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Imaging of cerebrovascular disorders: precision medicine and the collaterome

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Abstract

Imaging of stroke and neurovascular disorders has profoundly enhanced clinical practice and related research during the last 40 years since the introduction of computed tomography (CT) and magnetic resonance imaging (MRI) enabled mapping of the brain. We highlight recent advances in neurovascular imaging. We describe how the convergence of readily available data and new clinical trial paradigms will recast our methods for studying the neurovascular patient. The application of a precision medicine approach to the collaterome, a comprehensive synthesis of neurovascular pathophysiology, will entail novel methods for clinical trial randomization, collection of routine and clinical trial imaging results, data archiving, and analysis.

Keywords

stroke; imaging; collaterals; data science

Introduction

Imaging of cerebrovascular disorders has experienced extraordinary growth, advancing from the research stage to incredibly frequent use in the daily evaluation of patients. Research continues to focus on the development of novel imaging modalities and techniques, contrast agents, postprocessing, interpretation, and correlation with clinical aspects across a broad range of cerebrovascular disorders. In routine clinical practice, imaging of the brain parenchyma, vessels, and associated perfusion or blood flow patterns is reflected in the increasing availability of multimodal computed tomography (CT) and magnetic resonance imaging (MRI) around the world. This review highlights selected advances in the imaging of specific cerebrovascular disorders and underscores the evolution in the way imaging is being used and will be used to avert stroke and improve patient outcomes.

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Conflicts of interest

D. L. is a scientific consultant regarding trial design and conduct to Stryker (modest) and Covidien (modest). He was employed by the University of California, which holds a patent on retriever devices for stroke, at the time of this work.

This is a transformational period in stroke imaging, following a decade of technological innovations that rapidly introduced a variety of neurovascular imaging techniques. The dissemination of multimodal CT or MRI, including noninvasive angiography and perfusion imaging, enable a comprehensive evaluation of vascular disorders in the brain. These techniques were embedded in clinical trials such as MR RESCUE, where multimodal MRI was intertwined with endovascular versus medical treatment arms of the study.[1] However, as this study and others incorporated advanced imaging, the conclusions about the imaging findings were dwarfed by the main therapeutic outcome analyses, which were negative, like many other recent stroke trials. Despite a plethora of original scientific research reports that covered numerous aspects of imaging in the literature and heavy use of such techniques in routine practice, enthusiasm for stroke imaging has waned in recent years owing to concerns regarding logistics and costs.

We illustrate how imaging has evolved far beyond simply initial diagnosis to many other roles in the management of patients. The vast amount of data culled from these imaging studies provides a platform to individualize care, as is increasingly common in other areas of medicine. This precision medicine has leveraged individual patient-level data to direct treatment algorithms in other scenarios, including neurological disorders. Such individual variability in stroke is best exemplified by heterogeneity in collateral circulation and the role of the collaterome, the elaborate neurovascular architecture within the brain that regulates and determines the compensatory ability, response, and outcome of cerebrovascular pathophysiology.[2] As a result, imaging of cerebrovascular disorders is now poised to launch precision medicine approaches to stroke based on the collaterome and correlates from data commonly acquired in trials and daily practice. After reviewing recent advances, we consider how imaging, precision medicine, and the collaterome converge towards this goal and propose future innovative approaches formulated on imaging lessons from past stroke trials.

Latest imaging advances in 2014

During 2014, imaging of intracranial hemorrhage (ICH), ischemic stroke, large artery atherosclerosis, dissection, small vessel disease, and cerebral hemodynamics were featured throughout the literature. Novel techniques utilizing ultrasound for measurement of cerebral perfusion were also advanced.[3]

The utility of various imaging approaches for the longitudinal evaluation of patients with intracranial hemorrhage was addressed. The spot sign, reflecting potential contrast extravasation on CTA, and other markers received attention as potential predictors of early intracerebral hematoma growth and reflection of underlying pathophysiology.[4–9] Multicenter experience with spot sign detection has also been studied, revealing moderate inter-rater reliability.[10] Hematoma expansion and associated neurological deterioration provide a surrogate imaging marker for therapeutic interventions, although the causes of expansion remain elusive. While cytotoxic edema or perihematomal ischemia has been proposed as contributing factors, recent analysis demonstrated that neither perihematomal hypoperfusion nor systemic blood pressure changes were related to hematoma growth.[11]

Microscopic bleeds received significant study in the past year. A large series of 392 acute ischemic stroke revascularization cases with pretreatment susceptibility-weighted imaging (SWI) revealed that cerebral microbleeds (CMB) did not increase the risk for ICH or worsen outcome, even when CMB burden, predominant location, or presumed pathogenesis were considered.[12] New CMB after intravenous thrombolysis were reported using 3T MRI.[13] New CMB developed rapidly within 24 hours. The significance of these new CMB and their effect on cognitive and functional outcome warrants further investigation. The risk of subsequent intracranial hemorrhage or cerebral ischemia also seems to critically depend on location and overall burden.[14] The association of CMB with cognitive deficits and dementia has continued to focus on the topography of such lesions and the overall burden of these lesions in the brain.[5,15]

In one study, susceptibility-weighted imaging (SWI) detected intracranial hemorrhage and related blood degradation products reliably for up to several years after the initial event.[16] Although SWI has been available for several years, enabling exquisite detection of the venous architecture, blood products, and mineralization in and around the brain, recent work has emphasized the development of quantitative susceptibility mapping and susceptibility tensor imaging that will permit more detailed characterization in the future.[17]

Imaging advances have helped to streamline patient evaluation. In isolated perimesencephalic hemorrhage, it was suggested that an initial negative CT angiogram (CTA) may be sufficient for evaluation, owing to the quite specific nature of this disorder.[18] Similarly, in uncomplicated head injuries without focal neurological symptoms or traumatic subarachnoid hemorrhage, the utility of repeat outpatient non-contrast CT has been questioned.[19] Noninvasive angiography, including CTA, has become the mainstay for initial diagnosis of various types of cerebral aneurysms, as CTA performs well in this role while averting the risk of conventional cerebral angiography.[20] Wall shear stress and other computational fluid dynamics parameters available from a CTA may be useful to hone risk of aneurysm detection, particularly with smaller lesions that may be more difficult to characterize.[21] In a large series of 363 patients with intracranial aneurysms followed for a median of 2.1 years, it was demonstrated that 12% grew in size, with pivotal factors for growth including initial aneurysm size, dome/neck ratio, and multilobarity.[22]

Collateral blood flow patterns continue to be a key priority for noninvasive imaging approaches including multimodal CT and MRI. Some novel techniques have been introduced in the last year, and many other reports relate the potential impact on clinical decision making.[23,24] Imaging of collateral flow before treatment of ischemic stroke has become increasingly important. Numerous reports and analyses of large datasets reveal the critical impact of collaterals on revascularization, including with endovascular therapy.[25,26]

In acute ischemic stroke, the practical or logistic aspects of rapid imaging evaluation became a key priority, with several groups having published their experience of improving imaging triage with CT or MRI.[27] Ongoing work has helped develop novel approaches for imaging during endovascular or neurointerventional procedures. These approaches utilize flat-panel CT and low-contrast imaging techniques.[28]

Imaging of the brain with MRI may stratify risk in prevention of various disorders, including cardioembolic risk from atrial fibrillation. Individualized decision making using MRI characterization of prior ischemia can help difficult therapeutic decisions in atrial fibrillation.[29]

Intrinsic small vessel disease, evident as white matter hyperintensities (WMH) on MRI, have received greater attention recently, with studies correlating the risk of subsequent stroke and associated neurological sequelae.[30] After many years of variability in the detection and reporting of WMH, Ryu *et al.* described the development and Internet availability of a new system for rapid grading and interpretation of WMH.[31] The location or topography of lesions, in specific arterial segments or in ischemic territories, continues to be investigated as a promising way of determining etiology and of defining symptomatic arterial lesions.[32,33] For intracranial atherosclerotic disease, high-resolution MRI for plaque imaging and gadolinium enhancement features has gained momentum, although larger-scale studies are needed.[34, 35]

Other studies focus on the clinical impact of imaging in medical decision making for acute stroke and subsequent prevention of recurrent events. Innovative approaches continue to develop the intracranial applications of optical coherence tomography, near infrared spectroscopy, and other methods to measure cerebral perfusion, with an increased reliance on noninvasive techniques rather than more invasive approaches.[36] Multimodal CT and MRI have been used in both ischemic and hemorrhagic disorders, for initial diagnosis and for serial evaluation of these outpatients.[37–39] Imaging approaches have been adapted to the prehospital phase of stroke patient evaluation, with mobile CT gaining much attention within the last year. The STEMO investigators pioneered the use of this telemedicine approach, resulting in increased rates of intravenous thrombolysis and improved triage to centers with neurological expertise.[40] Importantly, these investigators have demonstrated a trend toward improved postdischarge status for both ischemic and hemorrhagic stroke patients. Ongoing work will have to address the cost effectiveness of this prehospital imaging approach and long-term neurological outcomes.

Other telestroke paradigms have incorporated a variety of imaging and related telecommunications technology. The recent news of positive randomized studies of endovascular therapy for acute ischemic stroke underscores the need for improved triage systems in a regional network.[41–43] Wide-scale deployment of advanced imaging techniques with either multimodal CT or MRI at local hospitals and remote neuroimaging expertise for triage to comprehensive stroke centers may be the next challenge.[44] Integration of imaging as an extension of the clinical exam and use for serial evaluation with real-time or immediate interpretation of findings will be a key focus of stroke imaging paradigms. Understanding the evolution of serial imaging findings, even in transfer from local to comprehensive stroke centers, will be critical.

There has been increased attention on the impact of collateral circulation as a determinant of lesion evolution and infarct growth.[26] Dynamic features of the collateral circulation and the associated risk of such imaging changes has become a new way of distinguishing patient populations. For instance, rapid neurological deterioration and infarct growth with poor

collaterals in some patients have been contrasted with the very slow course of lesion progression and increased therapeutic time windows in patients with robust collaterals. Owing to variability in availability of multimodal CT and MRI, cross-modality interpretation of various neurovascular imaging features will also be important. If the volume of endovascular stroke therapy increases due to recent positive trials, correlation of noninvasive imaging with conventional angiography and the use of serial or peri-procedural imaging will undoubtedly increase.

Outpatient use of serial multimodal MRI, including uses of magnetic resonance angiography (MRA) and perfusion-weighted imaging (PWI), has become increasingly common for tracking the dynamic changes of cervicocephalic arterial dissection, atherosclerotic disease, and potentially hemorrhagic lesions, from aneurysms to arteriovenous malformations. Even serial characterization of WMH with MRI may be used to determine slow versus fast progression of ischemic lesions and tailored approaches to stroke prevention.[31,45,46]

Precision medicine paradigm in stroke imaging

Although precision medicine conjures the idea of genomic determinants, owing to its conception in large-scale initiatives such as the Human Genome Project,[47] imaging features can be similarly utilized. Imaging features of individual patients are increasingly utilized to influence medical management and therapeutic decision making. As noted above, the recent literature emphasizes the delineation of patterns in hematoma growth, infarct evolution, arterial lesion changes, and hemodynamic fluctuations that distinguish certain patients from others with the same cerebrovascular diagnosis. These imaging features or variables provide a method to classify or describe individual patients, as in other applications of precision medicine. The extensive complexity of cerebral ischemia and marked heterogeneity in the course of cerebrovascular disorders is a perfect substrate for application of precision medicine. The International Stroke Genetics Consortium has endorsed such an approach stemming from the initial collection of biological samples and the more recent layering of associated imaging studies acquired in these subjects.[48] This concept of precision stroke imaging holds potential to unravel the physiology of the most common yet challenging neurovascular disorders from ICH to acute ischemic stroke, carotid stenosis, and intracranial atherosclerotic disease.

The collaterome as example of heterogeneity and the need for precision imaging

Precision medicine in stroke may employ an extensive range of imaging parameters and potentially vast data sets. Integration of the underlying pathophysiology or conceptual framework based on features such as the collaterome are necessary to best leverage these data sets. The collaterome is a variant of systems biology approaches to the brain that builds upon not only the integrated features of the neural architecture and vascular relationships, but the compensatory ability of collateral circulation to adapt to changes over time.[2] Unlike the connectome approach that solely considers the structural links of neural and glial elements or the angiome concept that similarly integrates just the vascular structures, the collaterome considers all neurovascular structural and functional relationships that

determine homeostasis and vascular pathology in the brain. As a result, the collaterome integrates the entire cerebral circulation, from arterial to microvascular and venous structures. The impact of such vascular compartments on tissue changes is determined by intracranial pressure dynamics and neurovascular regulation. There are correlates of such dynamic relationships across the entire spectrum of cerebrovascular disorders and in all temporal phases from acute to chronic. These considerations and their potential complexity highlight the need for systems imaging approaches such as the collaterome that integrate vessel pathophysiology with resultant perfusion and tissue changes. Multimodal imaging and serial acquisition across large data sets are therefore important, resulting in a huge number of variables.

Convergence of stroke imaging, precision medicine, and the collaterome

The next year and beyond herald the convergence of stroke imaging, precision medicine, and the collaterome as the natural intersection of data science in neurovascular disciplines. Stroke imaging provides the basis or data source for such innovation, whereas precision medicine may be adapted from other disciplines to better understand individual patient pathophysiology based on the systems biology of the collaterome. Momentum has accelerated with the widespread accumulation of stroke imaging data, the adoption of precision medicine approaches, and the recently established recognition that collateral status is a potent determinant across various cerebrovascular disorders. Simultaneous healthcare changes and the focus on long-term clinical outcomes validate the need to understand and utilize the huge amount of data pertinent to the course of a given patient.

In acute ischemic stroke, we now recognize that the most important concept regarding treatment decisions is how a specific therapeutic intervention influences specific baseline pathophysiology.[42,43] This was not always the case. As a specific treatment effect will undoubtedly be modified by baseline variables such as age, stroke severity, and other individual factors, the principal focus has been on introducing new treatments via the conduct of randomized controlled trials. It has been assumed that large-scale randomization will equilibrate or address such potent underlying distinctions between individual subjects. Consequently, there has been an overwhelming focus on the treatment effect rather than the influence of baseline pathophysiology.

It should be emphasized that much can be gleaned from the enormous investments funneled into clinical trials, beyond the impact of studying an investigational treatment. The recent publication of the MR CLEAN trial,[41] proclaiming the superiority of endovascular therapy over standard approaches, provides a suggestive example. The relative benefit of endovascular therapy was expressed by the odds ratio of improved clinical outcomes in the primary results. However, this mathematical calculation did not consider the influence of additional factors such as baseline pathophysiology. For instance, a much higher odds ratio or relative benefit of endovascular therapy may have been estimated if collateral status was considered, leveraging the imaging and angiography data collected in the trial. As in many other large endovascular trials, collaterals may improve outcome prediction or enhanced future selection paradigms if such results are translated into clinical practice or, alternatively, decisively proven by prospective trials that utilize collateral status for selection criteria.[43]

Clinical trial examples

An analysis of past clinical trials provides a window into how imaging may similarly alter future trial conduct. Many past trials did not collect or centrally adjudicate the vast imaging variables now recognized in the Common Data Elements (CDE) dataset. Determinants of hematoma expansion in ICH trials and infarct growth in ischemic stroke trials could conceivably have been ascertained by central adjudication of baseline hematoma volumes and early ischemic changes on quantitative measure such as ASPECTS grading.

In the most recent endovascular trials, incredibly limited recruitment numbers relative to projected sample size estimates fueled positive results, likely due to the incorporation of various imaging selection algorithms.[42,43] In the WASID trial of intracranial atherosclerotic disease, post hoc analyses of collaterals on conventional angiography proved potent in predicting ultimate patient outcomes, far beyond previously established outcome predictors, including degree of arterial stenosis.[49] The SONIA ancillary imaging study to WASID reflected WASID's patient selection using degree of arterial stenosis, yet subsequent imaging analyses demonstrated that fractional flow measures were pivotal in predicting outcomes, unlike degree of arterial stenosis.[50] In subsequent trials of intracranial atherosclerosis such as SAMMPRIS, the centrally collected imaging datasets provided the basis to validate the influential determinant of collaterals pioneered in WASID.[51] Large clinical trials therefore have the potential to leverage imaging data, much as original research findings perpetually underscore the value of stroke imaging in the broader literature. The plethora of previous negative trial data in stroke provided fertile ground to examine subgroups from an imaging perspective. Translation into clinical practice ultimately, however, requires prospective validation or dedicated studies such as recent positive endovascular trials in acute ischemic stroke where robust collateral grade was used for selection.[43] When more extensive imaging data are available with multimodal CT or MRI, we may advance our insight into the pathophysiology of these disorders. For instance, it has been recently recognized that venous outflow patterns in ischemic stroke may determine massive infarct expansion and intracranial pressure elevation.[52]

Imaging role in trials, registries, and routine clinical practice

The role of imaging for cerebrovascular disorders in clinical trials, registries, and routine clinical practice may be adapted to realize precision medicine approaches in large-scale networks. Other disciplines, such as cardiology, have embedded imaging approaches such as fractional flow reserve (FFR) to increase the efficiency of their clinical trials.[53] These new imaging approaches have been incorporated into clinical registry and routine clinical practice frameworks. FFR was originally based on relative intraluminal pressure gradients measured at angiography, proving superior to degree of arterial stenosis in selection of patients for percutaneous coronary intervention. Improved patient outcomes were realized with FFR, reduced costs were subsequently achieved with this imaging measure, and noninvasive CTA correlates were recently developed and validated to enhance patient triage in various settings.[54] These trials and studies of FFR provide a great example of how to better study and utilize imaging in the traditional clinical trial framework. The management of cerebrovascular disorders would clearly benefit from such parallel imaging approaches,

mirroring the success of FFR as a novel imaging parameter rather than invention of a new imaging modality.

Recent establishment of the National Institutes of Health (NIH) StrokeNet and the impressive endorsement of imaging and big data in the BRAIN initiative provide fertile ground for future implementation of data science to advance precision medicine and the collaterome.[55,56] The tools for widespread imaging acquisition, transfer, postprocessing, and data extraction now exist and are available. As we advance the development of novel therapies for cerebrovascular disorders, we may similarly propel the foundation for understanding critical neurovascular pathophysiology and improved patient outcomes that are independent of specific investigational treatments. Specific changes in the conduct of trials and registries, however, are needed at this juncture to realize such potential.

What we need from trials and registries

Future clinical trials and registries in cerebrovascular disorders must incorporate imaging in distinctly novel ways. Now that it is recognized that clinical variables alone may not address imbalances in factors revealed by imaging, it becomes important to use such imaging data to randomize patients. This approach has already been initiated in some acute ischemic stroke trials, where imaging at baseline is used to define patterns that may differentiate patients and their expected outcomes, removing the sole focus on the therapeutic intervention.[42,43]

Traditional selection criteria for randomized controlled trials have utilized clinical variables, supplemented by some imaging parameters such as site of arterial occlusion, yet other imaging correlates of potential heterogeneity, owing to collateral status or clot features, have only recently been implemented. Following the lead of cardiology trials that have advanced the use of physiological imaging measures such as FFR over the anatomical degree of arterial stenosis, studies of intracranial atherosclerosis could randomize across baseline features of FFR (represented on CTA or as signal intensity ratio across the culprit lesion on MRA) or collateral grade.[50] Simply stated, homogenous groups defined by anatomy such as site of arterial occlusion or categories such as middle cerebral artery distribution stroke do not equal homogenous groups by potentially influential functional measures similarly available from imaging studies. Equally important, study of cerebrovascular FFR in WASID/SONIA revealed that an entire group of patients excluded from SAMMPRIS, those with 40–69% stenosis, includes a substantial population of patients at high stroke risk when baseline physiology rather than anatomy is used for patient selection.[50] Thus, novel imaging approaches may extend useful treatments to wider populations of patients.

Aside from utilizing imaging defined by a trial or investigation as “study related” and therefore paid for by research funds, such trials should also collect and routinely extract common data elements (CDE) from routine imaging studies acquired in these subjects. Subjects’ consent to collection of important data in a clinical trial should not include all clinical variables and illogically ignore routine imaging that may be more informative about their clinical courses. Imaging studies should also be conducted in parallel and not necessarily contingent on therapeutic trial conduct. One may argue that various therapies may be combined and studied in a clinical trial where the main axis is defined by imaging of

the underlying pathophysiology. Realigning clinical trials with imaging around baseline pathophysiology may better yield information on underlying disease course and therapeutic effects rather than the traditional axis of trialing one therapy across heterogeneous patterns of influential pathophysiology.[57]

What we need from technology and infrastructure

Such changes in clinical trial and registry format mandate additional modification and use of technology and infrastructure. The disseminated use of advanced multimodal imaging at local sites with central telestroke triage provides one example of how technology in imaging acquisition, data transfer, automated postprocessing, and clinical decision-making tools can be used in the future. Infrastructure needs to be organized to handle central data archiving, including collection of source images to permit extraction of the imaging CDE and a multitude of analyses by groups of other investigators at future time points. The nature of imaging variables to be collected should also transform to include not just presence or absence of a finding, but quantitative measures. These variables must be flexible to change with the introduction of iterative technology or analysis capabilities to define new features such as the topographic heterogeneity in lesion patterns or temporal evolution of certain imaging changes. Variability in the availability of imaging modalities must be embraced and utilized to understand what cross-modality comparisons tell us about underlying pathophysiology.

Restricting systematic imaging acquisition helps the development of individual, isolated imaging techniques, but this traditional approach does not address the most important clinical questions about cerebrovascular disorders. Broad cohorts of patients with certain disorders should be included in future studies. For instance, noninvasive imaging makes it possible to study asymptomatic categories of disease as in CREST-2, where a variety of medical and surgical treatments are being trialed. Milder categories of disease should also be addressed, such as the patients with intracranial atherosclerotic lesions measuring only 40–69% of arterial stenosis. Clinical correlates or end points may also be guided by imaging insight, such as use of cognitive changes in subjects, rather than focusing solely on stroke recurrence. At present, each clinical trial essentially starts from scratch, recreating and recollecting all the data to define a select therapeutic question. Funding is also insufficient to sponsor all the potential ancillary imaging studies for each therapeutic trial. In future paradigms, the incorporation of imaging and the development of large imaging data sets in cerebrovascular disorders will allow for the layering of data and the building of rich resources for future research and even educational purposes. These databases may be used as teaching tools and future testing grounds for new analytic techniques.

Conclusions

The past year marks a transformational period in the use of imaging for cerebrovascular disorders, expanding upon the increasing availability of multimodal techniques to address some of the most important clinical questions. Imaging has permeated the conduct of clinical trials, registries, and routine clinical practice, enabling the use of big data to understand the course of individual patient outcomes. A broad range of imaging variables

may now be leveraged to implement precision medicine in cerebrovascular disorders, differentiating patients and reducing the heterogeneity defined by the collaterome and associated functional measures. The next few years offer a tremendous opportunity to maximize the use of imaging acquired in various scenarios to catapult research, clinical management, and education on many cerebrovascular disorders.

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