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 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) [4]

- Requires focused, high energy ultrashort 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[5]

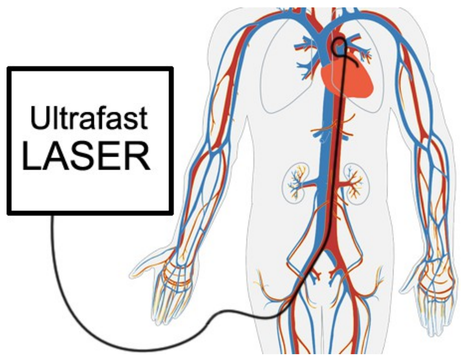

Figure 1.a The proposed ablation system can be implemented in a catheter similar to percutaneous coronary intervention (PCI) but with the added value of sub-surface ablation.

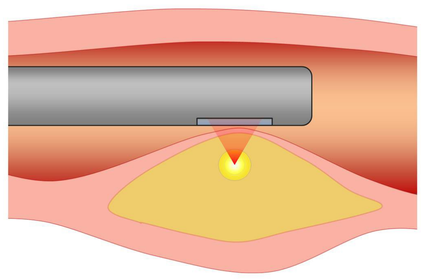

Figure 1.b The proposed device will destroy atherosclerotic plaque with focused high-energy, ultrafast pulses

Physical mechanism

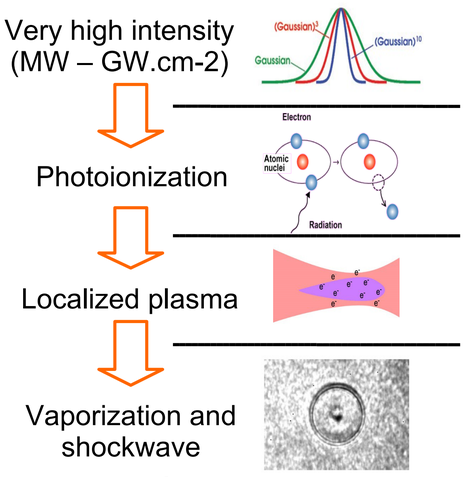

Figure 2.a

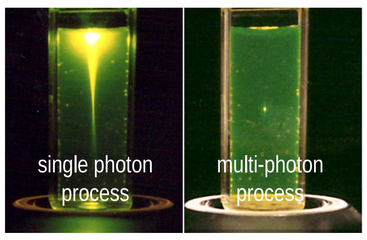

Figure 2.b

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

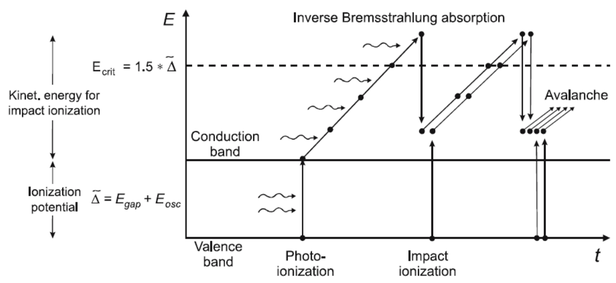

Figure 2.c. Cascade mechanism of multi-photon process[3].

Cellular viability

Figure 3.a **Figure 3.b** **Figure 3.c**

Figure 3. Ultrafast laser ablation of a C2C12 cellular culture with varying pulse energies. **a.** High energy pulses (1ps, 800nm, 8µJ). **b** and **c.** Lower energy pulses (1ps, 800nm, 0.5 µJ) focused on the cellular monolayer. TUNEL stain (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.

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

Figure 3.d Non-ablated TUNEL control.

Figure 3.e Non-ablated PI control.

Ultrafast laser ablation of plaque characterization

Investigate the mechanical effects of ultrafast laser ablation in plaque.

- Experiments are currently done *ex vivo* (in APOE mice aorta), in preparation for later *in vivo* testing
- Ablation performed in free space (NA 0.8, 1 kHz repetition rate, 1030 nm wavelength, 1 ps pulsewidth)

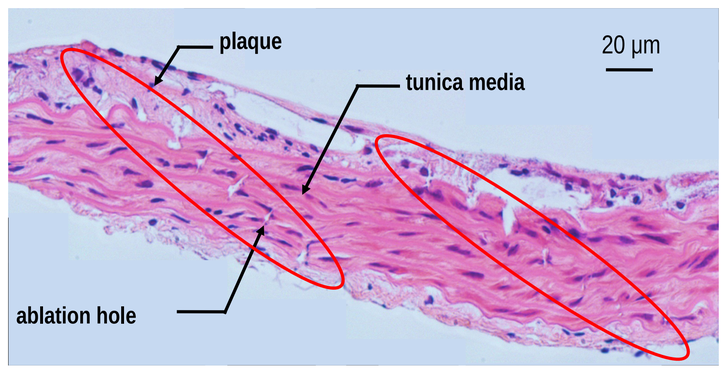

Figure 4.a Brightfield image of ablated, H&E stained mouse aorta.

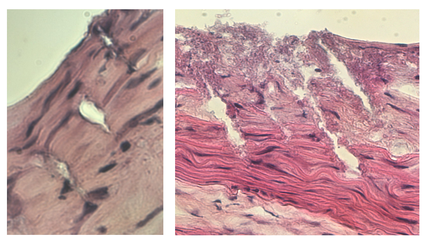

Figure 4.b. Illustration of filamentation in the sample at medium energies (left, 2 µJ NA 0.8) and high energies (right, 10 µJ NA 0.8).

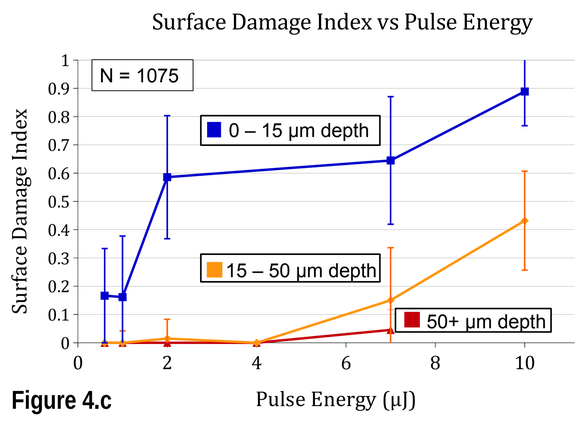

Figure 4.c

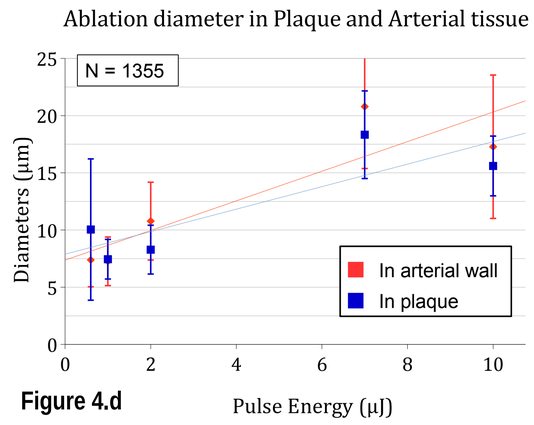

Figure 4.d

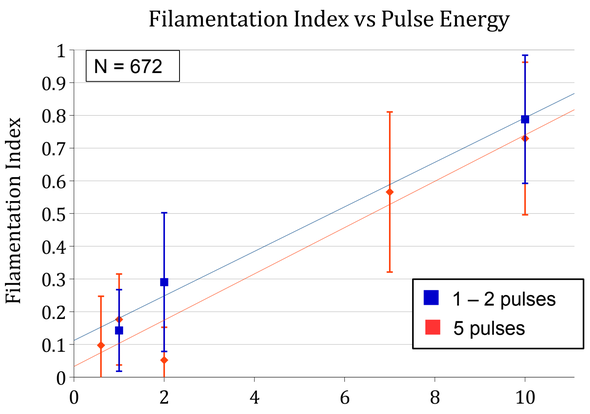

Figure 4.e

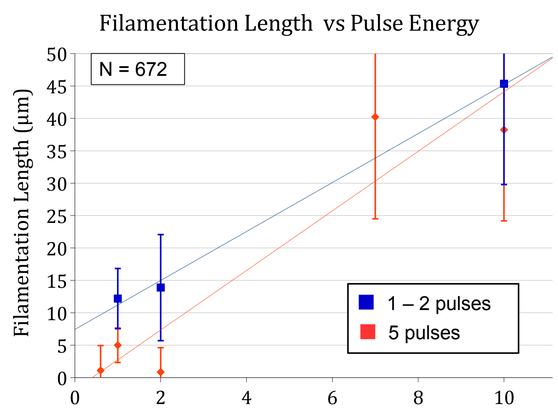

Figure 4.f

Figure 4. Set of data collected from 2000 characterized holes, from 6 different APOE -/- mice. **c.** An adjusted 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. **d.** 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. **e.** The adjusted probability of filament observation 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.

The catheter device

We are designing a catheter device to deliver and focus the high energy laser pulse to atherosclerotic plaque in the coronary artery.

Pulse delivery

- Deliver ~2 µJ ultrafast pulse to arterial plaque area (to be used inside of living specimens)
- Hollow-core photonic crystal fiber enables delivery of high energy ultrafast pulse

Catheter probe

- Build catheter probe to focus ultrafast pulses at a moderately high numerical aperture.
- Make catheter compatible with existing catheter technologies for insertion into artery

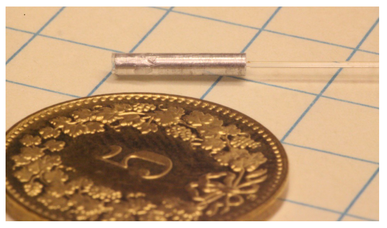

Figure 5.a First generation catheter probe

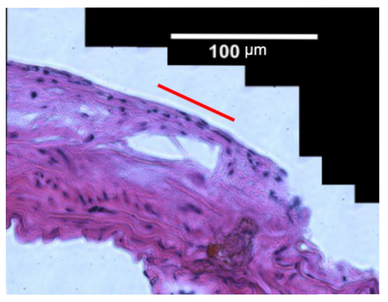

Figure 5.b 70x20x70µm³ ablated volume in plaque using the first generation catheter probe.

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*.

European Commission

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