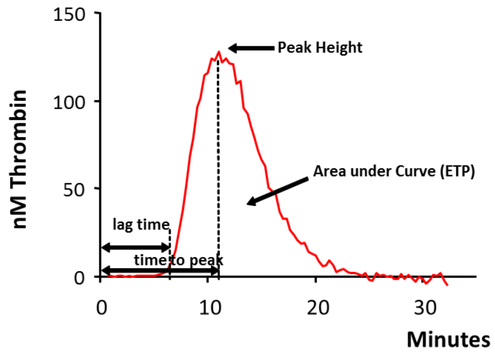
To investigate the clinical and laboratory determinants of thrombin generation (TG), measured in platelet rich plasma (PRP) and platelet free plasma (PFP), in individuals from the adult population-based Gutenberg Health Study (GHS).

Methods

Clinical data, standard laboratory markers and TG, investigated in both PRP (with adjusted platelet concentration of 150,000 platelets/µl) and PFP at 1pM TF, were available in 407 GHS individuals (randomly selected from the 5 year follow-up GHS cohort). The study sample shares the demographic characteristics and the distribution of traditional cardiovascular risk factors (CVRFs) and CVD with the population sample of the follow-up cohort.
Lag time, endogenous thrombin potential (ETP) and peak height were the investigated parameters of a TG curve. Multivariable linear regression analysis adjusted for age, sex, laboratory markers, antiplatelet and anticoagulant treatment was used to identify TG determinants.

Calibrated authomated thrombogram





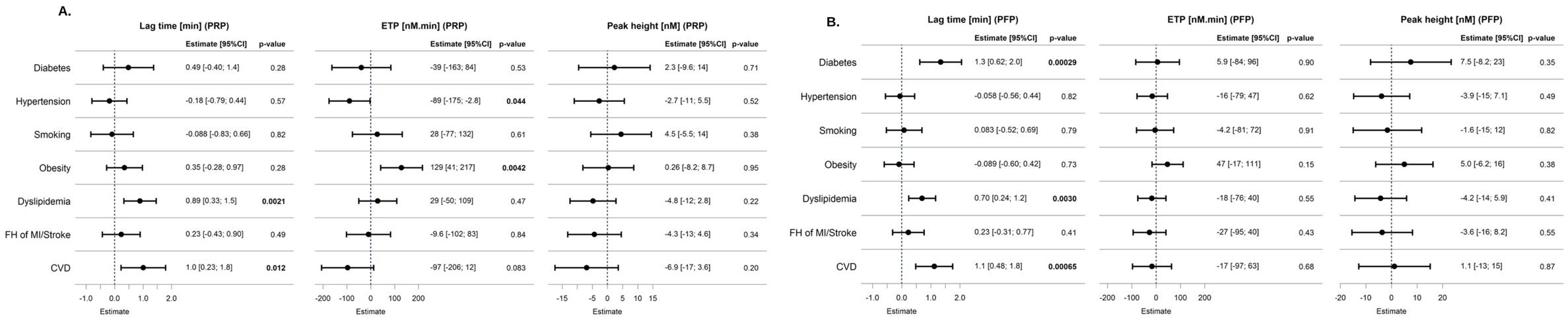
Subjects characteristics in the study sample and the follow-up cohort

		Subsample with TG analysis (N=407)	GHS sample (N=8367)
Sex (Women)		48.4% (197)	49.0% (4099)
Age (years)		59.5±10.7	60.0±10.7
BMI (kg/m²)		26.7 (24.1/30.2)	26.9 (24.2/30.2)
Cardiovascular risk factors	Diabetes	11.5% (47)	10.9% (909)
	Obesity	26.5% (108)	26.2% (2195)
	Smoking	15.5% (63)	15.2% (1269)
	Hypertension	54.1% (220)	55.3% (4625)
	Dyslipidemia	47.9% (195)	45.4% (3791)
	FH of MI/Stroke	20.4% (83)	23.7% (1980)
Cardiovascular diseases		19.6% (80)	21.5% (1803)
Antithrombotic agents		10.1% (41)	16.2% (1354)
Antiplatelet agents		6.4% (26)	12.4% (1039)
Anticoagulant agents		3.7% (15)	3.8% (315)
Lipid modifying agents		11.1% (45)	16.2% (1358)

The GHS sample is the follow-up sample of the first 10,000 study participants Cardiovascular diseases include: myocardial infarction, coronary artery disease, stroke, atrial fibrillation, heart failure and peripheral arterial disease. BMI, body mass index; FH of MI, family history of myocardial infarction

Results

Clinical determinants of TG in platelet rich plasma (A) and platelet free plasma (B)



Forrest plots presenting the clinical determinants of TG parameters, in an adjusted model for age, sex, cardiovascular risk factors (presented in the plot) and cardiovascular diseases (CVD), measured in platelet rich plasma (PRP, A) and platelet free plasma (PFP, B).

Laboratory determinants of TG in platelet rich plasma (A) and platelet free plasma (B)

A. PRP	Lag time [min]		ETP [nM.min]		Peak height [nM]	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Sex (female)	0.354 (-0.204; 0.913)	0.21	-23.1 (-114; 68.2)	0.62	-6.06 (-14.9; 2.78)	0.18
Age (10 years)	-0.007 (-0.236; 0.222)	0.95	-36.3 (-73.7; 1.14)	0.058	-1.43 (-5.06; 2.19)	0.44
MPV (fL)	-0.428 (-0.715; -0.141)	**0.0037**	12.8 (-34.0; 59.7)	0.59	4.97 (0.429; 9.52)	**0.033**
Leukocytes (10^9/L)	-0.006 (-0.082; 0.0687)	0.87	-11.8 (-24.1; 0.474)	0.060	-0.49 (-1.68; 0.699)	0.42
Platelets (10^9/L)	-0.005 (-0.009; -0.0009)	**0.017**	0.54 (-0.148; 1.23)	0.12	0.113 (0.0466; 0.18)	**0.00096**
Erythrocytes (10^9/L)	-0.232 (-0.876; 0.411)	0.48	49.2 (-56.0; 154)	0.36	4.12 (-6.07; 14.3)	0.43
Log_CRP (mg/l)	0.289 (0.063; 0.515)	**0.013**	66.0 (29.1; 103)	**0.00051**	2.67 (-0.905; 6.24)	0.14
HbA1c (%)	-0.083 (-0.376; 0.209)	0.58	-7.18 (-55.0; 40.6)	0.77	0.911 (-3.72; 5.54)	0.70
LDL (mg/dl)	0.0069 (0.0007; 0.013)	**0.029**	0.97 (-0.044; 1.99)	0.062	0.028 (-0.0705; 0.127)	0.58
HDL (mg/dl)	-0.0027 (-0.019; 0.013)	0.75	0.23 (-2.48; 2.94)	0.87	-0.0747 (-0.337; 0.187)	0.58
Log_Triglycerides (mg/dl)	0.235 (-0.429; 0.900)	0.49	-17.7 (-126; 90.9)	0.75	-9.38 (-19.9; 1.14)	0.081
Antiplatelet agents	0.179 (-0.752; 1.11)	0.71	-32.8 (-185; 119)	0.67	1.42 (-13.3; 16.2)	0.85
Anticoagulant agents	7.72 (6.46; 8.98)	**< 0.0001**	-369 (-575; -164)	**0.00048**	-14.1 (-34.0; 5.85)	0.17

B. PFP	Lag time [min]		ETP [nM.min]		Peak height [nM]	
	Beta (95% CI)	p-value	Beta (95% CI)	p-value	Beta (95% CI)	p-value
Sex (female)	0.122 (-0.358; 0.601)	0.62	6.45 (-60.0; 73.0)	0.85	3.27 (-8.48; 15.0)	0.59
Age (10 years)	0.287 (0.0901; 0.485)	**0.0045**	-16.5 (-43.9; 10.9)	0.24	0.973 (-3.86; 5.81)	0.69
MPV (fL)	-0.049 (-0.295; 0.197)	0.69	7.51 (-26.6; 41.6)	0.67	-1.02 (-7.04; 5.01)	0.74
Leukocytes (10^9/L)	-0.0406 (-0.105; 0.024)	0.22	-1.95 (-10.9; 6.98)	0.67	0.165 (-1.41; 1.74)	0.84
Platelets (10^9/L)	0.0008 (-0.003; 0.004)	0.65	0.237 (-0.26; 0.74)	0.36	0.022 (-0.066; 0.111)	0.62
Erythrocytes (10^9/L)	-0.032 (-0.583; 0.519)	0.91	70.3 (-6.20; 147)	0.072	6.17 (-7.35; 19.7)	0.37
Log_CRP (mg/l)	0.351 (0.156; 0.546)	**0.00046**	30.6 (3.61; 57.6)	**0.027**	4.07 (-0.705; 8.84)	0.096
HbA1c (%)	0.207 (-0.0438; 0.458)	0.11	-0.67 (-35.5; 34.1)	0.97	1.94 (-4.21; 8.09)	0.54
LDL (mg/dl)	0.0019 (-0.003; 0.007)	0.49	-0.578 (-1.32; 0.16)	0.13	-0.154 (-0.285; -0.023)	**0.022**
HDL (mg/dl)	-0.014 (-0.028; 0.0001)	0.053	-1.03 (-2.99; 0.94)	0.31	-0.181 (-0.528; 0.167)	0.31
Log_Triglycerides (mg/dl)	-0.091 (-0.661; 0.479)	0.75	-11.7 (-90.7; 67.4)	0.77	1.34 (-12.6; 15.3)	0.85
Antiplatelet agents	-0.22 (-1.03; 0.592)	0.60	16.2 (-96.4; 129)	0.78	-5.67 (-25.6; 14.2)	0.58
Anticoagulant agents	5.59 (4.51; 6.67)	**< 0.0001**	-260 (-410; -111)	**0.00071**	-31.9 (-58.3; -5.48)	**0.018**

Multivariable linear regression analysis of lag time, endogenous thrombin potential (ETP) and peak height as dependent variables, adjusted for age, sex, laboratory markers, antiplatelet and anticoagulant therapy in 400 GHS individuals. MPV, mean platelet volume; CRP, C-reactive protein; LDL, low density lipoprotein; HDL, high density lipoprotein.

Conclusion

Our findings support that TG, particularly in PRP, relates to traditional CVRFs in a representative sample from a population-based study. Assessment of procoagulant activity in a platelet dependent manner by TG is a promising tool for assessing individual risk for CVD.

References

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