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Cardiac Microvascular Obstruction: microvascular drug transport and lysis of microthrombi in a multi-scale model of the myocardial microcirculation

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Cardiac microvascular obstruction (MVO) is an injury of the myocardial microcirculation. It typically follows successful recanalization of the blocked coronary artery (primary occlusion) in myocardial infarction. MVO leads to under-perfusion of the affected tissue and has a negative impact on patient outcomes. Next to other occluding factors, MVO may be caused by microthrombi (debris from the primary occlusion) embolizing vessels of less than 200µm diameter [1].
For the systematic study of MVO and to test diagnostic and therapeutic approaches, we have developed a multi-scale in vitro model for MVO [2]. It comprises a microfluidic chip modeling a branching microvascular tree with vessel diameters ranging from 700 to 50µm. The chip is integrated into a model of the coronary circulation which is coupled to a left-heart mock loop. This experimental setup provides physiological flow conditions for the whole model. MVO is induced by injecting porcine microthrombi (~200µm) into the microfluidic chip where they randomly distribute and embolize some of the microchannels [3].
Infusion experiments with dye indicated that some microthrombi lead to a full occlusion of the respective microchannel such that mass transport toward the occluding microthrombus is very inefficient, whereas other microthrombi have a semi-occlusive or porous character such that advective transport toward the microthrombus is possible. Furthermore, we found that periodic fluctuations of the vessel volume, due to the contraction of the myocardium with every heartbeat, enable mass transport also in occluded vessels (intramyocardial pumping effect, [4]), like squeezing and soaking a dishwashing sponge.
Results from the dye infusion experiments suggest that it is possible to transport thrombolytic drugs to the microthrombi such that they can resolve the occlusions and help to reestablish blood perfusion to the myocardium. To identify the appropriate drug infusion protocol and the optimal drug dosages, we developed a second microfluidic setup with a single straight microchannel and constant flow. It ensures that the microthrombi in the chip are non-occlusive such that the drug can always reach the microthrombi. We found that microthrombi can be lysed up to 75% over the course of 20 minutes of perfusion if the thrombi are first exposed to a high drug concentration (alteplase) for 90 seconds. These results will be applied to the experimental setup with the full microvascular tree and intramyocardial pumping effect.

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