MRI of Microvascular Leakage Induced by Myocardial Contrast Echocardiography in Rats

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Abstract:

Microvascular permeabilization can be induced by ultrasound (US) interaction with contrast agent microbubbles and has a potential for drug delivery. The purpose of this study was to characterize the extent and magnitude of leakage induced in vivo in a rat model of myocardial contrast echocardiography (MCE). Conventional methods, such as Evans blue dye, show leakage on the surface of the heart but do not provide information about the disruption in the interior of the tissue. These methods are compared with in vitro Gd enhanced MRI imaging of the rat heart.

Methods:

CD hairless rats (Charles River) were anesthetized, cannulated, and placed in a 37° C degassed water bath. A GE Vingmed System V with cardiac phased array probe was the ultrasound source. The in situ peak rarefaction pressure amplitude (PRPA) was estimated to be 2.0 MPa. Image frames were triggered every fourth hearth beat from the ECG signal. Ultrasound contrast (5.0 ml of 50:1 diluted Definity) was infused over a 5 min period. For MCE, the infusion and triggered scanning was continued for 5 min followed by 10 min delay prior to sacrifice. For sham MCE, the two conditions of US alone and contrast agent alone were combined in the same animals. Evans blue dye and Omniscan (0.5 mmol/kg) were injected into the tail vein of all animals. Four experimental procedures were performed MCE with saline flush, MCE not flushed, sham flushed, and sham not flushed.

Following sacrifice, the hearts were placed in 4% low melting point agar for MR imaging. The MR experiment consisted of 12 interleaved slices of 1mm thickness yielding a voxel volume of12.2 nl. A spin-echo, multislice sequence was used with a TR/TE of 500/20 ms. Tissue relaxation rate, R_1^{Tissue}, of myocardium in the absence of contrast agent was measured to be 0.967 s^{-1}. All studies were performed on a 2.0T Varian Unity/Inova system. Gadolinium concentration was estimated by using the NMR signal equation, $S(TR) = S(0)(1 - Exp(-TR * R_1))$, solving for relaxation rate, $R1 = -\ln\left\{1 - \frac{S(TR)}{S(0)}\right\} TR^{-1}$ where $R_1 = R_1^{Tissue} + r_1[Gd]$, assuming Gd relaxivity of 4.1 (s mM) $^{-1}$, and substituting the yield $[Gd] = r_1^{-1}\left(R_1 - R_1^{Tissue}\right)$.

Results and Discussion:

Evans blue leakage was evident in both the sham and MCE rat hearts. Figure 1 shows the results of non-flushed sham and MCE hearts. The non-flushed hearts had no significant difference between MCE and sham experiments (P>0.2). For the flushed hearts, the dye content was 2.3 times greater in the MCE hearts than in the sham hearts (P<0.05).

Figure 2 shows (middle and left images) leakage of contrast agent into the tissue interstitium. Gd concentration can be estimated as outlined above.

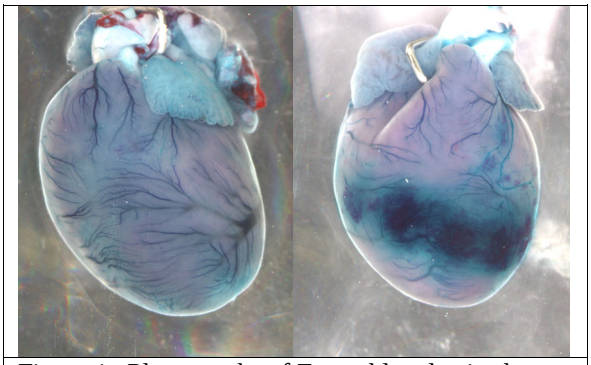
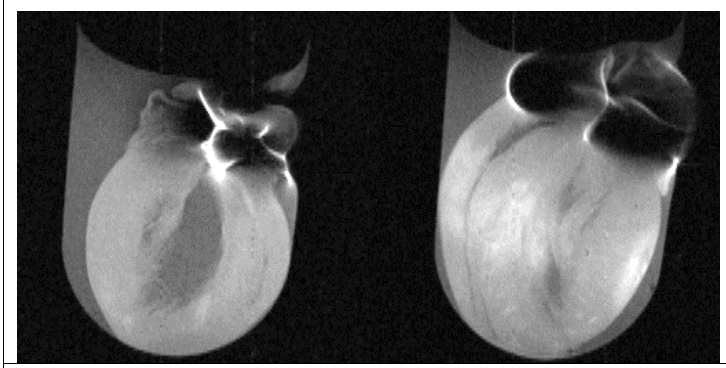


Figure 1. Photographs of Evans blue dye in sham (left) and MCE (right) experiments. Note the large blue area (right) where the capillary bed is disrupted by the combination of US contrast agent and US pulsing.



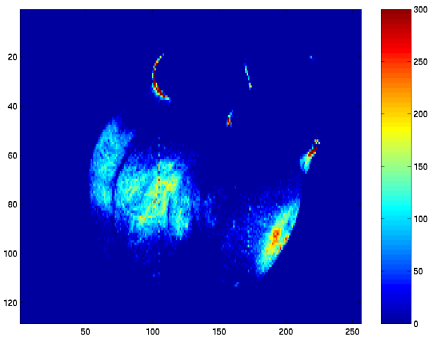


Figure 2. MR images of the rat hearts with sham (left) and MCE (middle) experiments and computed Omniscan concentration (micromolar) (right). Signal is enhanced by the presence of Gd that has leaked out where the US beam has disrupted the capillary bed. The artifact seen at the top of the images is due to a surgical staple, also seen in the photograph in Fig. 2. 3D rendering (not shown) of all images shows the extent of tissue disruption.

Conclusion:

The ultrasonic activation of contrast microbubbles represents a unique form of intervention for localized, microscale sites of capillary permeabilizatoin. MR visualization of this phenomenon allows quantitative, interstitial, three-dimensional evaluation of the extent of disruption.