Effect of Captopril treatment on platelet Tissue Factor expression in stroke-prone rats

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Introduction. ACE inhibitors (ACEI) have been proposed to exert anti-ischemic effects not only through their anti-hypertensive action but also through pleiotropic effects related to the athero-thrombotic process. In this regard, we have previously showed that captopril reduces expression of Tissue Factor (TF), the main activator of blood coagulation, in *ex vivo* cultured human monocytes. Platelets (both human and rat), which together with TF play a key role in thrombus formation, have been shown to express TF.

Aim. To investigate whether captopril modulate platelet TF expression in spontaneously hypertensive stroke-prone rats (SHRSPs).

Methods. Male SHRSPs were allocated to three groups receiving a standard diet (SD, n = 4) or a high-sodium permissive diet (HSD) plus vehicle (n = 14) or plus captopril (50 mg/kg/die; n = 14). Platelet and megakaryocyte (MK)-associated TF expression was analyzed by whole blood flow cytometry after 5 weeks of drug treatment. At the same time points, platelet associated thrombin generation was measured by CAT assay.

Results. The vehicle-treated rats developed hypertension, proteinuria and cerebral ischemia over 4 weeks of HSD. Concomitantly, the number of TF-positive platelets increased compared to normotensive SD-treated animals (64±6.7% vs 33.8±5%; $p<0.0001$). Captopril reduced the percentage of TF-positive platelets (32.8±10.6, $p<0.0001$). Similarly, expression of TF in MKs, the platelet progenitor cells, was increased in HSD compared to SD fed rats (47.8±6.8% vs 32.2±4%; $p=0.007$) and pharmacological treatment with captopril was able to prevent this upregulation (36.7±5.2%; $p=0.04$). Of interest, platelet capacity to generate thrombin was down-regulated in captopril- compared to vehicle-treated animals.

Conclusions. Data obtained suggest that hypertension upregulates platelet TF expression and treatment with captopril is able to revert this effect. It reduces also their prothrombotic capacity, extended the characterization of the antithrombotic properties of ACEI, in an in vivo model of hypertension. Moreover, they suggest also that the mechanism through which hypertension modulates platelets TF expression may be secondary to changes in MKs.