ST-Elevation Myocardial Infarction-Derived Coronary Microvascular Obstruction is NOT Thrombus Dependent: Results from a Porcine Coronary Model

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Background

Dynamic Microvascular Obstruction (dMVO) follows reperfusion therapy in a proportion of STEMI patients and causes "no-reflow" phenomenon in the worst cases, which exacerbates myocardial ischemia and leads to myocardial cell death. Dynamic MVO is a reliable predictor of early and late Major Adverse Cardiac Events including cardiac death, ischemic heart failure and stroke. 2

The pathophysiological mechanisms underlying dMVO are still poorly defined, particularly regarding the role of thrombus formation as a cause of small vessel occlusion. An animal model was designed and a study protocol developed to assess the association between thrombus formation and MVO using a porcine STEMI model. This model allowed for developing dMVO despite pre-procedural anticoagulation.

Methods

From June to August 2017 fifteen domestic pigs of German Landrace breed (50-60 kg) were administered with heparin to maintain an activated clotting time (ACT) level of ≥ 200 sec.

STEMI was created by transiently occlusion of the left anterior descending (LAD) coronary artery with a balloon using the CorFlow™ system (CorFlow Therapeutics, Baar, Switzerland) for 90 min. All pigs developed STEMI except for one. This was due to an anatomical variation with presence of numerous collateral branches of the LAD which prevented functional occlusion. Thus this pig was excluded from the study and the analysis.

The fourteen study pigs remained stable during the procedure and no reanimation was necessary. After the STEMI was confirmed by ECG dMVO was localized and measured by gadolinium contrast enhanced cardiac MRI (CMRI) (Fig. 1). All pigs survived all procedural steps and were euthanized at study completion. Histological sample collection was performed according to standardized myocardial segmentation to match CMRI imaging. 1

Detailed histology assessment and analysis was performed independently by two institutions at the Veterinary Pathology Institute (University of Zurich, Switzerland) and the CV Path Institute (Gaithersburg, MD, USA) using hematoxylin and eosin stain (HE), Carstairs and immunohistochemistry (against CD61, ICAM-1, VCA-M and INOS) to characterize morphologically dMVO and assess macro / microthrombosis.

Results

All study pigs developed MVO, which was observed in the apical and, to a lesser extent, mid cavity regions, in the segments assigned to the left anterior descending coronary artery (Fig. 2).

Histological hallmarks of MVO were microvascular hyperemia (Fig. 2), capillary endothelial cell swelling (Fig. 3), neutrophil leukocytosis and interstitial edema (Fig. 4) along with activation of endothelial cells, as indicated by expression of ICAM-1 (data not shown), VCAM-1 (Fig. 5) and INOS (Fig. 6). 1

Conclusions

This study has shown that prominent dMVO can be developed after STEMI was induced in fully anticoagulated animals, in which macro- and microvascular thrombosis is an extremely rare event. Microvessel occlusion is rather represented by erythrocyte-leukocyte stasis, endothelial cell swelling and myocardial interstitial edema resulting into myocardial depressurization. Main finding of this animal model shows that thrombus formation plays surprisingly a minor role in generating microvascular obstruction and explains the failure of anticoagulation to reduce MVO in clinical trials.

Implications

This new finding and understanding should be acknowledged when translated into clinical trials with humans and may shift paradigms for MVO genesis and therapy.