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MR-Guided, Focused Ultrasound: Applications to Essential Tremor and Other Neurologic Conditions

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reduced performance.[10] However, the addition of complex 360° shapes improved the angiographic outcomes for both Matrix and GDC coils—making the 2 more comparable.

In a detailed analysis, the actual benefit of Matrix surface modification was in the histopathologic results, which showed that Matrix-treated aneurysms showed improved endothelization, manifest as an absence of endothelialized clefts at the aneurysm neck (which are prevalent in GDC-treated aneurysms).[10] Endothelialized clefts have been proposed as the etiology for late angiographic recurrences.[5] Late recurrences have been reported at 3 years in up to 15% of aneurysms that had been completely occluded acutely and in short-term follow-up.[11] While the MAPS trial showed that in the short term, Matrix was essentially equivalent to platinum coils, the real benefits of surface modification may be manifest in the results at late (3- and 5-year) follow-up.

Furthermore, in subgroup analysis, when aneurysms were adequately occluded (Raymond-Roy scale 1 or 2), Matrix had significantly better outcomes with only 2.7% requiring retreatment compared with 9.6% ($P = .01$) with platinum coils.[12] However, aneurysms with residual flow (Raymond-Roy scale 3) demonstrated poor outcomes in both arms—Matrix (24.2%) and platinum (16.1%) ($P = .17$). These observations coincide well with the known polyglycolic/polylactic acid (PGLA) characteristics, the polymer coating on Matrix coils. When exposed to high-flow states, PGLA experiences an acceleration of breakdown, nullifying any potential gain due to the bioactive component of the coil. These results suggest that the short-term issues with Matrix were more likely related to the adequacy of mechanical occlusion rather than the efficacy of the bioactive coating.

We believe that collaborative doctor/industry relationships are an important synergistic dynamic that is essential for continued technologic advancement in our specialty. It is critical that high standards be set for new technologies, particularly for those designed to treat diseases with well-established safe therapies. Regimented postmarket data collection and evaluation should occur with all new technologies, ensuring that marketing claims are not confused with scientific evidence.[13] However, to mix concerns with technology marketing or limitations in the implementation of a technology with a perception of failure of the fundamental scientific premise would be a mistake.

In our opinion, the concept of platinum coil surface modification to stabilize or increase the rate of thrombus organization is still valid and continues to have promise for enhancing long-term aneurysm occlusion stability. Time will tell whether this benefit will be reflected in the late-term MAPS data; the current data do not negate the fundamental concepts of bioactive coatings. As such, continued innovation toward the development of better delivery mechanisms or more durable bioactive responses is entirely reasonable.

REFERENCES

1. Molyneux AJ, Clarke A, Sneade M, et al. **Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either cerecyte or bare platinum coils.** *Stroke* 2012;43:2544–50
2. White PM, Lewis SC, Nahser H, Sellar RJ, Goddard T, Gholkar A. **HydroCoil Endovascular Aneurysm Occlusion and Packing Study (HELPS trial): procedural safety and operator-assessed efficacy results.** *AJNR Am J Neuroradiol* 2008;29:217–23
3. Bouzeghrane F1, Naggara O, Kallmes DF, et al**. In vivo experimental intracranial aneurysm models: a systematic review.** *AJNR Am J Neuroradiol* 2010;31:418–23
4. Mawad ME, Mawad JK, Cartwright J, et al. **Long-term histopathological changes in canine aneurysms embolized with Guglielmi detachable coils.** *AJNR Am J Neuroradiol* 1995;16:7–13
5. Raymond J, Guilbert F, Metcalfe A, et al. **Role of the endothelial lining in recurrences after coil embolization: prevention of recanalization by endothelial denudation.** *Stroke* 2004;35:1471–75
6. Raymond J, Leblanc P, Morel F, et al. **Beta radiation and inhibition of recanalization after coil embolization of canine arteries and experimental aneurysms: how should radiation be delivered?** *Stroke* 2003;34:1262–68
7. Reul J, Weis J, Spetzger U, et al. **Long-term angiographic and histopathologic findings in experimental aneurysms of the carotid bifurcation embolized with platinum and tungsten coils.** *AJNR Am J Neuroradiol* 1997;18:35–42
8. Strother CM, Graves VB, Rappe AA. **Aneurysm hemodynamics: an experimental model.** *AJNR Am J Neuroradiol* 1992;13:1089–95
9. Turk AS, Aagaard-Kienitz B, Niemann DB, et al. **Natural history of the canine vein pouch aneurysm model.** *AJNR Am J Neuroradiol* 2007;28:531–32
10. Turk AS, Luty CM, Carr-Brendel V, et al. **Angiographic and histological comparison of canine bifurcation aneurysms treated with first generation Matrix and standard GDC coils.** *Neuroradiology* 2008;50:57–65
11. Raymond J, Guilbert F, Weill A, et al. **Long-term angiographic recurrences after selective endovascular treatment of aneurysms with detachable coils.** *Stroke* 2003;34:1398–403
12. McDougall CG, Claiborne Johnston S, Gholkar A, et al. **Bioactive versus bare platinum coils in the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) Trial.** *AJNR Am J Neuroradiol* 2014;35:935–42
13. Fargen KM, Frei D, Fiorella D, et al. **The FDA approval process for medical devices: an inherently flawed system or a valuable pathway for innovation?** *J Surg* 2013;5:269–75

EDITORIAL

MR-Guided, Focused Ultrasound: Applications to Essential Tremor and Other Neurologic Conditions

G. Suffredini and L.M. Levy

In this issue of the *American Journal of Neuroradiology,* a novel approach by means of MR-guided, focused sonography surgery (MRgFUS) is used to treat essential tremor.[1] The results indicate that clinical improvement is significantly related to total lesion size. No relationship was found between the imaging characteristics of the lesion and sonication number, power, or maximal temperature. Although the authors describe an important advance in the use of this procedure, the study also raises a number of questions regarding the broad application of this technique to various neurologic conditions.

The use of focused sonography to treat brain disorders has evolved over the past 70 years. In the 1950s, Francis and William Fry developed a system of converging sonography beams to pro-

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duce focal ablations in the brains of pigs and cats when applied through a craniotomy acoustic window.[2] The major limitation of this technology was the inability to focus sufficient sonography energy through the bony skull because of attenuation of acoustic energy. By the 1970s, their lab described the acoustic properties of the human skull[3] and successfully achieved trans-skull transmission of an intensely focused ultrasonic beam.[4]

During the past decade, sonography therapy has emerged as a minimally invasive therapy for movement disorders, neuropathic pain, and malignancies. In combination with MR imaging and MR thermometry, MRgFUS can produce focused ablations in the brain by thermal and nonthermal effects with millimeter accuracy.[5] Thermal (ablative) effects of MRgFUS occur when tissue is heated above 57–60°C, resulting in coagulative necrosis and tissue destruction. The degree of tissue necrosis is related to the focused sonography beam and can be monitored in real time with MR thermometry. Nonthermal (nonablative) effects of focused sonography result from acoustically induced interactions of microscopic gas bubbles or "microbubbles" with the surrounding vascular endothelium, a process termed "cavitation." These interactions cause disruption of endothelial cell tight junctions and result in disruption of the blood-brain barrier. Because the sonography intensity needed to produce microbubble-induced cavitation is several orders of magnitude lower than the intensity needed for thermal ablation, this disruption of the blood-brain barrier is only temporary and has been shown to be safe and effective in an animal model.[6]

Both thermal and nonthermal mechanisms of MRgFUS can provide novel therapeutic opportunities for the treatment of brain disorders. Focused sonography is ideal for ablation therapy because it can target deep brain structures including the thalamus, subthalamus, and pallidum regions. However, it is limited in treatment of lesions near the calvaria because of the attenuation effects of the skull, which are more pronounced at locations nearer to bone. Ablative therapies have been investigated as suitable minimally invasive alternatives for glioblastoma,[7] neuropathic pain,[8] and essential tremor.[9,10] Investigations for the treatment of Parkinson disease are currently underway.[11]

The short-lived disruption of the blood-brain barrier by MRgFUS provides a means to target delivery of drugs, antibodies, and stem cells to brain tissue.[12-14] Sonography has also been used to enhance revascularization in a process termed "sonothrombolysis." A recent meta-analysis of the use of sonography in ischemic stroke showed the therapy to be safe and effective.[15] MRgFUS enables targeted delivery of sonography to the clot location and has the potential to improve the treatment of acute ischemic stroke. MR imaging can identify clot location and serve as a treatment map for immediate focused sonography therapy. Focused sonography sonothrombolysis has also been proposed for the treatment of intracerebral hemorrhage.[16] In this setting, sonothrombolysis is used to liquefy the clotted blood within the intracerebral hemorrhage with consequent minimally invasive MR imaging–guided drainage of the liquefied clot.

The effectiveness and utility of sonography therapy can be augmented with nanotechnology. Thermal ablation is being evaluated by use of multifunctional drug delivery systems capable of triggering local hyperthermia in the presence of low-frequency sonography.[17] These systems provide a unique synergistic combination of chemotherapy, thermal therapy, and real-time imaging and are being investigated for the treatment of CNS malignancies. The present study by Wintermark et al[1] demonstrates the importance of lesion size in achieving symptom relief. Although total lesion size was significantly correlated to clinical improvement, the value of the imaging findings remains unclear. The time-dependent imaging characteristics of MRgFUS-induced brain lesions on T2-weighted imaging consists of 3 concentric zones: zones I and II appear as a result of coagulation and necrosis, and zone III appears as the most peripheral of the concentric zones and represents transient edema.[18] A larger zone III area is correlated with clinical improvement, but some of this improvement is lost as the edema resolves. Of interest, 2 patients with limited clinical improvement had imaging characteristics that were not very different from those with clinical improvement. This raises the concern of difficulties associated with accurately locating therapeutic targets. The ventrointermediate nuclei (Vim) are the thalamic relays of the cerebellothalamocortical tract and are the principal targets of MRgFUS in the treatment of essential tremor. Two methods may be used to locate the Vim: image-based coordinate targeting (direct method) and atlas-based targeting (indirect method). The latter approach is subject to potential inaccurate localization of the anterior and posterior commissures, an error that can be >5 mm. Direct identification is considered to be more accurate in identifying Vim and may be achieved with fractional anisotropy and color-coded vector maps.[19] Lesion identification in the current study was determined by atlas coordinates and clinical parameters evaluated in real time with sublesional sonication. In the 2 patients with limited therapeutic benefit, the MRgFUS was not repositioned, and the patients did not show sensory symptoms during treatment. Future studies may incorporate direct methods of Vim location during sonication to confirm target identification. Diffusion tractography may also be useful in evaluating the integrity of these tracts over time and in correlating their integrity with clinical symptoms. This approach could potentially help to identify valuable imaging information and provide useful targets for repeat therapy. Last, in the current study, total lesion size appeared to be unrelated to sonication number, power, or maximal temperature, presumably because of the small effect size and underpowered study. Determining the optimal use of these variables may improve the clinical utility of MRgFUS.

REFERENCES

1. Wintermark M, Druzgal J, Huss D, et al. **Imaging findings in MR-guided focused ultrasound treatment for patients with essential tremor.** *AJNR Am J Neuroradiol* 2014;35:891–96.
2. Fry WJ, Mosberg WH Jr, Barnard JW, et al. **Production of focal destructive lesions in the central nervous system with ultrasound.** *J Neurosurg* 1954;11:471–78
3. Fry FJ, Barger JE. **Acoustical properties of the human skull.** *J Acoust Soc Am* 1978;63:1576–90
4. Fry FJ. **Transkull transmission of an intense focused ultrasonic beam.** *Ultrasound Med Biol* 1977;3:179–84
5. Colen RR, Jolesz FA. **Future potential of MRI-guided focused ultrasound brain surgery.** *Neuroimaging Clin North Am* 2010;20:355–66
6. McDannold N, Arvanitis CD, Vykhodtseva N, et al. **Temporary disruption of the blood-brain barrier by use of ultrasound and**

microbubbles: safety and efficacy evaluation in rhesus macaques. *Cancer Res* 2012;72:3652–63
7. McDannold N, Clement GT, Black P, et al. **Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: initial findings in 3 patients.** *Neurosurgery* 2010;66:323–32
8. Jeanmonod D, Werner B, Morel A, et al. **Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain.** *Neurosurg Focus* 2012;32:E1
9. Lipsman N, Schwartz ML, Huang Y, et al. **MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study.** *Lancet Neurol* 2013;12:462–68
10. Elias WJ, Huss D, Voss T, et al. **A pilot study of focused ultrasound thalamotomy for essential tremor.** *N Engl J Med* 2013;369:640–48
11. **InSightec. A Feasibility Study to Evaluate Safety and Initial Effectiveness of ExAblate Transcranial MR Guided Focused Ultrasound for Unilateral Thalamotomy in the Treatment of Medication-Refractory Tremor Dominant Idiopathic Parkinson's Disease.** In: ClinicalTrials.gov. Bethesda, Maryland: National Library of Medicine (US). 2000 [cited 2013 Sept 1]. http://clinicaltrials.gov/ct2/show/NCT01772693. 2013
12. Burgess A, Ayala-Grosso CA, Ganguly M, et al. **Targeted delivery of neural stem cells to the brain using MRI-guided focused ultrasound to disrupt the blood-brain barrier.** *PLoS One* 2011;6:e27877
13. Jordao JF, Thevenot E, Markham-Coultes K, et al. **Amyloid-beta plaque reduction, endogenous antibody delivery and glial activation by brain-targeted, transcranial focused ultrasound.** *Exp Neurol* 2013;248C:16–29
14. Arvanitis CD, Livingstone MS, McDannold N. **Combined ultrasound and MR imaging to guide focused ultrasound therapies in the brain.** *Phys Med Biol* 2013;58:4749–61
15. Saqqur M, Tsivgoulis G, Nicoli F, et al. **The role of sonolysis and sonothrombolysis in acute ischemic stroke: a systematic review and meta-analysis of randomized controlled trials and case-control studies.** *J Neuroimaging* 2013 Apr 22. [Epub ahead of print]
16. Monteith SJ, Harnof S, Medel R, et al. **Minimally invasive treatment of intracerebral hemorrhage with magnetic resonance-guided focused ultrasound.** *J Neurosurg* 2013;118:1035–45
17. Yang HW, Hua MY, Hwang TL, et al. **Non-invasive synergistic treatment of brain tumors by targeted chemotherapeutic delivery and amplified focused ultrasound-hyperthermia using magnetic nanographene oxide.** *Adv Mater* 2013;25:3605–11
18. Martin E, Jeanmonod D, Morel A, et al. **High-intensity focused ultrasound for noninvasive functional neurosurgery.** *Ann Neurol* 2009;66:858–61
19. Yamada K, Akazawa K, Yuen S, et al. **MR imaging of ventral thalamic nuclei.** *AJNR Am J Neuroradiol* 2010;31:732–35

EDITORIAL

Simple MRI Metrics Contribute to Optimal Care of the Patient with Multiple Sclerosis

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MR imaging has been a critical element in multiple sclerosis care because it has been the basis, along with clinical measures, for testing treatment efficacy. MR imaging serves as a primary outcome measure in phase II and a secondary outcome measure in phase III clinical trials in MS.[1] There are now 10 approved MS disease-modifying drugs, all showing measureable impact in population studies on inflammatory disease as indicated by new T2 hyperintense and/or gadolinium-enhancing lesions on MR imaging. MR imaging initially impacted the field as an important component of diagnostic criteria,[2] in part because MR imaging is much more sensitive to early MS than are clinical features. For similar reasons, clinicians have embraced the practice of monitoring subclinical MR imaging activity for treatment decisions, though formal criteria for an actionable response to MR imaging activity in an individual patient have been limited (On-line Table 1). MR imaging monitoring is also critical for detecting complications of therapy—for example, infection (progressive multifocal leukoencephalopathy) or inflammation (immune reconstitution inflammatory syndrome).[3]

Several recent initiatives by the MS community have addressed the concept of individualized, more tailored, and sometimes more aggressive early treatment. Treatment escalation has only recently become feasible with the introduction of new, potentially stronger MS treatments based on differing mechanisms and molecular targets.[4] As a result, MR imaging activity will be increasingly used in clinical practice to determine whether patients are responding to treatment or may benefit from a change in treatment or escalation to higher-risk therapy (On-line Table 1). For example, the Canadian MS Working Group guidelines were updated in 2013,[5] on the basis of combinations of relapse, disability, and MR imaging scores, for recommendations classified as low, medium, or high concern. The Rio score, developed in Barcelona, was modified recently on the basis of a validation study to include only MR imaging activity and relapse indicators.[6] Enhancing lesions, followed by relapses and new T2 lesions during the initial 2 years, were the best predictors of disability 15 years later in treated (distinct from placebo) patients in the interferon (IFN) β-1a trial,[7] suggesting that persistent inflammatory disease activity in patients on IFN reflected nonresponse to therapy. An analysis by Dobson et al[8] from 11 studies with IFN-β treatment found that those who develop new MR imaging lesions on IFN-β within 2 years of starting therapy are at significantly higher risk of future relapses and/or disability worsening and that these patients can be identified after just 6–12 months of treatment.

The simple MR imaging measures of focal T2 hyperintense and enhancing lesions seem to contribute strongly to relapse and disability outcomes and contribute significantly to brain atrophy, a surrogate of disability. This association is highlighted in a recent meta-analysis by Sormani et al,[9] based on >13,500 patients with relapsing MS in 13 clinical trials. The correlation coefficients (R^2) with downstream disability for new/enlarging T2 lesions and brain atrophy were 0.61 and 0.48, respectively, with both measures retained in a final model with a combined R^2 of 0.75, strongly supporting the use of these MR imaging outcomes as clinical surrogate measures when applied in an appropriate clinical-/treatment-specific context.[9]

It is likely that in the future, advanced quantitative and functional measures by MR imaging will assume far greater impor-

Indicates article with supplemental on-line tables.

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