Microbubble Potentiated Ultrasound as a Method of Stroke Therapy in a Pig Model; Preliminary Findings

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Purpose

Low frequency ultrasound (LFUS) with intraarterial or intravenous microbubbles can recanalize thrombosed dialysis grafts and arteries. We develop a similar method for declotting intracranial arteries in an animal model in hopes of application to acute ischemic stroke therapy in humans.

Methods

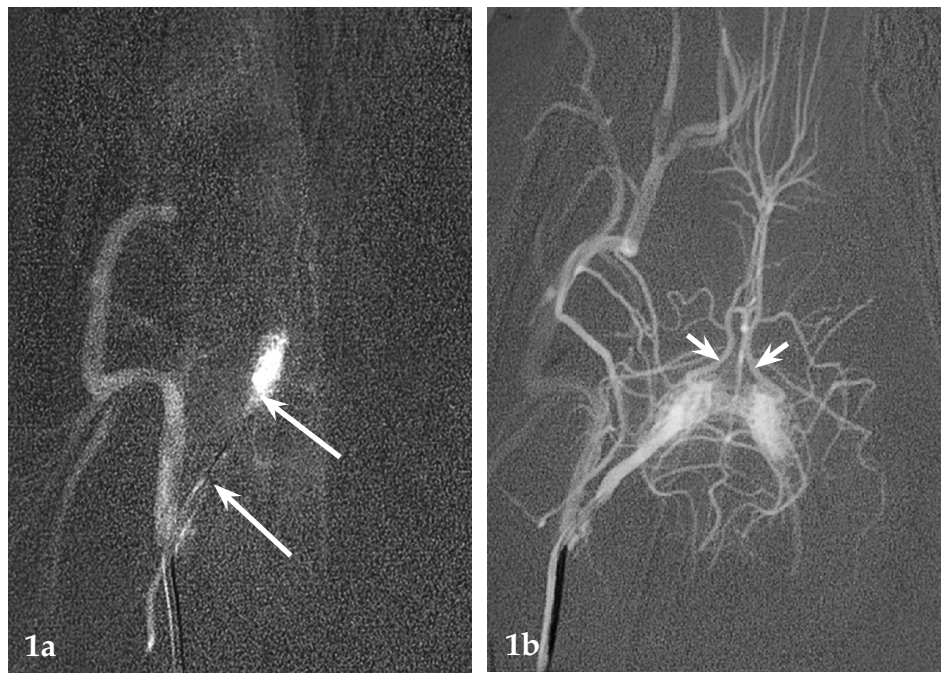
Swine of 30 to 35 kg received selective cerebral angiograms and 1 cc of 2 to 6 hour old clot was placed in one ascending pharyngeal artery and rete mirabile. In pigs the common carotid branches into left and right carotid arteries. Each of these supplies the appropriate ascending pharyngeal artery (APA), which in turn supplies the rete mirabile on one side. These tangles of tiny vessels (70 to 700 microns in diameter) merge to supply the internal carotid on each side and also meet on the midline providing side to side collateral connections. The clot occluded the primary brain blood supply from the APA and rete mirabile in the base of the skull.

Human Albumin Microbubbles Injectable Suspension Octafluoropropane Formulation (Optison, Amersham Health Corporation, Princeton, NJ) was then injected through the same catheter in 0.5 to 1.0 ml doses for a total of 4.5 ml in 21 min. Transcutaneous LFUS was applied for 24 min (from the first microbubble injection until 3 min after the last injection) with a hand-held 1 MHz 10 cm^2 transducer (Sonicator 716, Mettler Electronic, Anaheim, CA) at 2.2 W/cm^2 in pulsed mode, the highest power setting available on this machine. The transducer (coupled to the skin with standard ultrasound gel) was positioned just in front of the ear and behind the eye on the affected side of the pig and proper positioning was confirmed fluoroscopically. Repeat angiography was performed through 24 min. Saline controls used an identical process on the opposite side, and the initial selection of microbubble therapy or saline control was randomized.

Declotting was graded on a scale of 0-4, and flow used the 0-3 TIMI scale. Success was defined as declotting of grade 3 or more (> 70% clearing) with flow of 2 or more.

Results

Seven pigs received 14 declotting sequences. Average clot age was 217 min. Average declotting score was 3.1 and flow was 2.1 for microbubbles and 1.4 and 0.1 for saline controls, p = 0.016 in each. Success occurred with microbubbles in 6 of 7 attempts and in controls in 0 of 7 attempts, p = 0.031.



Figures 1a and 1b: Basal view selective angiograms of the ascending pharyngeal artery show (a) almost complete embolic occlusion of the artery and rete mirabile (long arrows) following clot injection and (b) complete recanalization of the artery and rete (grade 4) after 24 min of therapy. Note excellent filling of the opposite side of the rete that broadly connects to the injected side and excellent filling of both internal carotids (short arrows) originating from the rete as well as other cerebral vessels.

Conclusion

Successful delivery of adequate transcutaneous ultrasound and adequate microbubbles to destroy clot is demonstrated. LFUS with intraarterial microbubble augmentation rapidly lyses intracranial clot and restores flow at ultrasound ranges similar to those required in humans. Further development of this possible acute stroke therapy is justified.

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