Endothelial activation markers and constitutional hemorrhagic diseases: defining normal STA-Procoag-PPL values in patients with constitutional hemorrhagic diseases: WFH 2016

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Background

Cardiovascular disease, a major public health concern, is responsible for 30% of deaths among the European population.

This condition is associated with both clinical (aging, gender, smoking, obesity, hypertension, stress, etc.) and biological (diabetes, elevated factor VIII levels, hypercholesterolemia, etc.) risk factors. Cardiovascular disease must particularly be assessed in patients with constitutional hemorrhagic diseases aged ≥ 40 years, as their life expectancy has been multiplied by 10 over the last 60 years.

Most hemophilia cohorts, including female carriers, exhibited a reduced mortality risk associated with ischemic heart disease.

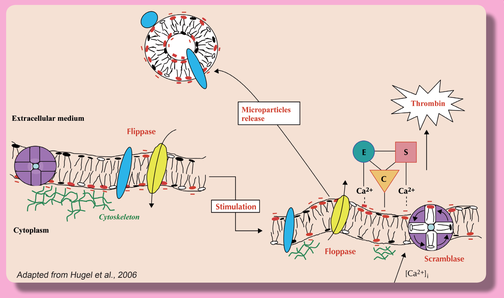
The reduced cardiovascular mortality and morbidity observed in this patient population is assumed not to be related to a reduction in risk factors or atherosclerotic processes, its sole explanation being the limiting thrombus formation following plaque rupture due to lower thrombin generation.

Study

A subject's prothrombotic state can be assessed by means of circulating microparticle levels. These microparticles, derived from phosphatidylserine flip-flop, can be detected using solid-phase capture or flow cytometry.

The pharmaceutical company, Diagnostica Stago, has recently released on the market a chronometric method correlating with the circulating microparticle levels: STA-Procoag-PPL.

Our monocenter prospective study primarily sought to establish the normal value range of this parameter in hemophilia patients without any cardiovascular symptoms.



The same assessment was performed in certain age-matched patients with primary hemostasis disorders like von Willebrand disease or various thrombopathies, as well as coagulation-factor deficiencies. Several studies have shown the usefulness of microparticle measurement as prothrombotic marker. It is therefore essential to know their baseline levels prior to integrating them in cardiovascular risk assessments. The following three prothrombotic markers were integrated in our study:

- 1) plasminogen activator inhibitor (PAI-1), which plays a role in the regulation processes, including cell adhesion and tissue remodeling;
- 2) D-dimer levels that indirectly reflect hypercoagulability;
- 3) von Willebrand antigen, a well-known endothelial activation marker.

Material and method

Microparticle assessment

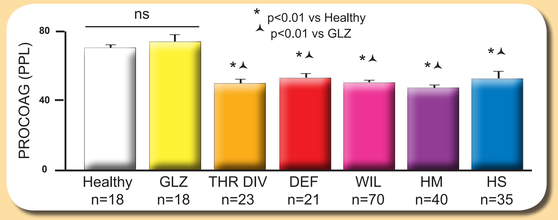
The STA-Procoag-PPL method consists of measuring, in the presence of calcium, the coagulation time when the addition of a procoagulant phospholipid-depleted plasma reagent renders the assay procoagulant phospholipid-dependent in the sample tested.

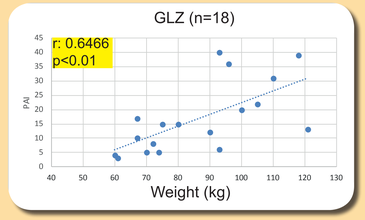
A shortened coagulation time measured using the STA-Procoag-PPL method likely reflects an increase in procoagulant phospholipid levels.

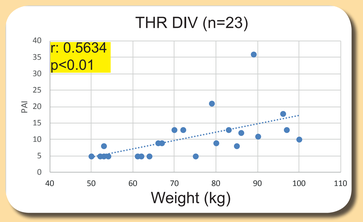
We therefore evaluated, using the STA-Procoag-PPL method, the microparticle levels along with those of D-dimers, von Willebrand antigen, and plasminogen activator inhibitor in a patient cohort comprising 40 severe hemophiliacs, 35 moderate or minor hemophiliacs, 70 von Willebrand disease cases, 21 patients with various coagulation-factor deficits, 23 with various thrombopathies, and 18 with Glanzmann disease.

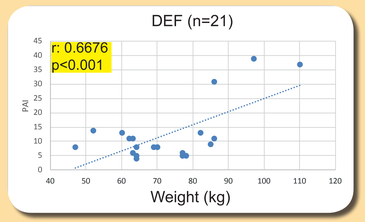
Results

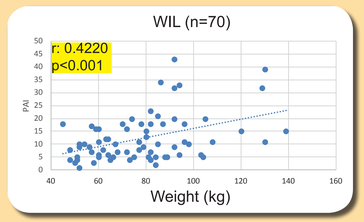
		Healthy	GLZ	THR DIV	DEF	WIL	HM	HS
PAI	Mean ± S.E.M	/	16.7 ± 2.9	10.6 ± 1.5	12.4 ± 2.2	12.3 ± 1.1	14.8 ± 1.4	13.4 ± 1.5
	n; [95% CI]	/	18; [10.6-22.8]	23; [7.5-13.6]	21; [7.7-17]	70; [10.2-14.5]	69; [12-17.5]	39; [10.5-16.4]
DDI	Mean ± S.E.M	/	350 ± 35	366 ± 48	465 ± 141	345 ± 28	507 ± 93	380 ± 35
	n; [95% CI]	/	18; [275-425]	23; [266-465]	21; [171-759]	70; [289-400]	69; [322-692]	39; [310-451]
VWF	Mean ± S.E.M	/	158 ± 17	118 ± 9	109 ± 8	54 ± 3	134 ± 8	113 ± 5
	n; [95% CI]	/	18; [122-194]	22; [100-137]	21; [92-125]	70; [49-59]	69; [118-149]	39; [102-123]
PPL	Mean ± S.E.M	70.8 ± 1.5	74.3 ± 4	50.3 ± 2.2	53.4 ± 2.4	50.7 ± 1.1	53.7 ± 2.9	47.7 ± 1.3
	n; [95% CI]	18; [67.7-73.9]	18; [65.7-82.8]	23; [45.6-55]	21; [48.4-53]	70; [48.4-53]	69; [47.9-59.5]	39; [45-50.4]











Excluding patients with Glanzmann thrombasthenia, our patient cohort displayed statistically shorter coagulation times than controls. There were no significant differences in microparticle levels, neither between hemophilia A and B patients, nor between moderate/minor versus severe forms. There was no significant difference in PAI-1 values across diseases, though statistical analysis revealed that the PAI value was more elevated with increasing weight, and vice versa, in patients with Glanzmann thrombasthenia, various thrombopathies, coagulation-factor deficiencies, or von Willebrand disease. Yet the correlation between weight and PAI values was not observed in patients with hemophilia, whether moderate or severe, which probably reflects abnormal fibrinolysis as described in hemophilia patients.

Conclusion

The hemorrhagic phenotype in patients with constitutional hemorrhagic diseases may be compensated for, at least to some extent, by their higher microparticle levels. This assessment should henceforth be included in the screening examination of patients with associated risk factors.

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