Abstract: **P380**

**Ticagrelor mediated cardioprotection after acute myocardial infarction is exponentiated by SSRIs**

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Introduction: Recent studies revealed that antiplatelet drugs like ticagrelor and cangrelor can protect the heart against reperfusion injury in animal models. Given that reperfusion injury is associated with an inflammatory response, we wondered how inhibition of the acute phase neutrophil influx affects and interferes with ticagrelor mediated cardioprotection. We chose a model where we utilized fluoxetine (Flx) to deplete platelet serotonin because acute neutrophil triggered inflammation is dampened in these mice and analyzed the outcome after myocardial reperfusion injury.

Purpose: The goal of this project was to evaluate the impact of inflammatory processes towards reperfusion injury and how or if this cross-reacts with other treatment strategies like antiplatelet therapy.

Methods: Mice were put on a Flx containing diet for 3 weeks. After administration of ticagrelor (100mg/kg loading; 50mg/kg twice afterwards), MI was induced for 30 minutes, followed by 24 hours of reperfusion. Heart function and infarct size was evaluated. Integrin expression on neutrophils was analyzed on circulating cells using flow cytometry.

Results: We found increased plasma serotonin levels after MI in WT mice (150±19 ng/mL) which was not affected by oral gavage of ticagrelor (145±13 ng/mL). Infarct size was markedly reduced in fluoxetine treated mice (38 in Flx, 53 in WT; % area at risk (AAR) and heart function compared to WT was significantly improved (24±2 % FS vs. 16±3 % FS in WT; FS=fractional shortening). WT mice had elevated transmigrated neutrophils in the AAR (14 vs. 28 in WT per mm² tissue). Circulating neutrophils had decreased expression of CD11b in Flx (70%) treated mice compared to WT. A series of in vitro experiments revealed that serotonin triggers degranulation of neutrophils (confirmed by electron microscopy and determination of plasma MPO levels). This also induced upregulation of CD11b expression on neutrophils, which was reversible by addition of a protein transport inhibitor. In the group of mice which received ticagrelor we found an even stronger protective effect on top of fluoxetine treatment when we looked at neutrophil integrin expression and infarct size.

Conclusion: We found that neutrophil infiltration into the heart after MI is associated with increased serotonin levels which leads to a significant reduction in myocardial necrosis. Mechanistically, this is due to enhanced CD11b expression which results in stronger neutrophil attachment to endothelial cells and subsequent transmigration. When serotonin depleted mice received a P2Y12 receptor inhibitor the outcome was improved even further. Given that antiplatelet therapy is part of the clinical routine after PCI our findings could open novel treatment strategies to control myocardial reperfusion injury.