Atherosclerotic plaque destruction by sub-surface ultrafast laser ablation

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Summary

We introduce plaque ablation using ultrafast laser pulses as a proposed treatment for the largest medical problem in Europe: cardiovascular disease. We characterize the affects of ultrafast laser ablation on plaque, investigate the affect on neighboring cells, and demonstrate ablation through a catheter device. These are the initial steps in developing this new treatment.

Proposed therapy

Atherosclerotic plaque destruction through multi-photon ablation, primarily for coronary plaque ablation.

The multi-photon ablation process occurs through ionization of the tissue with sufficiently high photon densities (TW/cm²).

- Requires focused, high energy ultrafast laser pulse delivery from the artery to the plaque
- Must preserve protective fibrous cap surrounding the plaque to avoid thrombosis
- The multi-photon nonlinearity enables sub-surface ablation

Physical mechanism

Very high intensity (MW – GW.cm-2)

- Photoinization
- Localized plasma
- Vaporization and shockwave

As opposed to absorption-based ablation, ultrafast laser ablation relies on Laser-Induced Optical Breakdown (LIOB), a high intensity ablation mechanism, which involves:

- A cascade ionization in the focal volume (Figure 2.c)
- Vaporization due to the high energy electron recombination, followed by cavitation and shockwave
- No thermal damage and low to no damage above the focal volume

Cellular viability

Ablation lines

Dead cells

Live cells

The cellular damage follows the ablation line closely, with apoptosis appearing within a range of 50 µm from the ablation line.

Conclusion

With its inherent subsurface targeting possibilities and short-range damage to surrounding cells, LIOB is an interesting tool for high precision surgical operations. Our experiments have not only shown a clean ablation of target areas of plaque ex vivo, but also pave the way to in vivo experiments by targeted removal of plaque via a catheter prototype. As we pursue our research in vitro and ex vivo, the upcoming use of Optical Coherence Tomography (OCT) and progress in our catheter design would allow us to target and monitor operation in vivo.

References


Figure 1.a The proposed ablation system can be implemented in a catheter similar to percutaneous coronary intervention (PCI) but with the added value of sub-surface ablation.

Figure 1.b The proposed device will destroy atherosclerotic plaque with focused high-energy, ultrafast pulses.

Figure 2.a Cascade mechanism of multi-photon process.

Figure 2.b

Figure 2.c

Figure 3.a Ultrasonic laser ablation of a C2C12 cellular culture with varying pulse energies. a. High energy pulses (2ps, 800nm, 8µJ). b. Lower energy pulses (2ps, 800nm, 0.5 µJ) focused on the cellular monolayer. TUNEL staining (a and b). Propidium iodide (PI) stain (c), in TUNEL staining, the cell nuclei appear in blue and the dead cell nuclei appear in green. In PI, the apoptotic cell nuclei appear in white.

Figure 3.b

Figure 3.c

Figure 3.d Non-ablated TUNEL control.

Figure 3.e Non-ablated PI control.

Figure 4. Set of data collected from 2000 characterized holes, from 6 different APOE -/- mice. a. An adjustable probability of surface damage when focusing at varying depths beneath the surface. It is evident that for focus spots targeted below 15µm deep that the surface was not damaged with pulse energy below 4µJ. b. The mean transverse diameter of ablation holes created in plaque (blue) and in the arterial wall (red). The tissue types have no significant difference in ablation hole size. c. The adjusted probability of filament formation around the ablation hole. f. The corresponding filament lengths. Even when taking the filamentation effect into account, the physical damage induced by ultrafast laser ablation is on the cellular scale.

Figure 4.a Brightfield image of ablated, H&E stained mouse aorta.

Figure 4.b Illustration of filamentation in the sample at medium energies (left, 2 µJ NA 0.8) and high energies (right, 10 µJ NA 0.8).

Figure 4.c Surface Damage Index vs Pulse Energy

Figure 4.d Ablation diameter in Plaque and Arterial tissue

Figure 4.e Filamentation Index vs Pulse Energy

Figure 4.f Filamentation Length vs Pulse Energy

Figure 5.a First generation catheter probe

Figure 5.b 700x270x75µm³ ablated volume in plaque using the first generation catheter probe.