Photo-mediated ultrasound therapy as a novel method to selectively treat eye vasculature

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PURPOSE

- Pathologic blood vessels and neovascularization are hallmarks for numerous retinal diseases (macular degeneration, diabetic retinopathy, retinal vein occlusions, retinopathy of prematurity, sickle cell retinopathy) and affect over 71 million people.
- Currently available therapies include conventional laser, anti-VEGF injections, photodynamic therapy (PDT), antivascular ultrasound therapy (AVUT), photothermolysis, and embolotherapy.
- Current therapies have several disadvantages: topical/systemic toxicity, financial burden ($2000/month), invasive injections, frequent (monthly) treatment, permanent retinal scarring, laser creep/expansion, sun avoidance requirement, choroidal hypoperfusion, time-sensitive.
- We have developed a novel technology termed Photo-mediated Ultrasound Therapy (PUT), which uses a combination of a low intensity laser concurrently with ultrasound to selectively treat vessels without damaging surrounding tissue.
- PUT Mechanism: Based on well-controlled induction and promotion of microcavitation bubbles in the target vessels. The shear stresses and microjets produced by microcavitation can result in vasoconstriction, blood clot formation, and hemorrhage.
- We present PUT results from chicken yolk sac membranes, rabbit ears, and rabbit choroidal vessels.

METHODS

Integrated therapeutic ultrasound (0.5 MHz bursts of 10% duty cycle at a rate of 10 Hz, H107 Sonic Concepts, Bothell, WA) + Pulsed Nd:YAG laser (Powerlite, Continuum), 532 nm, 3-ns pulse duration, 10-Hz repetition rate at the start of each ultrasound burst.1 Rabbits used in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, after approval of the University of Michigan IACUC (Protocol PRO00006486, PI Paulus).

RESULTS

Figure 3: PUT treatment of chicken yolk sac membrane demonstrating selective treatment of blood vessels without surrounding tissue damage (laser: 5 mJ, 10-Hz, 532 nm, 2 mJ/cm², Ultrasound: 1 MHz, 10-Hz rep, 10% duty cycle, 0.45 MPa), 4 minutes.

Figure 4: PUT on rabbit eye. (a, b) Blood perfusion maps measured by PenCam PSI System before and after PUT demonstrating diminished blood flow in the treated microvessels (white arrows) after PUT. Scale bar: 1000 μm. (c) Average blood perfusion rate before and after PUT treatment in 5 rabbits (Ultrasound peak pressure was 0.45 MPa, 1 Hz, 10% duty cycle, laser fluence was 20 mJ/cm², 584 nm). (d) Normal H&E rabbit ear. (e) H&E rabbit ear 7 days after PUT demonstrating fibrin clot (black arrow) with normal surrounding tissue.

Figure 5: PUT on rabbit choroid in 3 representative rabbits. Top line demonstrates fundus photographs before PUT. Middle line represents fundus photos 4 weeks after PUT demonstrating whitening with absent or reduced choroidal blood flow in treated area (black circle). Bottom line demonstrates indocyanine green (ICGA) angiography 4 weeks after PUT demonstrated absence or reduced choroidal blood flow in treated area (red circle).

Due to synergistic effect, PUT has much higher safety window than conventional laser.4
- Damage threshold of laser is 4.2 mJ
- Damage threshold of PUT is 0.22 mJ
- Safety window of 20 μm laser = 2.9
- Safety window of 100μm laser = 3.8

CONCLUSIONS

- PUT uses concurrent laser and ultrasound to selectively target arteries or veins without damaging surrounding tissue
- PUT is free of any exogenous dye or contrast agent
- PUT has a higher safety window than conventional laser
- PUT holds significant promise as a novel, non-invasive method to precisely target blood vessels in retinal vascular diseases by more selectively treating vasculature with minimized side-effects and no systemic photosensitizing dyes

New and abnormal blood vessels in the eye play a pivotal role in the leading cause of blindness, including macular degeneration, retinal vein occlusions, and diabetes. We develop a novel, noninvasive therapy using a combination of short nanosecond laser with ultrasound to very selectively treat blood vessels without damaging surrounding tissue. We investigate this treatment in chicken yolk sac membranes and rabbit eyes and demonstrate its selectivity. The selective treatment of the blood vessels persists for at least 1 month and likely indefinitely. This novel therapy drastically reduces side effects while allowing treatment in a non-invasive manner. This holds great potential to transform our care of patients with wet macular degeneration, retinal vein occlusions, and diabetes.

REFERENCES


Lay Abstract

Photo-mediated ultrasound therapy is a novel, non-invasive method to selectively treat blood vessels without damaging surrounding tissue. We investigated this treatment in chicken yolk sac membranes and rabbit eyes and demonstrated its selectivity. The selective treatment of the blood vessels persists for at least 1 month and likely indefinitely. This novel therapy drastically reduces side effects while allowing treatment in a non-invasive manner. This holds great potential to transform our care of patients with wet macular degeneration, retinal vein occlusions, and diabetes.

Disclosures

Yannis M. Paulus, Xinmai Yang, and Xueding Wang have a patent on PUT: “Method and Apparatus for Removing Microvessels”