CV Section News

Chairman's Message

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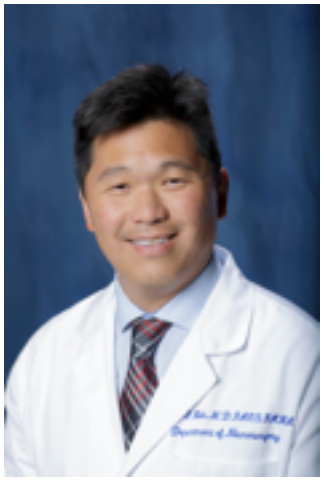


See You In Music City!

Brian L. Hoh, MD, FAANS, FACS, FAHA

As Chair of the AANS/CNS Cerebrovascular Section, I am excited to personally invite you to our upcoming Annual Meeting February 9-10, 2015 in Nashville, Tennessee. In a strategic decision made nearly a decade ago, our Section has been and will again this year have our Annual Meeting directly preceding the American Heart Association/American Stroke Association International Stroke Conference.

The meeting includes collaborative programming with our partner society the Society of Neurointerventional Surgery (SNIS) and our international partner, the Vascular section of the European Association of Neurosurgical Societies (EANS).

Our annual meeting chair, J Mocco, has put together an exciting but also provocative scientific program which addresses many of the controversies that face our field including recent acute ischemic stroke trials, MR CLEAN, ESCAPE, and EXTEND IA; controversies in AVM, brainstem cavernous malformation, and moya moya treatment; debates over flow diversion; and updates in billing and coding which affect us all. **Information and registration for the meeting can be found on our website: www.cvsection.org.**

Our Section has been busy and productive working on initiatives that concern and benefit our membership. In the last newsletter, I highlighted our initiatives in developing Fellowship Training Standards; working with the Joint Commission on improving criteria for Comprehensive Stroke Center Certification; and developing evidence-based Clinical Guidelines.

In this newsletter, I would like to highlight a few of our other many initiatives:

1. We are excited to announce our collaboration with the Neurosurgery Research & Education

Foundation in establishing the Charles G. Drake Fund which will support cerebrovascular research and fellowships in honor of this great neurosurgical giant in our field. More information can be found on our website: www.cvsection.org.

2. We are actively working with Neuropoint Alliance in creating a Cerebrovascular Module for the The National Neurosurgery Quality and Outcomes Database (N²QOD) Registry. This will be critically important to all of us with mandated quality and outcomes reporting, but is also timely because of the need for quality prospective registry data in an environment of controversial and conflicting results from recent clinical trials.

3. We have been working with the American Board of Neurological Surgery (ABNS) in developing a cerebrovascular-focus Maintenance of Certification (MOC) cognitive examination. As you are all aware, for ABNS MOC time-limited certification (applies to all ABNS Diplomates certified since 1999), a cognitive examination must be passed at the end of the ten-year cycle. There is currently a general neurosurgery, spine-focus and pediatric-focus MOC cognitive examination. For the benefit of our Section's membership, we have requested and the ABNS has agreed to work with us in developing a cerebrovascular-focus MOC examination.

I am personally excited about the great initiatives of our Section which are the product of the tremendous work, time, and effort of our members. I pledge to continue to work diligently for the benefit and greater interests of our members and our field. See you in Nashville!

SECRETARY'S MESSAGE

The AANS/CNS Section on Cerebrovascular Surgery continues to provide valuable benefits to its membership. Over the past year, the Section has represented the neurosurgical community through some of the most tumultuous and exciting times for cerebrovascular surgery in recent memory. With the ups and downs of various acute thrombectomy trials and the important need to ensure appropriate interpretation of the ARUBA trial, the section has been hard at work ensure cerebrovascular patients are protected and that they continue to have the option to receive the potentially life-saving procedures we provide.

Furthermore, we are excited for our upcoming annual meeting in Nashville, TN. The AANS/CNS Joint Cerebrovascular Section has partnered with the Society of NeuroInterventional Surgery (SNIS) and the European Association of Neurosurgical Societies (EANS) in planning and executing the annual meeting. The collaborative environment created at this joint meeting will further the mission of all three societies, and provide for an outstanding experience. This year Dr. William Mack represents the SNIS and Dr. Mika Niemela the EANS on the leadership team. The meeting program is innovative, and thought provoking, with an emphasis on ensuring there is outstanding evidence based discussion.

The meeting will be held in the downtown area, close to world-class music venues, professional sports complexes, numerous fine and casual dining options, a multiple cultural activities – such as Schermerhorn Symphony Center and the Frist Center for the Visual Arts. In contrast to past meetings in the Nashville area, when the meeting was held outside of town, this upcoming year should truly provide an outstanding venue. Drs. Peter Nakaji and myself will serve as the co-chairs of this year's annual meeting.

Our Executive Council continues work on policy development, education, research, and collaboration with numerous organizations and specialists focused on cerebrovascular disease. Numerous recent guidelines have been reviewed by the section, with those efforts led by Dr. Kevin Cockroft, Dr. Henry Woo continues to report important changes in coding and insurance coverage, and Dr. Sander Connolly has made important strides in the development of a national outcomes database for cerebrovascular surgery.

The section continues its educational efforts, with a continuum of endovascular and cerebrovascular training in order to provide residents level-appropriate training over the breadth of their training.

Perhaps one of the most exciting developments over the past number of months has been the outstanding progress on our website (http://www.cvsection.org/). Dr. Babu Welch and his team

have made it a very useful tool to our membership. If you haven't visited the site recently, we recommend you do. There are many new functions and resources.

The CV Section remains a critical piece of the cerebrovascular landscape. We are committed to advocating for patients and advancing the care of cerebrovascular disease worldwide. We encourage all neurosurgeons and cerebrovascular practitioners to become involved in our educational, research and advocacy activities. It is only through our dedicated membership's efforts that we will continue to provide these important opportunities.

J Mocco, MD, MS

Schermerhorn Symphony Center, Nashville, TN

TREASURER'S MESSAGE

I am happy to report that the Joint Cerebrovascular Section continues to be in excellent financial standing. The JCVS/SNIS Joint Annual Meeting in San Diego, CA was a tremendous success – combining an outstanding scientific program and strong discourse among speakers and participants while also being financially successful. We very much look forward to the upcoming JCVS/SNIS Joint Annual Meeting in Nashville, TN and hope that you will join us.

The Fundraising Committee is very active in the section's efforts towards raising the funds necessary for this meeting, and is also making great progress towards funding the Robert Dempsey Resident Award in Cerebrovascular Research, the Brain Aneurysm Foundation Christopher C. Getch Chair of Research, and the DePuy-Synthes Cerebrovascular Resident Research Award for 2015.

These fundraising efforts are made possible through generous sponsorship from our numerous industry partners – many of which represent new commitments established this year. Recent partnerships include a five-year agreement with Toshiba American Medical Systems, a two-year agreement with MicroVention, a one-year agreement with Edge Therapeutics, a one-year agreement with Depuy-Synthes, and a one-year agreement with KLS Martin. We wish to thank each of our new partners for their generosity and support. I also would like to thank the members of the Fundraising Committee for their hard work and efforts over the past year: Drs. Adnan Siddiqui, Alex Khalessi, Ray Turner, Mustafa Baskaya, J Mocco, and Brian Jankowitz. Lastly, I would like to acknowledge the section's contributions to the Washington committee ($10,000), the Neurosurgery Research and Education Foundation ($20,000), and the recently established NREF Charles Drake fund to support cerebrovascular research and education ($10,000) – contributions that demonstrate our commitment to leading the field of cerebrovascular disease at the level of advocacy, education, and research.

Guidelines Corner

Kevin Cockroft, MD, MSc

CV Section Guidelines Sub-Committee Chair

The CV section guidelines sub-committee had another busy year in 2014. The section continued its long standing relationship with the American Heart Association/American Stroke Association (AHA/ASA). We were fortunate to have writing group representatives on several AHA/ASA projects. In addition, in conjunction with the Joint Guidelines Committee of the AANS/CNS, we reviewed and subsequently recommended for endorsement several projects of interest to CV section members (Table 1). The section also began a new relationship with the Neurocritical Care Society (NCS). Arun Amar, MD (CV Section) and Mike Huang, MD (Trauma/Critical Care) will be neurosurgery representatives to the NCS Guidelines Committee. David Seder, MD will serve as a representative from the NCS to the CV section. A small group from the section's guidelines committee reviewed the NCS Evidence-Based Guidelines for the Management of Large Hemispheric Infarction and subsequently recommended AANS/CNS endorsement.

The CV section also remains well represented in guidelines efforts for neurosurgery in general. I became chair of the AANS/CNS Joint Guidelines Committee (JGC) at the October CNS meeting and Sepideh Amin-Hanjani, MD continues to serve as a co-vice chair of the JGC. Dr. Amin-Hanjani and Brian Hoh, MD both serve as co-vice chairs for the CNS Guidelines Committee. While the JGC is charged mainly with reviewing guidelines documents for possible AANS/CNS endorsement, the CNS guidelines committee's mission is to aid in the creation of new guidelines from within neurosurgery. Approved projects may receive funding and logistical support through the CNS.

In the coming months more guidelines activity is anticipated both through the AHA/ASA and NCS. The CV section will also be reviewing its appointments to the JGC. The conscientious, thorough and timely reviews of our guidelines group members are greatly appreciated. If you would like to get involved in evidenced based guideline reviews, either at the section level or through the JGC, please contact me at kcockroft@psu.edu.

CV Guidelines Committee Activities – 2014

Title	Sponsor	CV Writing Group (Reps)	Reviewers	Status
Risk of Cervical Arterial Dissection After Cervical Manipulation Including Chiropractic Manipulative Therapy	AHA/ASA	Felipe Albuquerque	Pascal Jabbour (Lead Reviewer) Nick Bambakidis, Bill Mack, John Reavey-Cantwell, Henry Woo	Endorsed by AANS/ CNS. Published August 2014.
Guidelines for the Primary Prevention of Stroke	AHA/ASA	John Wilson	Kevin Cockroft, MD (Lead Reviewer) Steve Casha, Kathryn Holloway, Bill Mack, John Reavey-Cantwell, Krystal Tomei	Endorsed by AANS/ CNS. Published October 2014.
Guidelines for the Management of Spontaneous Intracerebral Hemorrhage	AHA/ASA	Bernard Bendok	Sepi Amin-Hanjani, MD (Lead Reviewer) Jeffrey Olson, Michael Huang, Paul Arnold, J Mocco, Daniel Hoh, Cheerag Upadhyay, Kimon Bekelis	JGC review completed. Awaiting writing group response.
Guidelines for Management of Unruptured Intracranial Aneurysms	AHA/ASA	G Thompson, K Cockroft, S Connolly, S Amin-Hanjani, C Ogilvy, A Ringer	J Mocco (Lead Reviewer) Kimon Bekelis, Dan Hoh, Kathryn Holloway, Michael Huang Alex Khalessi, Elad Levy, Jeff Olson Adair Prall, Tim Ryken, Cheerag Upadhyaya	Initial review completed. Awaiting writing group response.
Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Thrombolysis	AHA/ASA	Alex Khalessi	Adnan Siddiqui (Lead Reviewer) Chirag Gandhi, Brian Jankowitz Scott Simon, S tacey Quintero-Wolfe	Initial review completed. Awaiting writing group response.
Evidence-Based Guidelines for the Management of Large Hemispheric Infarction	NCS	Arun Amar	Babu Welch (Lead Reviewer) Stavropoula Tjoumakaris, Chirag Gandhi Jared Knopman, Clemens Schirmer	Review completed. Endorsement recommended.
Management of Brain Arteriovenous Malformations	AHA/ASA	Jason Sheehan	TBA	In preparation.

AHA/ASA – American Heart Association/American Stroke Association
NCS – Neurocritical Care Society

Cerebrovascular Section Website Continues to Grow

Babu Welch, MD

Since the retooling of the Cerebrovascular Section Website in January of 2014, the website committee has continued to find new ways to disseminate and collect information pertinent to the membership in a platform that is accessible and adaptable to our mobile community Over the past year the viewership of the website continues to grow as evidenced by the > 50% new viewers that visit the site each month. The Twitter feed (@cvsection) for the site has grown slowly and has 60 followers. In the coming year we will focus on maturing the Case Forum section for members to communicate and share ideas about complicated therapies. The Education Editors will update Fellowship opportunities to improve the members access to the to best talent possible. Please contact Asterios Tsimpas (atsimpas@gmail.com) or Amir Dehdashti (Adehdashti@NSHS.edu) with your fellowship updates to assist them with this goal.

Please continue to visit website at cvsection.org for updates on news, meetings, and community referrals throughout the year. Your profile and password information can be maintained through your AANS profile.

Membership Update

William Mack, MD

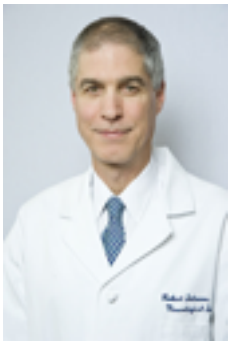
The membership of the Section continues to grow with 2262 members (389 active, 102 lifetime, 53 international, 39 adjunct, 1679 resident/fellow). Membership benefits have included discounted rates for print subscription to the journal Stroke, priority access to seminars and courses at the Annual Meeting, and receipt of the Cerebrovascular Section Newsletter. The section has proposed and enacted several new membership initiatives over the course of the year. We have created a student membership category in order to encourage early participation of medical students. This was approved by the parent organizations: the CNS on November 6, 2014, and the AANS on November 22, 2014. The goal is to foster excitement and continued involvement in the section throughout their careers. Further, we have created an international developing country membership category. This initiative will allow membership at dues rates lower than the standard international levels. This membership category should foster inclusion and collaboration with a broad group of cerebrovascular surgeons worldwide.

MEETING UPDATES

CV Section Annual Meeting (2015)

J Mocco MD, MS CV Section Program Chair
Peter Nakaji MD, CV Section Program Co-Chair
William J. Mack MD, SNIS Program Chair

The AANS/CNS Joint Cerebrovascular Section Annual Meeting will take place on February 9th and 10th, 2015, with collaborative programming from SNIS and the European Association of Neurosurgical Societies (EANS). Held in advance of the International Stroke Conference in Nashville, TN, this meeting demonstrates the Section's consistent commitment to excellence in the neurosciences and patient care, and growing collaborations in cerebrovascular treatment. At this exciting time of major changes in the vascular space, including the recent completion of many major clinical trials, the AANS/CNS Joint Cerebrovascular Section Annual Meeting will provide a unique opportunity for our community to discuss the changing nature of the vascular landscape. To that end, this year¹s meeting will be marked by sessions over the two days enabling participants to enjoy outstanding programming across a wide range of cerebrovascular topics. Headlining the educational tracks are session blocks dedicated to stroke trials, carotid stenosis, large & giant aneurysm treatment, as well as a lively debate on the treatment of AVMs. In addition to scientific sessions, specific meeting highlights include the popular annual Luessenhop Lecture, this year given by Dr. Robert Solomon.



International Stroke Conference Program Committee Update (2015)

Babu Welch, MD

International Stroke Conference Program Committee Update
The 2015 International Stroke Conference will take place February 11-13 in Nashville, Tennessee immediately following the Combined Cerebrovascular Section meeting. With suggestions from the membership, the ISC program committee (Kevin Cockroft, William Mack, and Babu Welch) was able to include multiple sessions on the management of unruptured

aneurysms, Moyamoya disease and the natural history of arteriovenous malformations. Particularly interesting to the general audience will be a session on “Vascular Malformation Controversies Commonly Encountered in the Office” and “Neuroinflammation and Cognitive Dysfunction in Aneurysmal Subarachnoid Hemorrhage”. The Section is well represented in this international community with more than 11 members contributing to the selected sessions. As always the committee appreciates the input of the membership in selecting sessions. Please feel free to forward ideas to us for the next meeting in February 2016.

Upcoming Meeting with CV section Sessions:

AANS Meeting (Washington, D.C., May 2-6th, 2015): CV section organizers: Peter Nakaji MD and Adam Arthur MD

CNS Meeting (New Orleans, LA, September 26-30th, 2015): CV section organizers: Adam Arthur MD and Brian Jankowitz MD

Technology Forum: Minimally Invasive Removal of Intracranial Hematomas

Andrew F. Ducruet, M.D.

Spontaneous intracerebral hemorrhage (ICH) is the stroke subtype associated with the highest morbidity and mortality. Craniotomy with clot evacuation remains the first-line surgical treatment for patients with surgically-accessible ICH causing significant mass effect and progressive neurological deficit. Although this surgical approach remains well accepted in this subset of patients, the efficacy of hematoma evacuation for the majority of conscious patients presenting with ICH has been called into question. The results of the STICH [1, 2] trials have highlighted the clinical equipoise which exists for the vast majority of ICH patients. In evaluating the results of these trials, it has been suggested that traditional methods of clot evacuation, particularly for deep seated clots or those in eloquent brain territories, may contribute to morbidity due to violation of otherwise normal brain. As a result, minimally-invasive surgical (MIS) approaches of clot evacuation are currently experiencing a renaissance. A recently published meta-analysis suggests that MIS techniques may improve outcomes relative to conservative management and traditional craniotomy [3]. Several such techniques have been investigated including stereotactic catheter placement followed by thrombolytic instillation and drainage over several days, as well as endoscopic-guided clot evacuation. Additionally, new technologies are emerging which both facilitate accurate catheter placement as well as hematoma evacuation.

One important technique of minimally-invasive hematoma evacuation involves the stereotactic image-guided placement of a catheter followed by intra-cavitary instillation of fibrinolytic agent.

This method is currently being rigorously tested in a Phase III clinical trial. The MISTIE Trial (Minimally invasive surgery plus rtPA for intracerebral hemorrhage evacuation) calls for stereotactic placement of a sheath into the hematoma cavity followed by immediate manual hematoma aspiration [4]. A ventricular catheter is then inserted through the sheath along the long-axis of the hematoma and tPA is instilled into the hematoma every 8 hours, for a total of 9 doses. In a preliminary study employing this technique, a 46% reduction in clot volume was observed compared to a 4% reduction over the same time frame using traditional medical management [4]. Long-term phase II trial results were presented at the International Stroke Conference in 2013 by Hanley et al. Along with a more rapid reduction in clot volume, patients in the surgical arm demonstrated improved clinical outcomes as well as shorter hospital stays and decreased hospital costs.

The use of an endoscope in ICH evacuation has also become popular among some practitioners because it allows for minimal bone removal and brain exposure and enables direct visualization during the process of hemostasis. Several series have suggested that, relative to open craniotomy, endoscopic management facilitates more complete clot evacuation, promotes earlier recovery and leads to better functional outcomes at a potentially lower cost [5, 6]. Similarly, in a small study comparing endoscopic evacuation to stereotactic catheter drainage, endoscopic management demonstrated smaller residual clot volumes, shorter ICU stays and better functional outcomes at 6 month follow-up [7].

A number of novel devices are currently being developed to facilitate the MIS evacuation of ICH. The Apollo system (Penumbra, Alameda, CA) is one such device that combines an aspiration/irrigation system with a proprietary ultrasonic technology that clears the catheter during the aspiration process. The first published report describes the use of this device in a cadaveric model [8]. In this study, an 8F sheath was placed directly into a clot using cone-beam (flat-panel detector) CT guidance. The Apollo system was then advanced through the sheath and the hematoma was evacuated, with cone-beam CT used to monitor the extent of evacuation. Using the device in this manner allows for a hematoma to be removed rapidly through a relatively small-caliber sheath. In a subsequent report from the same group, 3 patients with spontaneous ICH underwent minimally invasive evacuation using the Apollo device [9]. In this study, an endoscope was advanced through a 19F sheath which had been placed using frameless stereotactic guidance. The Apollo device was then inserted though the working channel of the endoscope and the hematoma was evacuated under direct visualization. In each case, the majority of the parenchymal hemorrhage component was rapidly evacuated, and all patients showed impressive and often immediate improvement following the procedure (mean NIHSS improvement from 19 to 5.7). Although further study is necessary, clot aspiration devices such as the Apollo catheter may enable rapid and efficient minimally invasive clot evacuation without the need for thrombolytic instillation.

Craniotomy remains the first-line technique for evacuation of an ICH in surgical candidates presenting with acute neurologic compromise secondary to mass effect. The disappointing results of this same procedure applied to the larger cohort of conscious ICH patients has led to renewed interest in MIS approaches to hematoma evacuation. The surgical management of ICH is poised for rapid and significant change, with several new technologies for clot evacuation in early stages of development. Moving forward, it will be critical to rigorously

evaluate these new techniques in the context of ongoing clinical trials and prospective registries to definitively establish which patient populations might benefit from MIS hematoma evacuation.

1. Mendelow, A.D., B.A. Gregson, H.M. Fernandes, G.D. Murray, G.M. Teasdale, D.T. Hope, A. Karimi, M.D. Shaw, D.H. Barer, and S. investigators, Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. Lancet, 2005. 365(9457): p. 387-97.
2. Mendelow, A.D., B.A. Gregson, E.N. Rowan, G.D. Murray, A. Gholkar, P.M. Mitchell, and S.I. Investigators, Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet, 2013. 382(9890): p. 397-408.
3. Zhou, X., J. Chen, Q. Li, G. Ren, G. Yao, M. Liu, Q. Dong, J. Guo, L. Li, J. Guo, and P. Xie, Minimally invasive surgery for spontaneous supratentorial intracerebral hemorrhage: a meta-analysis of randomized controlled trials. Stroke, 2012. 43(11): p. 2923-30.
4. Morgan, T., M. Zuccarello, R. Narayan, P. Keyl, K. Lane, and D. Hanley, Preliminary findings of the minimally-invasive surgery plus rtPA for intracerebral hemorrhage evacuation (MISTIE) clinical trial. Acta Neurochir Suppl, 2008. 105: p. 147-51.
5. Nagasaka, T., M. Tsugeno, H. Ikeda, T. Okamoto, S. Inao, and T. Wakabayashi, Early recovery and better evacuation rate in neuroendoscopic surgery for spontaneous intracerebral hemorrhage using a multifunctional cannula: preliminary study in comparison with craniotomy. J Stroke Cerebrovasc Dis, 2011. 20(3): p. 208-13.
6. Cho, D.Y., C.C. Chen, C.S. Chang, W.Y. Lee, and M. Tso, Endoscopic surgery for spontaneous basal ganglia hemorrhage: comparing endoscopic surgery, stereotactic aspiration, and craniotomy in noncomatose patients. Surg Neurol, 2006. 65(6): p. 547-55; discussion 555-6.
7. Nishihara, T., A. Morita, A. Teraoka, and T. Kirino, Endoscopy-guided removal of spontaneous intracerebral hemorrhage: comparison with computer tomography-guided stereotactic evacuation. Childs Nerv Syst, 2007. 23(6): p. 677-83.
8. Fiorella, D., A. Arthur, and S. Schafer, Minimally invasive cone beam CT-guided evacuation of parenchymal and ventricular hemorrhage using the Apollo system: proof of concept in a cadaver model. J Neurointerv Surg, 2014.
9. Fiorella, D., F. Gutman, H. Woo, A. Arthur, R. Aranguren, and R. Davis, Minimally invasive evacuation of parenchymal and ventricular hemorrhage using the Apollo system with simultaneous neuronavigation, neuroendoscopy and active monitoring with cone beam CT. J Neurointerv Surg, 2014.

Technical Forum: The Elusive Art of Predicting Which Aneurysm Will Bleed

Ketan R. Bulsara MD

The rapid improvement in MRI technology has allowed us to directly visualize intracranial aneurysms with unprecedented clarity, and thus provided some possible radiographic markers that may help predict the natural history of a particular aneurysm. This technical forum will provide three perspectives on this rapidly evolving field.

Molecular Imaging of Cerebrovascular Lesions using Ferumoxytol-Enhanced MRI

David M. Hasan, MD

University of Iowa Carver College of Medicine, Department of Neurosurgery

Inflammation is a key component in the pathogenesis of cerebrovascular lesions. A new agent has emerged as promising possibility for imaging cerebrovascular lesions. This agent is ferumoxytol – a specific paramagnetic magnetic resonance (MR) contrast agent. Ferumoxytol is an iron oxide nanoparticle coated by a carbohydrate shell that is used in MRI studies as an inflammatory marker as it is cleared by macrophages. Ferumoxytol-enhanced MRI allows noninvasive assessment of the inflammatory status of cerebral aneurysms and arteriovenous malformations and, possibly, may differentiate "unstable" lesions that require early intervention from "stable" lesions that can be safely observed.[1-4] Indeed, in a pilot study, 30 unruptured aneurysms in 22 patients were imaged 24 hours post ferumoxytol infusion using T2*-GE-MRI sequence. 18 of these aneurysms were also imaged at 72 hours post ferumoxytol infusion (Figure 1). Aneurysm dome tissue was collected from four patients with early MRI signal changes, five patients with late MRI signal changes, and five patients with ruptured aneurysms. The tissue was analyzed using immunostaining for expression of cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), microsomal prostaglandin E2 synthase-1 (mPGES-1) and macrophages. In 23% (7/30) of aneurysms, ferumoxytol-associated signal change in aneurysm walls was observed within the first 24 hours. Four of these aneurysms were surgically clipped. The remaining three were managed conservatively with observation; all three (100%) ruptured within six months (Figure 2). 53% (16/30) of aneurysms showed ferumoxytol-associated signal changes in aneurysm walls at 72 hours. Eight of these aneurysms were surgically clipped, and eight were managed conservatively, and all eight (100%) aneurysms remained unruptured and showed no increase in size at six months. Immunostaining showed that aneurysms with early MRI uptake and ruptured aneurysms had similar expression of COX-2, mPGES-1, and macrophages. Expression of these inflammatory molecules was significantly higher in aneurysms with early MRI uptake versus aneurysms with late MRI uptake. Our pilot study suggests that Ferumoxytol-associated signal changes in aneurysm walls within the first 24 hours strongly suggest aneurysm

instability and warrant urgent intervention.[5] In addition, we were able to use this technique to monitor the attenuation effect of aspirin on the inflammatory process in the wall of human cerebral aneurysm.[6,7] Also, our group used this technique to monitor the inflammatory process in human AVMs.[8]

References:

1. Hasan D, Mahaney KB, Magnotta VA, Kung DK, Lawton MT, Hashimoto T, Winn HR, Saloner D et al. Macrophages imaging within human cerebral aneurysms wall using ferumoxytol-enhanced MRI: a pilot study. Arterioscler Thromb Vasc Biol 2012; 32:1032-8
2. Chalouhi N, Jabbour P, Hasan D: Inflammation, macrophages, and targeted imaging in intracranial aneurysms. World Neurosurg. 2014;81:206-8
3. Chalouhi N, Jabbour P, Magnotta V, Hasan D: Molecular imaging of cerebrovascular lesions. Transl Stroke Res. 2014;5:260-8
4. Chalouhi N, Jabbour P, Magnotta V, Hasan D: The emerging role of ferumoxytol-enhanced MRI in the management of cerebrovascular lesions. Molecules. 2013;18:9670-83
5. Hasan D, Chalouhi N, Jabbour P, Dumont AS, Kung DK, Magnotta VA, Young WL, Hashimoto T, Winn HR, Heistad D: Early changes in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm: a pilot study. Stroke 2012; 43:3258-65
6. Hasan D, Chalouhi N, Jabbour P, Dumont AS, Kung DK, Magnotta VA, Young WL, Hashimoto T, Winn HR, Heistad D: Evidence that acetylacetic acid attenuates inflammation in the wall of human cerebral. J Amer Heart Assoc 2013: DOI 10-1161/JAHA.112.000019
7. Hasan DM, Chalouhi N, Jabbour P, Magnotta VA, Kung DK, Young WL: Imaging aspirin effect on macrophages in the wall of human cerebral aneurysms using ferumoxytol-enhanced MRI: preliminary results. J Neuroradiol. 2013;40:187-91
8. Hasan DM, Amans M, Tihan T, Hess C, Guo Y, Cha S, Su H, Martin AJ, Lawton MT, Neuwelt EA, Saloner DA, Young WL: Ferumoxytol-enhanced MRI to Image Inflammation within Human Brain Arteriovenous Malformations: A Pilot Investigation. Transl Stroke Res. 2012;3(Suppl 1):166-73

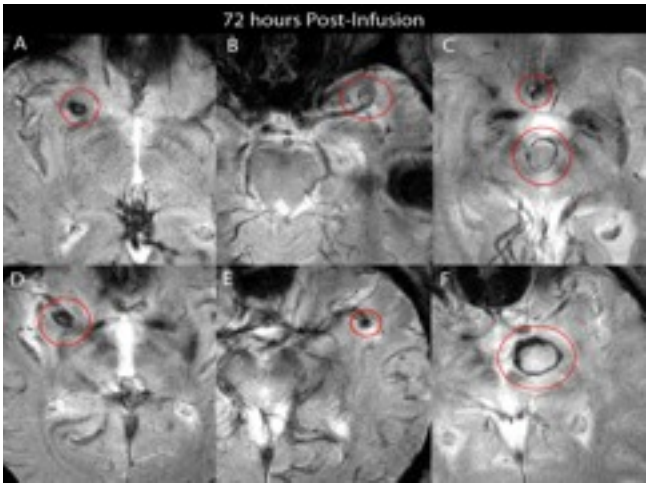


Figure 1. Images from 5 patients who received 5 mg/kg of ferumoxytol - all images are taken 72 hours post-infusion. A) Right MCA aneurysm, B) left MCA aneurysm, C) basilar tip and anterior communicating artery aneurysms, D) right MCA aneurysm, E) left MCA aneurysm, F) basilar tip aneurysm.

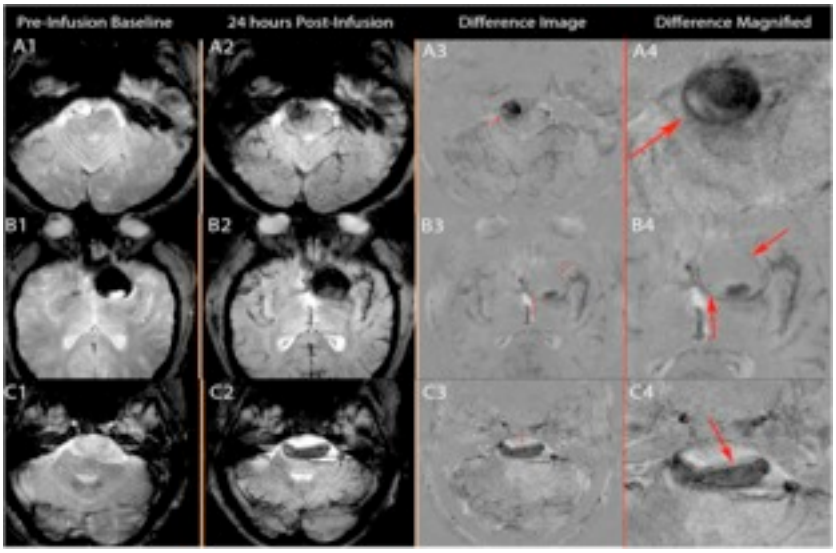


Figure 2: T2* GE MRI sequence at baseline and 24 hours post-infusion showing early signal changes in the walls of three cerebral aneurysms. Difference images (last two panels) demonstrate the relative signal loss after ferumoxytol infusion. All three aneurysms eventually ruptured within six months

High Resolution Vessel Wall Imaging (VWI) of Intracranial Aneursyms

Charles Matouk MD
Yale Department of Neurosurgery, New Haven, CT

An accumulating body of evidence from multiple, clinical lines of investigation point to vessel wall inflammation as an important factor in aneurysm growth and rupture.

1. **Studies of human aneurysm tissue.** In two landmark studies that recovered human aneurysm tissue at the time of surgery, the degree of inflammatory cell infiltration was shown to be higher in ruptured compared with unruptured aneurysms.[1,2]
2. **Epidemiological studies of unruptured aneurysms.** In a post-hoc analysis of the ISUIA dataset, patients who took aspirin (at least 3-times per week) had a significantly

lower odds of hemorrhage (OR 0.27; 95% CI, 0.11-0.67, *P*=0.03) compared with non-aspirin users.[3]

3. **Advanced MR imaging protocols.** Using ferumoxytol-enhanced MRI, Hasan et al. demonstrated pronounced early uptake of ferumoxytol (an inflammatory marker of macrophages) in the vessel wall of unstable aneurysms.[4] More recently, Vakil et al. found increased wall permeability in high risk compared to low risk aneurysms using a different imaging technique, dynamic contrast-enhanced MRI.[5]

Taken together, these data are compelling and focus our attention on the vessel wall as central to aneurysm disease pathogenesis and to determinations of rupture risk.

High-resolution MR vessel wall imaging (MR-VWI) of intracranial aneurysms

Conventional vascular imaging techniques (CTA, MRA, and catheter angiography) are essentially "lumenograms," and can offer only indirect clues to disease in the intracranial vessel wall. Direct imaging of the intracranial vessel wall is hampered by the small size of target vessels, their tortuosity, and relatively deep location. It is only recently that advanced imaging protocols using high-resolution 3T MRI have been adapted from the coronary and carotid literature to resolve the intracranial vessel wall in routine clinical practice.[6] These techniques are collectively referred to as "black-blood imaging" and rely on the suppression of blood and CSF signals, thereby revealing the interposed vessel wall. Early experience using intracranial high-resolution MR-VWI focused on steno-occlusive disease and demonstrated contrast enhancement of the vessel wall in inflammatory vasculopathies, e.,g., cerebral vasculitis and symptomatic atherosclerotic plaque.[6-8] We therefore hypothesized that vessel wall enhancement would also be associated with ruptured intracranial aneurysms. In a preliminary report of 5 patients with aneurysmal subarachnoid hemorrhage (SAH), MR-VWI showed thick, concentric vessel wall enhancement of the ruptured aneurysm. Importantly, 3 patients harbored multiple aneurysms, but only the ruptured aneurysm enhanced.[9] This was the first description of contrast-enhanced, high-resolution MR-VWI in patients with aneurysmal SAH. These findings have been confirmed and extended in larger clinical series by independent research groups using different "black-blood imaging" techniques.[10-11] For example, Edjlali et al. described circumferential wall enhancement in 16 of 17 ruptured aneurysms.[10] Nagahata et al. found wall enhancement in 60 of 61 ruptured aneurysms.[11] Taken together, these findings demonstrate the strong association between ruptured status and wall enhancement in aneurysmal SAH. To date it is not known whether wall enhancement predates (or predicts) aneurysmal rupture. However the recent finding by Edjlali et al. that circumferential wall enhancement was more frequently observed in unstable (and unruptured) aneurysms provides a foundation for longitudinal prospective cohort studies to answer this question.[10]

The application of advanced MR imaging techniques, including high-resolution MR-VWI, will continue to contribute to a better understanding of intracranial aneurysms, and thereby lead to better care for our patients.

References

1. Frosen J et al. Remodeling of saccular cerebral aneurysm wall is associated with rupture: histological analysis of 24 unruptured and 42 ruptured cases. *Stroke* 35:2287-93;2004.
2. Kataoka K et al. Structural fragility and inflammatory response of ruptured cerebral aneurysms. A comparative study between ruptured and unruptured cerebral aneurysms. *Stroke* 30:1936-1401;1999.
3. Hasan D et al. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. *Stroke* 42:3156-62;2011).
4. Hasan D et al. Early change in ferumoxytol-enhanced MRI signal suggests unstable human cerebral aneurysm: a pilot study. *Stroke* 43(2):3258-65;2012.
5. Vakil P et al. Quantifying intracranial aneurysm wall permeability for risk assessment using dynamic contrast enhanced MRI: a pilot study. ***Stroke 45:***A124;2014. [Oral abstract presented at International Stroke Conference.]
6. Swartz RH et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. *Neurology* 72:627-34;2009.
7. Mandell DM et al. Vessel wall MRI to differentiate between reversible cerebral vasoconstriction syndrome and CNS vasculitis: preliminary results. *Stroke* 43:860-2;2012.
8. Vergouwen MD et al. Eccentric narrowing and enhancement of symptomatic middle cerebral artery stenoses in patients with recent ischemic stroke. *Arch Neurol* 68:338-42;2011.
9. Matouk CC et al. Vessel wall MRI identifies the site of rupture in patients with multiple intracranial aneurysms: proof of principle. *Neurosurgery* 72:492-6;2013.
10. Edjlali M et al. Does aneurysmal wall enhancement on vessel wall MRI help to distinguish stable from unstable intracranial aneurysms? *Stroke* 45:3704-6;2014.
11. Nagahata S et al. Wall enhancement of the intracranial aneurysms revealed by magnetic resonance vessel wall imaging using three-dimensional turbo spin-echo sequence with motion-sensitized driven-equilibrium: a sign of ruptured aneurysm? *Clin Neuroradiol* 2014 Oct 21 [Epub ahead of print]

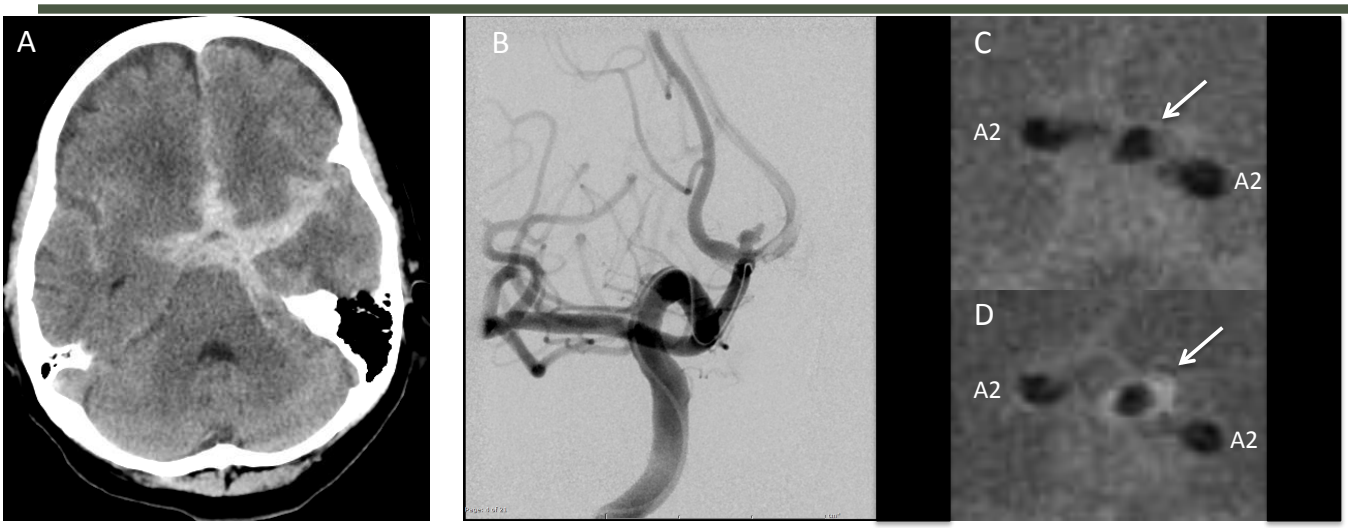


Figure: axial noncontrast CT brain demonstrating diffuse SAH with a left-sided preponderance and significant blood in the interhemispheric fissure. **B**, a digital subtraction angiogram (AP view) demonstrates a dysmorphic anterior communicating artery aneurysm with apical bleb. T1-weighted black blood vessel wall sequences (axial) before **(C)** and after **(D)** the administration of gadolinium demonstrate thick vessel wall enhancement (arrow). Note the absence of enhancement in the A2 segments.

Dynamic Contrast Enhanced MRI

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Ruptured intracranial aneurysms (IA) result in grave subarachnoid hemorrhage-related clinical outcomes. Epidemiological data indicates 4-6% of the population harbors an IA, but < 1% will actually rupture. Incidental discovery of IAs on standard CT/MR imaging poses a clinical dilemma: whether or not to treat an asymptomatic aneurysm. If left untreated, aneurysm rupture is associated with a >50% risk of neurological morbidity and mortality. Conversely, microsurgical clipping and endovascular treatment approaches have inherent procedure related risks. Several large prospective studies including the ISUIA and UCAS have established the current standard of reference for guiding treatment selection, but provide only broad parameters of hemorrhagic stroke risk based on various patient (age, race, cerebrovascular risk factors, environmental exposure) and aneurysm anatomic risk factors (size, morphology, aspect ratio, location).[1,2] The management of IA could be significantly improved if more specific aneurysm risk stratification approaches are developed. Several investigators have explored the role of aneurysm hemodynamics associated with aneurysm rupture, using either computational fluid dynamics or in vivo 4D flow MRI techniques.[3,4] Others

have postulated that aneurysm wall pathology may provide insight via inherited or acquired gene expression and/or advanced vessel wall imaging techniques to identify markers of inflammation.

Vascular Biology/Epigenetics: The pathogenesis of IA growth and rupture is complicated, however chronic inflammation has been postulated to play an important role. Animal and human studies have found heightened macrophage infiltration and expression of inflammatory-related molecules (MMP-2, CXCR-4, NF-kB, TNF-a, MCP-1) in the aneurysm wall, all of which may contribute to the histological changes observed in resected IA samples (collagen loss, disruption of the elastic lamina, thinning walls).[5,6] The understanding of vascular biology and genetic mediators serves as fertile ground for understanding the formation and growth of IAs and may guide the future development of biologically active endovascular devices, coils and stents.

Advanced Imaging: Although non-invasive imaging can detect aneurysms, prospective studies using hemodynamic flow imaging, advance fluid dynamic modeling, or even anatomic morphology have been unable to shown a direct causal (i.e. predictive) link to aneurysm rupture or remodeling (which carries a 12-fold risk of rupture). However, using Dynamic Contrast Enhanced (DCE) MRI, a widely available imaging technique developed to quantify blood-brain barrier permeability, we have obtained interesting results in our evaluation of IA. The overall hypothesis is that local inflammatory changes in the IA wall results in significant disruption/thinning of the vessel wall, and greater permeability to the contrast agent. These effects can be quantified as an increase in k^{trans} using the multi-compartmental leakage model proposed by Tofts et al.[7] In a pilot study of unruptured IAs, we noted significant increase in k^{trans} was an independent predictor of IA risk as determined by commonly used morphological metrics (Figure 1).[8]

Conclusion: The algorithm for treating unruptured, asymptomatic IAs represents a persisting clinical challenge. Goals for absolute risk stratification will ultimately depend on a multivariable assessment of the patient, aneurysm anatomic factors, and potentially new laboratory/imaging techniques to evaluate aneurysm hemodynamics and aneurysm wall pathobiology.

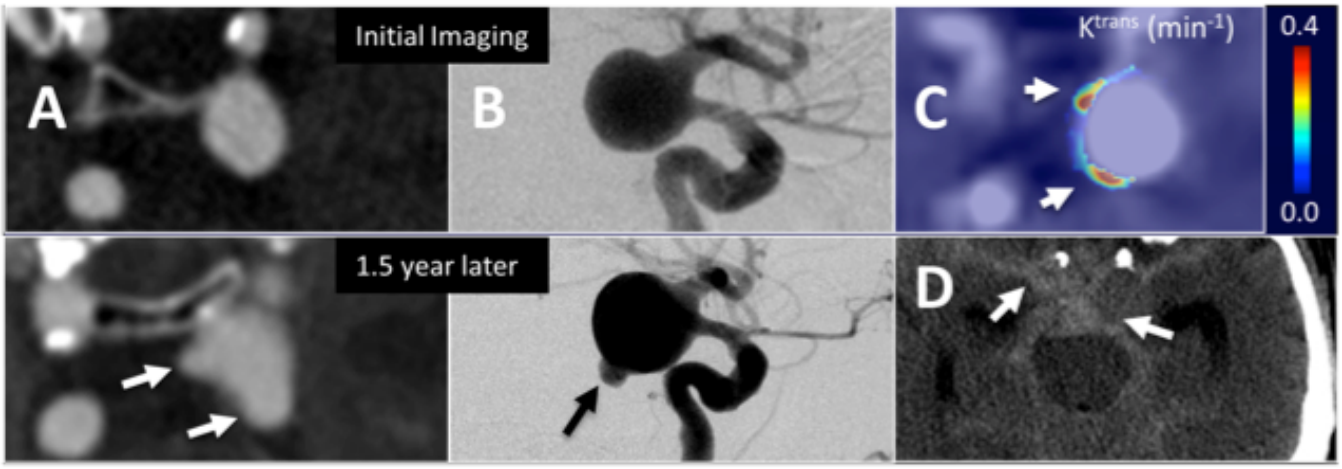

Figure 1 The evolution of an untreated PComm IA in a 61 year old male demonstrates that elevated k^{trans} at baseline correlated with aneurysm bleb formation. Morphological changes over 1.5 years are observed in CTA (A) and DSA (B) findings; however, initial DCE-MRI demonstrated two nearly identical regions with high k^{trans} (C - arrows) suggesting focal aneurysm wall pathology–resulting in eventual aneurysm progression and SAH seen on non-contrast CT (D – arrows)

References:

1. Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet. 2003 Jul 12;362(9378):103-10.

2. UCAS Japan Investigators, Morita A, Kirino T, Hashi K, Aoki N, Fukuhara S, Hashimoto N, Nakayama T, Sakai M, Teramoto A, Tominari S, Yoshimoto T. The natural course of unruptured cerebral aneurysms in a Japanese cohort.N Engl J Med. 2012 Jun 28;366(26):2474-82.

3. Cebral JR, Mut F, Weir J, Putman C. Quantitative characterization of the hemodynamic environment in ruptured and unruptured brainaneurysms. AJNR Am J Neuroradiol. 2011 Jan;32(1):145-51.

4. Schnell S, Ansari SA, Vakil P, Wasielewski M, Carr ML, Hurley MC, Bendok BR, Batjer H, Carroll TJ, Carr J, Markl M. Three-dimensional hemodynamics in intracranial aneurysms: influence of size and morphology. J Magn Reson Imaging. 2014 Jan;39(1):120-31

5. Hasan D, Chalouhi N, Jabbour P, Dumont AS, Kung DK, Magnotta VA, Young WL, Hashimoto T, Winn HR, Heistad D.Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm: a pilot study. Stroke. 2012 Dec;43(12):3258-65.

6. Shi C, Awad IA, Jafari N, Lin S, Du P, Hage ZA, Shenkar R, Getch CC, Bredel M, Batjer HH, and Bendok BR. Genomics of Human Intracranial Aneurysm Wall. Stroke 2009, 40 1252-1261.

7. Tofts PS, Brix G, Buckley DL, Evelhoch JL, Henderson E, Knopp MV, et al. Estimating kinetic parameters from dynamic contrast-enhanced t(1)-weighted mri of a diffusable tracer: Standardized quantities and symbols. *J Magn Reson Imaging*. 1999;10:223-232

8. Vakil P, Ansari SA, Eddleman, CS, Batjer, HH, Bendok, BR, Carroll TJ. Quantifying Intracranial Aneurysm Wall Permeability for Risk Assessment using Dynamic Contrast Enhanced MRI: A Pilot Study. AJNR in press.

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Nashville, Tennessee

February 20-22, 2015
North American Skull Base Society Meeting, Tampa, Florida

May 2-6, 2015
AANS Annual Meeting
Washington, D.C.

June 18-21, 2015
Cerebrovascular Complications Conference, Jackson Hole, Wy

September 26-30th, 2015
CNS Annual Meeting
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