Intra-pulse monitoring of microbubble destabilization during ultrasound-induced blood-brain barrier opening

A. Novell[1], H.A.S. Kamimura[1,2], A. Cafarelli[3], M. Gerstenmayer[1], J. Flament[2], J. Valette[2], P. Agou[1], E. Selingue[1], A. Conti[1], R. Aron Badin[2], P. Hantraye[2] and B. Larrat[1]

[1]Neurospin, Institut des Sciences du Vivant Frédéric Joliot, Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA), Gif-sur-Yvette, France ; [2]Molecular Imaging Research Center (MIRCen), Institut de Biologie François Jacob, Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA), Fontenay-aux-Roses, France ; [3]The BioRobotics Institute, Scuola Superiore Sant'Anna, Pontedera, Italy

Background, Motivation and Objective

Ultrasound-induced blood-brain barrier (BBB) opening is a promising technique for local delivery of therapeutic molecules into the brain. While inertial cavitation regime revealed through passive cavitation detection (PCD) has been associated with potential damage, there is still no consensus in the presence and exploitation of specific nonlinear frequency components such as ultra-harmonics (UH). We propose an intra-pulse monitoring of UH evolution during BBB opening procedure. We hypothesize that the destabilization of microbubbles exposed to ultrasound (US) results in the generation of UH content.

Statement of Contribution/Methods

The approach was validated *in vivo* for BBB opening in rats and non-human primates (NHP). US bursts (0.50 MHz, 10 ms for NHP; 0.65 MHz, 7 ms for rats) were applied every 100 ms for 30 s. PCD was performed during ultrasound exposure for monitoring the microbubble activity. The signal detected by the PCD transducer was acquired by an oscilloscope and transferred to a personal computer using a software developed in Python for signal processing. For each burst, the backscattered signal from microbubbles was divided into 75 consecutives windows of 128 µs. The 1st window was used as a reference to estimate the evolution of UH amplitude through the burst duration. The brain integrity after ultrasound-induced BBB opening was controlled by MRI imaging. T_2w images were acquired at the end of the sonication to detect the potential presence of hemorrhages or edema at the disruption site. For rats, observations were confirmed after the sacrifice of animals by the presence of potential damages in the sonicated area.

Results/Discussion

Our results demonstrated that the generation of UH was an instantaneous phenomenon that occurred during the pulse transmission (typically > 3 ms for NHP), few seconds after the beginning of the US protocol (Fig. 1B). A substantial intra-pulse change of UH level (+ 8dB) was related to the occurrence of unwanted side effects such as hemorrhage and edema on both rats and NHP. The number of UH occurrences was correlated with brain damage severity. The intra-pulse monitoring of UH was demonstrated to be very sensitive to predict unsafe outcomes of US. This new parameter can be used to tune closed-loop systems avoiding the potential late detectability of inertial cavitation to potential harmful US conditions.

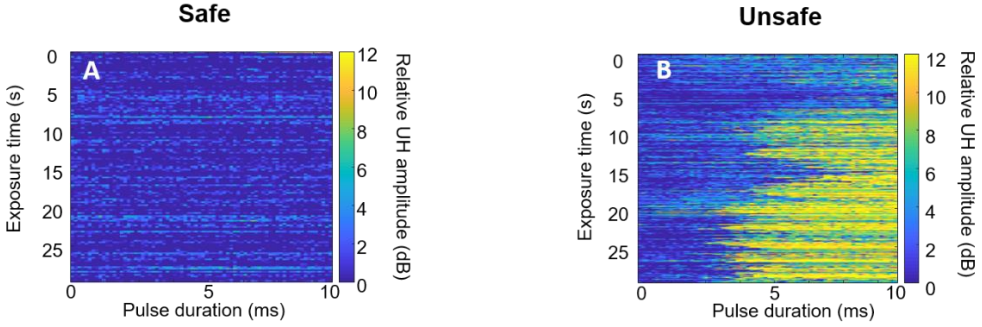

Figure 1: Intra-pulse signatures of safe (A) and hemorrhagic (B) BBB opening in NHP