E-selectin and sICAM-1, biomarkers of endothelial function, predict recurrence of venous thromboembolism in young patients

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Background: Risk factors for atherosclerosis and venous thromboembolism (VTE) overlap and are mostly associated with endothelial dysfunction (ED). We hypothesized that ED is present in patients after acute pulmonary embolism (APE) and predicts the risk of VTE recurrence.

Methods: To the study were enrolled 82 patients (38 F; aged 38 ± 11 years) with history of APE that had occurred 1.1 ± 0.7 year before the enrollment. Forty-three patients had a history of provoked APE, while in 39 cases no significant risk factors were found and unprovoked APE was diagnosed. Results were compared with 30 age- and sex-matched healthy controls (15 F; aged 38 ± 12 years). . In order to evaluate endothelial function in patients with history of APE flow-mediated dilation (FMD) of the brachial artery and assessed biomarkers of ED (sVCAM-1, sICAM-1, ADMA, E-selectin) were measured. Subsequently all patients were followed up for at least 12 months (median 36; range: 12-72 months) in an outpatient clinic for VTE recurrence.

Results: *Endothelial function*

Endothelial function was impaired in patients with APE history compared to the controls assessed using FMD% (5.3 (0.8-20.3) vs. 13.8 (4.1-24.3); p<0.0001) or biomarkers, such as sVCAM-1 (631 ng/ml (105 - 2382) vs. 495 ng/ml (348 - 934); p=0.04) and sICAM-1 (679 ng/ml (279-1006) vs. 600 ng/ml (394-766); p=0.002). Endothelial dysfunction defined as FMD<4.5% was significantly more frequent in patients with history of APE than in controls (45% vs. 3%, p<0.0001). There were no significant differences in endothelial function between patients with history of provoked and unprovoked VTE.

Follow-up and risk of recurrent VTE

We identified 19 episodes of recurrent VTE after discontinuing oral anticoagulation therapy. 15 (35% female) recurrences of VTE in patients with history of idiopathic APE and 4 (100% female) recurrences in patients after provoked APE. 1 patient developed CTEPH.

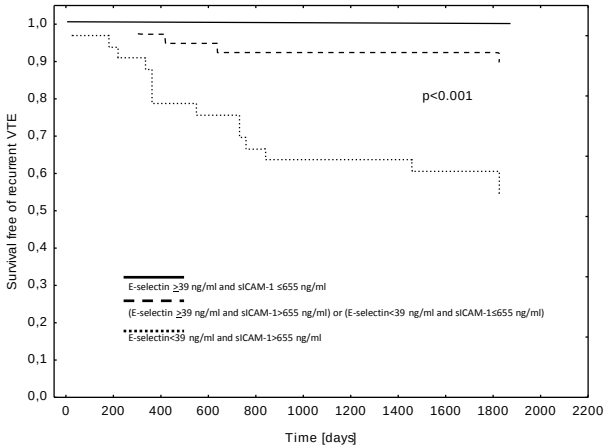
In patients with recurrent VTE, E-selectin concentrations were lower than in the rest of the APE group (22 ng/ml (7-65) vs. 34 ng/ml (11-111), p<0.035), while sICAM-1 levels tended to be higher (712 ng/ml (432-1006) vs. 671 (279-886), p=0.06).

In the multivariate analysis history of unprovoked APE, E-selectin and sICAM-1 were statistically significant predictors of recurrent VTE (HR 3.3, 95%CI: 1.1-10.1; 0.96, 95%CI: 0.93-0.99, p<0.02 and 1.004, 95%CI: 1.001-1.007, p=0.04, respectively; p<0.001).

The AUC ROC for E-selectin in prediction of recurrent VTE was 0.647 (95%CI: 0.532-0.750; p=0.03), for sICAM-1: 0.645 (95%CI: 0.529-0.749; p=0.06).

The cut-off point <39ng/ml for E-selectin had 95% sensitivity and 36% specificity, PPV 32% and NPV 96% in prediction of recurrent VTE, while the cut-off point >655 ng/ml for sICAM-1 had 83% sensitivity, 48% specificity, PPV 32% and NPV 91% in prediction of recurrent VTE.

In the group with unprovoked APE 17 patients presented with both E-selectin levels <39ng/ml as well as sICAM-1 levels >655 ng/ml, and 11(65%) were diagnosed with recurrent VTE. Concentrations of E-selectin <39ng/ml or sICAM-1 levels >655ng/ml were present in 20 patients from the u-APE group and 4 (20%) of them had recurrent VTE. Among the group with provoked APE E-selectin levels were <39 ng/ml and sICAM-1 levels exceeded 655 ng/ml in 16 patients; 4 (25%) of them were diagnosed with recurrent VTE. E-selectin concentration <39ng/ml or sICAM-1 level >655 ng/ml was found in 19 patients with history of provoked APE, but none of these patients suffered from recurrent VTE, as in the group of patients with E-selectin concentration ≥39 ng/ml and sICAM-1 level ≤ 655 ng/ml.



Conclusions: APE patients have impaired endothelial function, as indicated by FMD assessment and biomarker levels. Low concentrations of E-selectin and high levels of sICAM-1 are associated with high risk of recurrent thromboembolism.