SUPPLEMENTAL METHODS

Imaging of ATP-Release

Optical imaging of luciferin-luciferase activity was performed to temporally and spatially assess vascular ATP release in wild-type (n=7) and Pan1$^{-/-}$ (n=4) mice. Mice were injected with D-luciferin (Thermo Fisher, Waltham, MA) (3 mg I.P.) 30 minutes before MB cavitation and with firefly luciferase (Thermo Fisher) (25 μg, I.V.) 1 minute prior to completion of US exposure. Control sham-treated animals (n=3) were studied using similar injection protocol but without US exposure. Optical imaging (IVIS Spectrum, Caliper Life Sciences) was performed at 5, 10, 15, and 20 min after completion of US using medium binning. Upon completion of in vivo imaging, animals were re-injected with luciferin I.P. and the heart and lungs were removed within 5 minutes for ex vivo optical imaging. Data are expressed as photons/s/cm^2.

Cavitation Detection

Passive cavitation detection (PCD) in an *ex vivo* heart model was used to confirm inertial cavitation of MBs. A freshly harvested pig heart was flushed with heparinized saline at 37° C and placed in a tank filled with deionized degassed water. The left main coronary artery was cannulated and lipid-shelled decafluorobutane MBs were infused at a rate of 1×10^7 min^{-1}. A spherically focused broadband (10 KHz to 20 MHz) hydrophone (Y-107, Sonic Concepts, Inc., WA) with a focal width of 0.4 mm was fixed so that the anterior myocardium was positioned at the focal depth of 20 mm. The therapeutic ultrasound transducer was positioned confocally to the hydrophone, at a 70° relative angle. Ultrasound parameters were identical to those used *in vivo* except that both an intermediate and high MI (0.6 and 1.3, respectively) were applied to represent the range of acoustic pressures expected *in vivo*. Returning signals were digitized and saved in a 4-channel oscilloscope (Waverunner, Teledyne LeCroy, Chestnut Ridge, NY) using sequence mode. Frequency-amplitude spectra averaged from 15 exposures were generated with Matlab (MathWorks, Natick, MA).