Ultrasound with Oxygen-microbubbles in Ischemia-Reperfusion Injury and Repair

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Background, Motivation and Objective

Ischemia-reperfusion (I/R) injury plays a crucial effect in the tissue functional repair after myocardial infarction, thrombolysis, and organ transplantation. The increased vascular shear stress by ultrasound with microbubble cavitation has been used to enhance blood perfusion for reducing I/R injury. However, the increased intracellular H_2O_2 by microbubble cavitation might also aggravate vessel damage because the excessive accumulation of intracellular H_2O_2 is the major mechanism of I/R injury. Since microbubble cavitation presented two opposite effects for I/R injury and repair, the interplay of the shear stress and intracellular H_2O_2 should be discussed. Notably, oxygen (O_2) is a repairing factor in I/R injury by promoting ATP generation. Therefore, our study applied oxygen-microbubbles (O_2-MBs) to regulate the interplay of I/R injury and repair.

Statement of Contribution/Methods

In this study, the acute hind-limb ischemia mouse model (N=8) was used to investigate the I/R injury and repair after O_2-MBs treatment. A microvessel clip was clamped on the femoral artery for 60 min ischemia and then removed the clip for reperfusion. A treatment dose of $2x10^7$ O_2-MBs were intravenously injected into mice for 20 min sonication by a commercial ultrasound imaging system (Terason t3000). During the I/R treatment process, one fiberoptic probe (OxyFlo and OxyLite, Oxford Optronics) was subcutaneously placed on the downstream of the femoral artery to record the blood flow and oxygen partial pressures (pO_2). After 24 h, the vascular bioeffects such as vessel density, viability, and immunity were stained by CD31, DAPI, and CD11b, respectively.

Results/Discussion

The *in vitro* pO_2 of homemade O_2-MBs ($2x10^7$ MBs/mouse) was 149±4 mmHg, and then increased to 176±10 mmHg after 30 s sonication. In the I/R mice model, blood flow and pO_2 were reduced to 49±15% and 56±27%, respectively, after 60 min ischemia. The recovery, which was the enhancement from ischemia to 60 min reperfusion, of blood flow was 22±28% and 66±15% in the control and O_2-MBs groups (p=0.075), respectively, and pO_2 was 3±12% and 48±16% (p=0.042). The histological results revealed significant increment of immune cell infiltration (1.30±0.42-fold, p=0.045) under the O_2-MBs treatment relative to the control vessels. The enhanced blood perfusion, tissue oxygenation, and immunity might promote ATP generation and necrotic cells swallowed by immune cells to assist tissue repair under O_2-MBs cavitation. In future works, the intracellular H_2O_2 and *in vivo* vascular bioeffects under various O_2-MBs doses are introduced to regulate the interaction of I/R injury and repair.