Magnetic resonance–guided, high-intensity focused ultrasound sonolysis: potential applications for stroke

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Stroke is one of the leading causes of death worldwide and a significant source of long-term morbidity. Unfortunately, a substantial number of stroke patients either are ineligible or do not significantly benefit from contemporary medical and interventional therapies. To address this void, investigators recently made technological advances to render transcranial MR-guided, high-intensity focused ultrasound (MRg-HIFU) sonolysis a potential therapeutic option for both acute ischemic stroke (AIS)—as an alternative for patients with emergent large-vessel occlusion (ELVO) who are ineligible for endovascular mechanical thrombectomy (EMT) or as salvage therapy for patients in whom EMT fails—and intracerebral hemorrhage (ICH)—as a neoadjuvant means of clot lysis prior to surgical evacuation. Herein, the authors review the technological principles behind MRg-HIFU sonolysis, its results in *in vitro* and *in vivo* stroke models, and its potential clinical applications. As a noninvasive transcranial technique that affords rapid clot lysis, MRg-HIFU thrombolysis may develop into a therapeutic option for patients with AIS or ICH. However, additional studies of transcranial MRg-HIFU are necessary to ascertain the merit of this treatment approach for thrombolysis in both AIS and ICH, as well as its technical limitations and risks.

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THE incidence of ischemic and hemorrhagic stroke worldwide is 110–130 and 55–60 cases per 100,000 people, respectively.²¹ In the United States, stroke is the fifth leading cause of death and a significant source of morbidity.^{27,53} Although intravenous tissue plasminogen activator (IV-tPA) remains the standard of care in eligible patients with acute ischemic stroke (AIS), concurrent endovascular mechanical thrombectomy (EMT) with latest-generation devices is recommended in select patients with emergent large-vessel occlusions (ELVOs).^{36,60,70} Unfortunately, fewer than 10% and 15% of patients with AIS are eligible for IV-tPA and EMT, respectively.^{12,64} With respect to intracerebral hemorrhage (ICH), clot evacuation and decompressive craniectomy appear to decrease death in select patients but have not been proven to reduce morbidity.^{18,26} Therefore, a substantial number of patients with stroke either are ineligible or do not significantly

benefit from current optimal medical and surgical treatment. To address this void, investigators recently made technological advances to render transcranial sonolysis a potential therapeutic option for both AIS—as an alternative for patients with ELVO who are ineligible for EMT or as salvage therapy for patients in whom EMT fails—and ICH—as a neoadjuvant means of clot lysis prior to evacuation.^{10,46,51,71}

The term “sonothrombolysis” refers to ultrasound-mediated thrombolysis with the concurrent use of adjuvant therapy (for example, tPA, microbubbles); on the other hand, the term “sonolysis” is used when no concurrent adjuvant therapy is employed to achieve clot lysis.⁶³ Although the concept of sonolysis was first proposed by Anschuetz and Bernard in the 1960s, it was not until the introduction of transcranial Doppler ultrasonography (TCD-US) in the 1980s that technological advances permitted the applica-

ABBREVIATIONS AIS = acute ischemic stroke; DSA = digital subtraction angiography; ELVO = emergent large-vessel occlusion; EMT = endovascular mechanical thrombectomy; ICH = intracerebral hemorrhage; IV-tPA = intravenous tissue plasminogen activator; MCA = middle cerebral artery; MRg-HIFU = MR-guided, high-intensity focused ultrasound.

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tion of ultrasound in an intracranial setting.^{1,5,42,47} In so doing, novel applications for the treatment of stroke were realized. Following in vitro and in vivo studies in the 1990s, the initial clinical application of low-intensity ultrasound-enhanced sonothrombolysis was reported by Alexandrov et al., who observed better and faster recanalization in AIS patients treated with IV-tPA who underwent concurrent TCD-US.^{3,7,22,42,55} Subsequent randomized clinical trials offered encouraging results for low-intensity, high-frequency (> 300 kHz) ultrasound-enhanced sonothrombolysis.^{4,16,20,49,54,69}

Magnetic resonance–guided, high-intensity focused ultrasound (MRg-HIFU) sonolysis offers several advantages over ultrasound-enhanced sonothrombolysis, which is merely an application of diagnostic ultrasonography and therefore requires IV-tPA administration and is easily attenuated by thicker regions of the calvaria. In addition, ultrasound-enhanced thrombolysis is operator dependent, and its therapeutic effect is achieved on the order of hours after continuous application. Hence, this technique is only applicable in approximately 2%–27% of AIS patients treated with IV-tPA and achieves complete recanalization rates of 27%–78%.^{4,19,20,28,37,49,56} Furthermore, given its negligible thermal effects and the stagnancy of the clot, low-intensity sonothrombolysis is not applicable to ICH.^{1,2,9,68} In contrast, MRg-HIFU thrombolysis is an emerging stand-alone therapy for rapid transcranial clot disintegration in patients with ELVO and ICH and, according to in vitro and in vivo models, can potentially achieve recanalization and liquefaction rates of 63%–93% and > 95%, respectively.^{10,25,30,45,50,51,73,75} Herein, we review the technological development, preclinical results, and future applications of MRg-HIFU thrombolysis.

Technology and Techniques

Magnetic resonance–guided HIFU thrombolysis relies on the piezoelectric effect to generate acoustic waves, which travel transcranially and focally transmit energy to the clot, resulting in lysis via cavitation.⁵⁹ The power output of HIFU is typically on the order of 10^2 – 10^4 W/cm², and several technological advances have enabled safe and efficient delivery of this power. Hemispheric, large-aperture, multielement phased-array transducers minimize focal skull attenuation by spreading acoustic energy across a wide region of the calvaria.^{23,32,33,67} A continuously chilled degassed-water interface between the transducers and the patient's shaved, clean scalp not only decreases scalp heating but also improves acoustic wave coupling.^{23,67} Phase correction terms are necessary to maintain target phase alignment and improve HIFU efficiency in the setting of the heterogeneous bony architecture of the calvaria and are computed for each individual transducer based on a prior CT scan of the head.^{13,14,23,38,67} Thermal MRI monitoring is critical in preventing untoward thermal ablation of tissue since the various parameter estimates for each transducer cannot precisely anticipate individual patient scalp, skull, and intracranial tissue idiosyncrasies.^{23,35,67}

Inertial acoustic cavitation is the primary mechanism by which MRg-HIFU thrombolysis achieves clot disintegration.^{6,11,33,45,57,71,73} Acoustic waves impart momentum

to the fluid immediately surrounding the clot, creating microbubbles.^{45,73} These microbubbles rapidly collapse along the clot surface, emitting shock waves and liquid jet speeds of more than 1 km/sec, which promote thrombolysis.^{9,31,71} The optimal frequency to effectively induce localized inertial cavitation while minimizing surrounding tissue injury depends on several factors. High frequency (usually on the order of MHz) is necessary to produce a sufficiently focused ultrasound beam. However, high-frequency ultrasound is more rapidly attenuated by the calvaria.^{23,72} Calvarial attenuation is less of a concern with low-frequency ultrasound, which generates more robust cavitation. However, low-frequency waves can be difficult to focus, resulting in thermal and mechanical damage to adjacent tissues.^{6,23,58,68,72}

Several techniques have been developed to improve the safety and efficiency of MRg-HIFU thrombolysis. The presence of intracranial standing waves secondary to resonance from acoustic reflections within the cranial vault can have unpredictable and detrimental effects, including the formation of unexpected hot spots and an elevated risk of ICH.^{8,16,67} One method of decreasing the likelihood of standing-wave formation is to sharpen the focal volume by increasing the emission frequency.^{15,67} Additionally, given that standing waves are more likely to accumulate during extended ultrasound exposure, pulsed sonication can reduce the risk that is associated with resonance.^{6,10,67} Pulsed sonication has also been found to yield superior ELVO recanalization rates in preclinical studies.^{6,62,73} Another method to mitigate standing-wave formation is via multifrequency sonication.^{40,41} Not only does multifrequency HIFU decrease resonance, but it also allows for simultaneous multiregional cavitation, which improves selectivity of the focal point to cavitation, and permits cavitation mapping.^{17,66}

In Vitro Studies

Several in vitro models have demonstrated the effectiveness of appropriately selected HIFU parameters for thrombolysis (Table 1). Westermarck et al. showed that marked thrombolysis of clots in a degassed water–filled bowl could be achieved using an acoustic focus from a 1.1-MHz HIFU transducer with a pulsed sequence for 30 seconds, compared with the use of 30 shock waves or continuous HIFU.⁷² Rosenschein et al. were able to achieve a thrombolysis rate of 91% at optimum pulsed-HIFU parameters (1.5 MHz, 1:25 duty cycle, 200- μ sec pulse length) and showed that arterial damage ensues following prolonged exposure to HIFU (45 W/cm² for $\geq$ 5 minutes).⁶² Maxwell et al. investigated the relationship between HIFU intensity and thrombolysis rate using a 1-MHz pulsed-HIFU transducer.⁴⁵ Complete fractionation was achieved at peak pulse mean intensities of $\geq$ 3600 W/cm² (corresponding to $\geq$ 8-MPa peak negative pressures) within 5 minutes of treatment. The aforementioned studies also measured debris size following lysis and showed that at least 93% of debris particles were subcapillary in caliber (< 8 μ m in diameter).^{45,62} Wright et al. varied pulse length and acoustic power while keeping total imparted energy constant in a 1.51-MHz pulsed-HIFU in vitro clot

TABLE 1. Summary of studies using in vitro and in vivo models to determine the safety and feasibility of HIFU for thrombolysis

Authors & Year	Transcranial	Methods	Results
Pajek et al., 2014	Yes	1) In vitro model: rabbit clots suspended in artificial flow system w/ injected microbubbles; 2) in vivo: rabbit ELVO model: 2 × 2 × 2-mm clots inserted into lt ICA, resulting in proximal MCA infarction Parameters: 1.51 MHz, varied acoustic power (19–137 W), varied pulse length (0.1 or 1 msec), 2-sec duration	1) Mean threshold intensity to achieve inertial cavitation was 49 ± 9 W; 2) overall recanalization rate 71%
Hölscher et al., 2013	Yes	1) In vitro model: human clot suspended in ex vivo human calvaria in a hemispheric, degassed-water transducer; 2) in vivo: rabbit ICA ELVO model Parameters: 220 kHz, varied acoustic power (100–400 W), varied pulse width (0.1–200 msec), varied duty cycle (5%–50%), 30-sec duration	1) Thrombolysis rates ranged from 10% to 42%, >400 W acoustic output needed to achieve clot fragmentation, higher duty cycles & longer pulse width yielded increased thrombolysis rates; 2) 10% recanalization rate, primarily a feasibility study
Burgess et al., 2012	Yes	In vivo model: rabbit ELVO model: 2 × 2 × 2-mm clots inserted into lt ICA, resulting in proximal MCA infarction Parameters: 1.5 MHz, varied acoustic power (275–550 W), 1-msec burst of 1-Hz pulse frequency, 20-sec exposure	Recanalization rates in the 275-, 415-, and 550-W groups were 0% (0/4), 50% (2/4), and 71% (5/7), respectively; basal brain surface bleeding in 25% (1/5), w/o associated vessel damage; mean time from ischemic confirmation on DSA to recanalization 59 mins
Wright et al., 2012	No	1) In vitro model: rabbit clots suspended in degassed-water tank; 2) in vivo: 1-cm rabbit femoral artery occlusion Parameters: 1.51 MHz, varied acoustic power (120–300 W), varied pulse lengths (0.1–1 msec), 0.1% duty cycle	1) Clot erosion vol increased w/ power & pulse length, increased pulse length associated w/ reduced pulse size; 2) 1-msec pulse length at 300 W achieved partial restoration in 63% (5/8) femoral arteries, w/ 1 minor bleed
Maxwell et al., 2011	No	In vivo model: 2-cm thrombus in pig femoral veins Parameters: 1 MHz, varied average peak negative pressure (49–105 W/cm ²), 5 cycle bursts at 1-kHz pulse frequency	58% (7/12) cases showed improved flow; 75% (3/4) femoral veins showed minor zones of hemorrhage
Maxwell et al., 2009	No	In vitro model: 4 × 20-mm cylindrical canine clots placed in tube, suspended in degassed-water tank Parameters: 1 MHz, varied peak average intensities (150–7000 W/cm ²), 5 cycle bursts at 1-kHz pulse frequency	At ≥3600 W/cm ² , significantly increased thrombolysis rate observed; clots completely lysed in 1.5–5 min; >96% of clot debris <5 µm in diameter
Rosenschein et al., 2000	No	In vitro model: bovine ICA segments w/ intraluminal bovine clots immersed in tank w/ degassed water Parameters: 1) focal spot average intensity 40 W/cm ² , varied pulse length (50–400 µsec), varied duty cycles (1:10–1:40), 4-min exposure; 2) varied average intensity (10–55 W/cm ²), 200-µsec pulse length, 1:25 duty cycle	1) Optimal pulse length & duty cycles were 200 µsec & 1:25, respectively, to yield 90% ± 1% thrombolysis efficiency; 2) no sonographic evidence of clot at optimal 40-W/cm ² intensity, 93% ± 1% of clots became subcapillary (<8 µm) in size, histological analysis showed mild tissue damage w/ ≥5 mins exposure
Westermarck et al., 1999	No	In vitro model: 5-mm-thick human clot suspended in bowl w/ degassed water Parameters: 1) 1.1 MHz, 16-element array, continuous emission, 30-sec exposure; 2) 1.1 MHz, 30-W average output, 16-element array, pulsed emission at 67 Hz w/ 38-msec pause time, 30-sec exposure	1) 11% ± 6% clot weight reduction; 2) 99% ± 2% clot weight reduction

ICA = internal carotid artery.

model and demonstrated a direct relationship between these 2 parameters and clot erosion.⁷³ In a transcranial in vitro model using human clots suspended in ex vivo human calvariae, Hölscher et al. attained thrombolysis rates of 10%–42% and found that > 400 W of acoustic output was needed to achieve clot fragmentation.²⁹

In Vivo Studies

In vivo studies that have assessed the feasibility of HIFU thrombolysis are scarce (Table 1). Maxwell et al. developed a porcine thrombus model using 2 balloon cath-

eters inflated to trap a 20-mm segment of the femoral vein, into which thrombin was infused.⁴⁶ Ultrasound-guided pulsed HIFU was performed using a 1-MHz transducer to generate peak pulse mean intensities of 9800–21,000 W/cm² (corresponding to peak negative pressures of 14–19 MPa). A total of 12 cases were assessed, 10 (83%) of which demonstrated signs of luminal cavitation. Of these 10 cases, 7 showed Doppler ultrasonographic evidence of improved flow. Assessment of vessel damage in the 12 HIFU-treated cases was confounded by injury due to catheter insertion and balloon dilation. Wright et al. used

TABLE 2. List of studies using in vitro and in vivo models to determine safety and feasibility of HIFU for ICH

Authors & Year	Transcranial	Methods	Results
Harnof et al., 2014	Yes	1) In vitro model: 300-ml clot introduced in ex vivo human skull; 2) in vivo: porcine lobar ICH model; 3) in vivo: in vivo porcine 3-ml ICH model implanted w/in ex vivo human skull Parameters: 230 kHz, varied acoustic power (600–900 W), pulsed sonication, 10% duty cycle, 5- to 10-sec duration	1) 50% (9/18) sonications resulted in liquefaction w/o thermal effect; 2 & 3) clot liquefaction achieved w/ modest increase in surrounding tissue temperature
Monteith et al., 2013	Yes	1) In vitro model: human clots placed in wells suspended in ex vivo human calvaria; 2) in vivo: swine ICH model; 3) in vitro: ex vivo human ICH model w/ implanted 40-ml human blood clots Parameters: 230 kHz, varied acoustic power (750–3950 W), varied pulse width around 100 μ sec, varied duty cycle around 10%, 30-sec duration	1) Optimal thrombolysis parameters were 3950 W, 1-kHz pulse repetition rate, 10% duty cycle, duration of 30 sec, average vol of 3.6 ml lysed; 2) complete lysis of 4-ml ICH w/o additional brain injury performed; 3) >95% liquefaction rate permitting minimally invasive aspiration

a rabbit femoral artery clot model with vascular clamps to occlude a 1-cm segment.⁷³ Pulsed HIFU was performed with a 1.51-MHz transducer to generate acoustic powers of 185, 215, and 300 W using 1-msec pulses. Partial flow restoration rates were 0% (0/5), 50% (1/2), and 63% (5/8) at these settings, respectively. However, none of these cases demonstrated complete flow restoration. One minor bleed (1–2 drops) that occurred in the 300-W group resolved within 2 minutes. These studies demonstrated the feasibility of extracranial thrombolysis using HIFU.

Burgess, Pajek, and colleagues performed in vivo studies of intracranial ELVO thrombolysis using MRg-HIFU.^{10,57} In the first of these 2 studies, a model of embolic stroke was developed by injecting 8-mm³ rabbit blood clots, prepared and assessed in vitro, into the left internal carotid artery of anesthetized rabbits and confirming middle cerebral artery (MCA) occlusion via digital subtraction angiography (DSA). Magnetic resonance imaging localization of the clot was performed using fast gradient-echo and time-of-flight sequences. Pulsed HIFU was performed using a 1.51-MHz transducer to generate acoustic energies of 275–550 W in 1-msec bursts with a 1-Hz pulse repetition frequency. Sonication proceeded from distal to proximal in 0.75-mm increments. Recanalization was assessed using DSA. Respective recanalization rates in the 275-, 415-, and 550-W groups were 0% (0/4 animals), 50% (2/4), and 71% (5/7). Histological examination revealed intact and undamaged arteries and arterioles. In 1 of the latter 5 cases, there was evidence of bleeding from the base of the brain, without associated vessel damage. Small regions of Prussian blue staining were observed in distal cortical regions, indicating that most debris cleared the proximal cerebral vasculature. The mean time from confirmation of the clot via DSA to recanalization was 59 minutes. In the second study by this same group, intravascular perfluorocarbon droplets were shown to reduce the necessary HIFU intensity output required to achieve MCA clot thrombolysis by 76% in a similar rabbit model of AIS. The recanalization rates were 71% in the group receiving 1-msec pulse durations. These studies demonstrated the feasibility of transcranial MRg-HIFU thrombolysis for AIS.

Two in vivo studies have demonstrated the feasibility of transcranial MRg-HIFU in ICH sonolysis (Table 2).^{25,50} Monteith et al. determined optimal HIFU parameters in

an in vitro model in which human clots were suspended within ex vivo human calvaria and lysed with a pulsed 230-kHz transducer.⁵⁰ Optimal parameters of 3950 W of acoustic output, a pulse repetition rate of 1 kHz, and a 10% duty cycle yielded complete lysis of 3.6-ml clots on average. Subsequently, these optimal parameters were applied to both an in vitro ICH model in which a 40-ml clot was implanted in an ex vivo human brain and an in vivo swine ICH model and demonstrated a > 95% liquefaction rate permitting minimally invasive clot aspiration and complete lysis of 4-ml clots without additional brain injury, respectively. Harnof et al. used a pulsed, 230-kHz transducer with 700 W of acoustic output, a 10% duty cycle, and a 5-second duration to achieve complete liquefaction in a model of porcine ICH implanted in a cadaveric human calvaria.²⁵ Minimal, nondamaging thermal effects were observed in surrounding brain regions.

Potential Applications

Transcranial MRg-HIFU thrombolysis is an emerging technology that has the potential to be a valuable addition to the AIS and ICH treatment armamentarium. Regarding AIS treatment, MRg-HIFU sonolysis offers several advantages over sonothrombolysis. Given that IV-tPA alone can require several hours to achieve recanalization, MRg-HIFU could be performed concurrently to achieve more rapid thrombolysis and superior recanalization rates. Additionally, the application of MRg-HIFU as a sole treatment modality would circumvent tPA administration and associated complications.⁷⁴ Furthermore, MRg targeted therapy not only limits untoward thermal effects of HIFU but also decreases operator dependence. Compared with EMT, MRg-HIFU may offer a completely noninvasive therapy for AIS secondary to ELVO. However, the potential benefits of this therapy must be weighed against the risks of unintended thermal damage to brain parenchyma due to heating of the skull base (that is, during treatment of proximal occlusions) or calvaria (that is, during treatment of distal occlusions). Compared with EMT, MRg-HIFU thrombolysis may yield superior disintegration rates in cerebral venous sinus thrombosis since these clots are typically larger in caliber; however, current application may be limited to deep-seated thromboses.^{34,44,65}

Regarding ICH treatment, the current standard of care includes correction of underlying coagulopathies, optimization of blood pressure and serum glucose, anticonvulsant therapy for new-onset seizures, and CSF diversion in patients with hydrocephalus.²⁶ The role of surgical intervention for ICH continues to evolve. The results of recent randomized trials suggest that catheter-based hematoma evacuation may be advantageous in select patients.^{24,48,52} However, an important consideration in this approach is catheter alignment along the long axis of the clot, which can be challenging without compromising critical structures.⁵¹ Alternatively, MRg-HIFU sonolysis is not only noninvasive but also selectively targets clots of any shape, located in any deep brain region. Thus, MRg-HIFU sonolysis may be a particularly effective therapy for patients with intraventricular hemorrhage for whom surgical clot evacuation is not beneficial.²⁴ One drawback of MRg-HIFU is its inability to lyse clots within 2 cm of the calvaria because of bony attenuation and heat generation; however, these superficial clots are more likely to be amenable to surgical evacuation.^{39,61} In addition, technical complexity and time requirements represent limitations to the current application of MRg-HIFU sonolysis in both AIS and ICH. However, we anticipate that these limitations will become obviated with the more widespread use of MRg-HIFU and technological advancements in the future.

Conclusions

Magnetic resonance–guided HIFU thrombolysis utilizes hemispheric, large-aperture, multielement phased-array transducers to transmit acoustic energy in a pulsed fashion to disintegrate intracranial clots via inertial cavitation. Several preclinical studies have demonstrated the feasibility of this therapy. As a noninvasive transcranial technique that affords rapid clot lysis, MRg-HIFU thrombolysis may develop into a treatment option for AIS or ICH. However, additional studies of transcranial MRg-HIFU are necessary to ascertain the merit of this therapeutic approach for thrombolysis in both AIS and ICH, as well as its technical limitations and risks.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Ilyas, Chen. Acquisition of data: Ilyas. Analysis and interpretation of data: Ilyas, Chen. Drafting the article: Ilyas. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ilyas. Administrative/technical/material support: Kalani, Park. Study supervision: Kalani, Park.

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