Tissue entraining gel was prepared according to a method [1], and 1% of nano-drots were sprayed and injected directly into the gel via a 19 gauge needle. The temperature was monitored by submersing a 12 mm probe into the gel, and five different points were sampled from the gel volume (cytometer #2) to quantify the temperature elevation (Fig. 4). The optimal sono-sensitizers concentration was 0.2% v/v in terms of tissue perfusate volume, which is consistent with previous reports [4, 10].

The efficacy of HIFU in combination with sono-sensitizers was assessed by injection of gadolinium chelate at the end of the experiment monitored with T1 weighted image (Fig. 4). Two metrics were assessed: 1) The relative enhancement of the T1 contrast in a region of interest (ROI) of 2 pixels in diameter around the warmest point, after injection of sono-sensitizers. 2) The circular pattern, the temperature enhancement achieved was 6.81 °C (Fig. 3). The achieved temperature elevation before injection of sono-sensitizers and the red line the temperature elevation after injection of sono-sensitizers. Figure 5. PEF on the thermal image of a 2 pixel-diameter ROI, integrals of temperature and metrics calculations for different treatment conditions.

Results
Tissue entraining gel was prepared according to a method [1], and 1% of nano-drots were sprayed and injected directly into the gel via a 19 gauge needle. The temperature was monitored by submersing a 12 mm probe into the gel, and five different points were sampled from the gel volume (cytometer #2) to quantify the temperature elevation (Fig. 4). The optimal sono-sensitizers concentration was 0.2% v/v in terms of tissue perfusate volume, which is consistent with previous reports [4, 10].

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Discussion
The enhancement of the MRgHIFU therapy using endovascular sono-sensitizers demonstrated a relatively uniform, strong and tunable perfusion pattern, and enhancement in the temperature elevation induced by HIFU at a fraction of the same sono-sensitizer concentration as the perfusion fluid. This 1.2% enhancement is consistent with previous studies [10, 11] on tissue perfusion rate, and shows that HIFU efficiency can be improved by combining sono-sensitizers with MRI-guided HIFU procedures.

Conclusion
The use of endovascular sono-sensitizers in combination with HIFU provides an effective method for the ablation of highly perfused tumors. Ablation of highly perfused tumors is challenging due to the heat sink effect. Previous studies demonstrated that an enhancement in temperature elevation by 10% to 25% is achieved by the injection of sono-sensitizers. In this study, we demonstrated that the use of endovascular sono-sensitizers in combination with HIFU can achieve a temperature elevation of 6.81 °C (at 0.2% v/v concentration of sono-sensitizers) in a highly perfused tumor.

Acknowledgements
References
Figures

Figure 1. a) Set up of the ‘artificial kidney’ in the dedicated holder avoiding motions placed in the MR-compatible perfusion machine. Perfusion tank, 1. ‘artificial kidney’, 2. HIFU transducer, 3. water for acoustic coupling, 4. ultrasonic gel for power dissipation. b) T1 weighted Image acquired with a 3T MR scanner and a loop coil. 1. agar gel matrix, 2. ‘artificial kidney’ surrounded by agar gel matrix and covered by standard ultrasonic gel, 3. 3D printed holder, 4. 1 cm scale bar, 5. circulating fluid input. Figure 2. Temperature elevation at the focal point as function of the time for the fixed focal point pattern. The blue line describes the temperature elevation before injection of sono-sensitizers. Figure 3. Magnitude images with temperature map of a 1 cm diameter 9 × 10 mm 2 ROI, before injection of sono-sensitizers. Figure 4. High resolution T1-weighted MR image in axial plane of ‘artificial kidney’ composed of tissue mimicking gel packed with a filling of sonosensitizers. Figure 5. Overview of the temperature elevations in a 2 pixel-diameter ROI, integrals of temperature and metrics calculations for different treatment conditions.