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EDITORIAL

How can imaging in acute ischemic stroke help us to understand tissue fate in the era of endovascular treatment and cerebroprotection?

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Introduction

The most frequent cause of ischemic stroke is occlusion of an intracranial or cervical artery, disturbing brain tissue perfusion. Decrease in cerebral perfusion below key thresholds progressively causes benign oligemia (reduced flow without tissue dysfunction or injury), synaptic dysfunction (impaired neuronal function without tissue injury), incomplete infarction (neuronal cell loss without paninfarction of tissue), and complete infarction (irreversible damage—"tissue death"), unless blood flow is rapidly restored. Endovascular treatment (EVT) is highly effective at recanalizing the occluded blood vessel. It became the standard of care in 2015 for patients with stroke due to large vessel occlusion (LVO), and, since then, outcomes for this subset of stroke patients have radically improved [1–5]. Nevertheless, many patients do not do well, even if EVT is performed fast, and the occluded blood vessel is quickly recanalized.

Part of the reason for the variation in patient outcomes despite rapid recanalization is that the transition from normal tissue to infarction is not a simple, linear process, but rather highly complex and heterogeneous [6]. An important factor is that the brain has several types of tissue components including neurons, glia, endothelium, and the neurovascular unit. These components are vulnerable to ischemic injury both in shared and unique ways. Therapeutic agents may target all components or only subsets. A recently proposed classification recognizes (1) neuronoprotection, the preservation of neurons; glioprotection, the preservation of glia, mainly astrocytes but also oligodendroglia; and vasculoprotection (or endothelioprotection), the preservation of endothelial cells, pericytes, and the blood–brain barrier (BBB) [7].

An additional fundamental factor is that the pathophysiology of tissue injury varies in distinct temporal periods, which we have for simplicity divided into pre- and post-reperfusion phases. Prior to reperfusion (i.e.,

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while ischemia is ongoing), both necrotic, apoptotic, and additional cell death pathways are activated. Necrotic cell death occurs during the first hours after onset and is mediated by energetic loss of ability to maintain membrane ionic currents. Apoptotic cell death is delayed and is mediated by activation of cell suicide pathways, resulting in DNA fragmentation and degradation of cytoskeletal and nuclear proteins. Post-reperfusion, a variety of reperfusion injury processes can occur, including production of reactive oxygen species and local inflammation. Apoptosis continues and pre-clinical intra-vital microscopy and human clinical studies indicate that there is often persistent microcirculatory obstruction despite large vessel recanalization[8].

Physiologic reasoning suggests that cerebroprotection will work best, and perhaps only, if ischemia is temporary; restoration of blood flow eventually needs to occur to prevent infarction. Cerebroprotective treatment trials in the pre-reperfusion era repeatedly failed, and undoubtedly the absence of reperfusion to alleviate ischemic tissue stress was a major cause [9]. Now that EVT has become the standard of care, ideal conditions have been created for cerebroprotective agents to be reassessed in human ischemic stroke. Consequently, cerebroprotection has become a focus of renewed interest and hope, and multiple cerebroprotection trials of various compounds and strategies are currently being conducted.

However, because of the variability of the currently tested neuroprotective strategies (in terms of timing of administration, mechanism of action, interactions with other treatments, etc.), we argue a critically important step to maximize success of such future therapies is to identify and apply neuroimaging techniques appropriate to each of the distinctive injury processes active in different brain tissues and different time periods of human brain ischemia.

Box 1. Outline

- Endovascular treatment (EVT) has sparked renewed interest in cerebroprotection. We have, however, an at best rudimentary understanding of the recovery potential of tissue during the various stages from ischemia to infarction, which is important for cerebroprotectant selection and timing of administration
- In this review, we outline:
  1. Knowledge gaps concerning tissue fate during the various stages of acute ischemia
  2. Knowledge gaps regarding mechanisms of action of various cerebroprotectants
  3. Why current routine imaging tools do not accurately reflect tissue fate and how this limitation could be overcome
  4. The importance of imaging tissue fate in cerebroprotectant trials
  5. A suggested roadmap for developing a magnetic resonance imaging-based "toolbox," which could enable us to better understand the mechanisms of tissue fate during human cerebral ischemia

Mechanisms of tissue injury and targets for cerebroprotection

Six particularly important broad mechanisms of tissue injury may be delineated in human cerebral ischemia. These are (1) early net water uptake compensating extracellular ion depletion (ionic edema) triggered by severe ischemia with cerebral blood flow (CBF) < 15 ml/100 g/min [10]; (2) cellular injury that advances during the initial ischemic period prior to reperfusion; (3) microcirculatory arrest with no-reflow phenomenon after macro-reperfusion that perpetuates ischemia; (4) oxidative and inflammatory injury that starts immediately after reperfusion; (5) BBB disruption which could result in sustained vasogenic edema and hemorrhagic transformation by the pressure head of restored perfusion; and (6) late secondary injury that includes the elaboration of prolonged apoptotic processes that were initiated prior to and continue despite reperfusion.

Correspondingly, there are six broad classes of neuronal/neurovascular unit protection: (1) "ionic edema reducers," agents that inhibit ion channel dysfunction; (2) "bridging cerebroprotection," agents that slow or arrest progression to infarction during the initial ischemic period; (3) "microcirculatory flow restorers," agents that improve perfusion by disaggregating platelets and reducing small vessel endothelial edema; (4) "neural/neurovascular reperfusion injury preventers," agents that block oxidative and inflammatory processes that lead to additional neuronal cell death, edema, and BBB disruption; (5) "BBB stabilizers," agents that restore BBB integrity or indirectly prevent worsening by modulating external factors such as blood pressure; and (6) "delayed cerebroprotection," agents that block apoptotic processes preventing late secondary injury. It is also likely that agents or interventions may act by more than one mechanism. For example, hypothermia slows down progression to infarction, stabilizes the BBB, and suppresses the inflammatory response [11] (Table 1).

Problems with cerebroprotection in human acute ischemic stroke models

While hypothermia is a mainstream therapy for temporary global ischemia after resuscitated cardiac arrest and many cerebroprotective agents have led to promising results in both temporary and permanent animal models of ischemia, the effectiveness of hypothermia and cerebroprotective agents in focal human ischemia has not yet definitively been proven [22].

One important reason for the repeated failures in translation of cerebroprotective agents may be the past

Table 1 Exemplar cerebroprotective interventions in development classified according to their broad physiologic target

Intervention	Bridging cerebroprotection	Microcirculatory flow restorers	Neural reperfusion injury preventers	BBB stabilizers	Ionic edema reducers	Delayed cerebroprotection
NA-1 [12]	X		X			
Hypothermia [13]	X		X	X	X	
Remote ischemic conditioning [14]	X	X				
Fingolimod [15]	X		X	X		
Glibenclamide [16]					X	
Minocyclin [17]			X	X		
Normobaric hyperoxia [18]	X			X		X
RNS60 [19]	X		X	X		X
Fasudil [20]	X	X				

Many currently studied cerebroprotectants target multiple ischemic injury pathways. For a more comprehensive review, see Mulder et al. (2021) [21]. *NA1*, nerinetide*; BBB*, blood–brain-barrier

approach of usually advancing to human trials agents that worked both in permanent as well as transient occlusion animal models. It is now generally recognized that it is unrealistic to expect that cerebroprotective agents would be of benefit in permanent human ischemia. These agents may slow the consumption of penumbral tissue that is under ischemic stress, but they cannot preserve threatened tissue indefinitely. If reperfusion does not occur, the tissue will eventually progress to infarction. The reason why cerebroprotection in permanent occlusion works in rats but not in humans could be because many rodent permanent occlusion models produce large, malignant infarcts for which benefit may be conferred by edema-reducing drug effects rather than neuronoprotective drug effects [23].

With the advent of EVT, occluded blood vessels can now be re-opened quickly and reliably, and for the first time, we can mirror in humans the ischemia–reperfusion sequence of the temporary occlusion model in animals. There do remain several challenges to successful translation even in an era of frequent reperfusion therapy in human patients. First, in rats, the administered drug can reach ischemic tissue via diffusion in addition to via blood flow, while this effect is negligible in humans with large strokes [22]. Second, the transient-induced ischemia in some animal models is very brief, e.g., 1 h, which does not accord well with the longer duration of ischemia in humans, even among patients who do receive reperfusion therapy, although prehospital start of neuroprotection enables treatment within the first 60 min in many patients [24]. Third, in animal models, stroke induction is often mechanical (e.g., with temporary placement of intraluminal filaments or neurovascular clips), while in humans, it is most often caused by thromboembolism—thromboembolism may be more often associated with downstream emboli and no-reflow phenomena [25]. Fourth, pre-clinical animal models generally use young animals with few comorbidities, while human stroke patients are most often elderly with multiple comorbidities [26]. Fifth, treatment effect sizes are often determined by histologically measured infarct volumes in pre-clinical studies as opposed to long-term functional outcomes in human clinical trials [26]. Sixth, some agents beneficial in pre-clinical models may have systemic toxic effects in humans not evident in animals. Nonetheless, none of these challenges with transient occlusion stroke models are as insuperable as with permanent stroke models. The reperfusion era in human ischemic stroke lays the foundation for a subsequent successful cerebroprotection era.

Renewed interest in cerebroprotection

The increased potential for success of cerebroprotective agents is reflected in the recent launch of a new wave of human clinical trials. Multiple compounds, devices, and strategies with different modes of delivery and mechanisms of action are currently being investigated (Table 1). A search in January 2022 of ongoing phase I–III adult human cerebroprotection studies on ClinicalTrials.gov yielded 55 results. One particularly promising cerebroprotectant agent, nerinetide (NA1), interferes with post-synaptic density protein 95-mediated signaling pathways and thereby reduces neuronal excitotoxicity. It is an agent whose main effect is a bridging neuroprotectant but also potentially with benefit for reperfusion injury. It was shown to improve clinical outcomes in acute ischemic stroke patients treated with EVT without concurrent intravenous alteplase in the ESCAPE-NA1 trial, while also resulting in a 13% reduction in infarct volume on 24-h imaging [12]. The ongoing ESCAPE-NEXT trial (ClinicalTrials.gov Identifier: NCT04462536) seeks to confirm these results. Remote ischemic conditioning in the ambulance following stroke code activation (e.g., REMOTE-CAT, ClinicalTrials.gov Identifier: NCT03375762) is an approach with both bridging

cerebroprotectant and microcirculatory flow restoration features. RNS60 is an anti-inflammatory cerebroprotectant candidate (ClinicalTrials.gov Identifier: NCT04693715) that could potentially reduce inflammatory injury after reperfusion. Glibenclamide, a compound that has been shown to reduce cerebral edema and improve functional outcome in pre-clinical studies [27], is currently being tested in the CHARM trial (ClinicalTrials.gov Identifier: NCT02864953). Transcranial direct current stimulation before and/or after recanalization (e.g., TESSERACT-BA, ClinicalTrials.gov Identifier: NCT04061577) and intra-arterial delivery of verapamil following EVT (e.g., ClinicalTrials.gov Identifier: NCT03347786) are potential forms of delayed cerebroprotection, while normobaric hyperoxia during EVT (e.g., OPENS-2, ClinicalTrials.gov Identifier: NCT04681651) may stabilize the BBB. An additional strategy is intra-arterial infusion of a cerebroprotective agent into the ischemic field immediately after reperfusion is achieved, such as regional hypothermia following successful reperfusion (e.g., RE-HIBER, ClinicalTrials.gov Identifier: NCT04554797); this approach targets reperfusion injury and delayed cerebral neuroprotection.

It should be noted that many of these strategies are being implemented at various stages of the ischemic cascade and therefore with different modes of administration. This has important implications for study design. For example, bridging cerebroprotectants in the pre-hospital setting would need to be safe with intracranial hemorrhage, compatible with other treatments (e.g., thrombolysis), and easily administered (e.g., through intravenous infusion). In the in-hospital setting, intra-arterial delivery of the agent directly into the region of hypoperfused brain could be performed [28].

Importance of imaging in cerebroprotection trials

Additional sources of hope for the advance of cerebroprotective therapy in the present era are diverse advances in imaging that have the potential to increase human trial success. Multimodal CT and MR imaging can improve selection of informative patients for trial enrollment, provide unique insights into stroke pathophysiology and agent mechanism of action, and serve as key physiologic biomarkers of treatment effect in early-stage human trials.

Roles of imaging in patient selection

It is important to enroll in clinical trials patients experiencing the particular processes of injury that a cerebroprotective agent is intended to treat. Neuroimaging can crucially inform this selection (Table 2). The most long-established neuroimaging selection approach for cerebroprotectant trials is penumbral imaging with CT or MRI. Only patients with moderate to substantial penumbral tissue have the potential to respond to bridging cerebroprotective agents [29, 30]. A more recent innovation is imaging the intensity of ischemic stress upon still salvageable tissue with techniques such as the hypoperfusion intensity ratio. Patients with more extreme current ischemia will be "fast progressors" who will be more informative regarding the effect of a bridging cerebroprotectant than patients with more slowly evolving lesions [31, 32]. Imaging ischemia location helps select patients for neuronoprotection (cortical involvement) or glioprotection (white matter involvement). A potential future selection tool is permeability imaging to identify patients with early BBB disruption for endothelioprotection. Imaging demonstrating the achievement of reperfusion identifies the best candidates for agents active against reperfusion injury. Serial MRI demonstrating early diffusion abnormality reversal after reperfusion may select appropriate patient candidates for agents targeting late, apoptotic-mediated injury [33].

Role of imaging in dissecting stroke pathophysiology and cerebroprotective agent mechanism of action

Several of the determinants of tissue fate at the various stages of acute ischemic stroke have already been delineated, at least broadly, by neuroimaging investigations. But many aspects remain to be understood. For example, in patients with complete reperfusion (expanded thrombolysis in cerebral infarction (eTICI) 3), what is the frequency and consequence of microcirculatory arrest/no-reflow phenomenon at the tissue level? A standardized imaging protocol could allow us to consistently catalog the different tissue viability states and their associated imaging features. Working backward, we could then use this information to better understand what may be happening at the cellular and microvascular level, where neuroprotection plays a role.

Expansion and refinement of an imaging-based "natural history" catalog of the pathophysiological processes that occur throughout the entire infarct evolution process would yield techniques that could be applied to assess distinct mechanisms of cerebroprotective action (Table 2). Different steps in the elaboration of ischemic tissue injury are associated with specific imaging features, including necrotic cell death, microcirculatory arrest, reperfusion injury, and apoptosis [36]. For cerebroprotectants with expected single modes of action, imaging could confirm if the mechanistic effect occurs in humans as anticipated or could unveil additional beneficial or harmful effects at other pathophysiologic stages. For cerebroprotectants with expected multiple, pleiotropic modes of action, imaging could confirm the anticipated activity profile in humans and delineate the relative contributions of each effect to aggregate agent

Table 2 Neuroimaging techniques to assess distinct cerebroprotective mechanisms

	Bridging cerebroprotection	Microcirculatory flow restorers	Neural reperfusion injury preventers	BBB stabilizers	Ionic edema reducers	Delayed cerebroprotection
DSA with no reflow		+ + +		-		
Perfusion imaging resolution of no flow		+ + +				
Infarct growth	+ + +					+
Infarct growth within no reflow field	+ + +	+ + +		-		+
Infarct growth outside of penumbra zone	+ + +		+ + +			+
Infarct growth in reperfused field	+ + +		+ + +			+ + +
Delayed infarct growth				+		+ + +
Penumbra salvage	+ + +	+ + +				-
Diffusion tensor imaging	+ + +					
Atrophy	+ + +					+ + +
Atrophy (selective neuronal loss)	+ + +	+ + +				+ + +
Macrophage iron particle imaging		+ + +	+ + +			
Cytotoxic edema			+ + +	-	+ + +	
Permeability imaging[a]				+ + +	+ +	
HARM sign[b]				+ + +	+	
Mild radiologic hemorrhagic transformation				+ + +	+	
Severe radiologic hemorrhagic transformation				+ + +	+	
Vasogenic edema				+ + +	-	
Secondary reappearance of injury after DWI reversal	-	-	-	-	-	+ + +

Each row represents a potential imaging feature following acute ischemic stroke, along with possible associated cerebroprotective mechanisms. Serial imaging could aid our understanding of cellular/molecular processes at the tissue level, thereby allowing us to make more informed decisions on if, when, and how to implement cerebroprotectant strategies. For example, late secondary injury is a described, yet poorly understood phenomenon that may serve as a future therapeutic target for neuroprotection [33]. As shown above, most of these are multifactorial in nature, with multiple mechanisms likely occurring simultaneously

[a]Can be visualized with, e.g., water exchange index sequences [34] or by measuring capillary permeability (K^{trans}) or BBB leakage with dynamic susceptibility contrast MRP (K_2)[35]

[b]Requires prior gadolinium administration

DSA, digital subtraction angiography; *BBB*, blood–brain-barrier; *HARM*, hyperintense acute reperfusion marker; *DWI*, diffusion-weighted imaging

action. For cerebroprotectants whose mechanisms of action are only incompletely understood, imaging could identify agent modes of activity.

Timing of cerebroprotection is also essential, as different pathophysiologic processes transpire at various epochs after ischemia onset. Therefore, for the best chance of a good functional outcome, timely administration/implementation of the compound or strategy, in addition to complete and rapid reperfusion, is of critical importance. In the case of bridging cerebroprotectants, for example, prehospital implementation could slow down penumbral consumption, thereby extending the time window for reperfusion therapies. This could be critical in situations where, e.g., long transport delays are expected. In the post-hospital arrival, pre-EVT/pre-thrombolysis phase, agents that target mechanisms of reperfusion injury could be administered, to decrease the likelihood of feared complications such as hemorrhage. However, because many cerebroprotectants have incompletely understood or pleiotropic effects, appropriate timing of administration for maximum benefit will need to be determined. Mechanistic imaging studies could help identify the optimal time point for agent administration based on its mechanism of action, for example, early start of agents that exert bridging neuroprotection and later start for agent that avert reperfusion injury.

Role of imaging as a physiologic outcome measure in cerebroprotection trials

Imaging outcomes reflecting specific modes of cerebroprotective action can play several useful roles in human clinical trials. They can be useful as primary or leading secondary endpoints in phase I or II proof of concept and dose optimization studies because they more directly index agent treatment effect than do clinical outcomes. Many factors besides agent effect contribute to patient outcome on

Table 3 Limitations of current post-EVT imaging protocol

Limitations of 24-h post EVT imaging
• "Snapshot" in time
• Provides limited information on the infarct growth curve
• Provides limited information on the natural history of infarction (e.g., hemorrhagic transformation)
• Provides no information on the mechanism of infarction (e.g., infarction due to incomplete reperfusion vs. "downstream" cytotoxicity occurring despite complete reperfusion)
• "Late-stage" processes that can lead to a breakdown of the blood–brain-barrier and further tissue death (inflammation, vascular remodeling) generally not yet initiated at 34 h (as they may occur > 36 h) [52]

EVT, endovascular treatment

the most common clinical endpoint in acute stroke clinical trials, level of global disability outcome on the modified Rankin scale. Level of prestroke disability, comorbidities at onset, supervening infections, deep venous thrombosis, pulmonary embolism, and late recurrent stroke all influence 90-day disability, introducing noise that dilutes the strength of the relation of cerebroprotective agent effect to final clinical outcome. In contrast, imaging measures are often more tightly linked to agent action, enabling them to provide readouts of whether an agent is beneficial and the best dose to employ with smaller sample sizes than do clinical outcomes. An example is the phase II trial of NA1 in patients undergoing neuroendovascular coiling of asymptomatic cerebral aneurysms that use the imaging outcome of burden of post-procedure diffusion injury to provide proof of concept demonstration of cerebroprotective effect in humans [37]. This imaging finding confirming anticipated treatment effect in humans "de-risked" the decision to proceed to large phase III trials in acute ischemic stroke using noisier clinical outcomes as the primary endpoint.

An additional advantage of imaging endpoints in phase II dose optimization trials of cerebroprotective agents is they can be ascertained within the first week of patient dosing, rather than needing to wait 90 days for final clinical outcome. For studies using adaptive dose-finding in which patients are gradually assigned in greater proportion to doses showing the most benefit, the rapid availability of imaging endpoints permits more rapid feedback into the decision model making treatment of the next patient more informative [38, 39]. Imaging endpoints can also play important roles as auxiliary outcomes in phase III pivotal trials. Imaging endpoints generally cannot serve as the primary outcome in pivotal trials because agents may have off-target effects not assessed by the imaging measure that may impair rather than enhance clinical outcome. But imaging endpoints can provide important supportive and explanatory information in phase III trials, reinforcing confidence in the primary outcome result. For example, the Food and Drug Administration's accelerated approval pathway permits approval of a drug for a serious or life-threatening illness if there remains some uncertainty regarding clinical benefit from the primary outcome, but drug is also shown to have an effect on an imaging biomarker reasonably likely to predict a clinical benefit to patients [40].

Routine acute ischemic stroke imaging in clinical practice and its limitations

At baseline, most often a non-contrast CT (NCCT) and CT angiogram (CTA) are performed, providing important information regarding the brain parenchyma and craniocervical vasculature. Sometimes, in addition, a CT perfusion study is performed, directly visualizing the region at risk due to ischemia and indirectly providing information regarding the viability of the brain tissue. Multimodal MR imaging is less often employed as an initial study. When performed, it provides similar information to multimodal CT and more directly and reliably assesses tissue viability. The information gained from baseline imaging depends not only on the modality used but also the imaging time point. With NCCT, for example, it is challenging to detect decreased brain tissue radiodensity in patients presenting in the early (< 3-h) time window. Furthermore, with all current technologies, determining the ischemic core, e.g., brain tissue presumed to be irreversibly damaged and that will progress to infarction, is only possible with less than perfect accuracy [41, 42].

Post-treatment imaging at 24 h usually consists of parenchymal with MRI or CT imaging, with MRA/CTA often and perfusion MR or CT sometimes added. Follow-up imaging can guide management by quantifying the infarct volume that has evolved at 24 h, detecting early complications such as hemorrhagic transformation, and identifying blood-CSF barrier disruption via the HARM sign [43, 44]. Together with the patient's clinical status, these factors aid in the prognostication of patient outcomes.

However, a substantial amount of information may be lost in the interval between the reopening of the vessel and delayed (24) post-treatment imaging (Table 3). For example, we currently do not precisely know whether and how infarct growth changes over time. Also unclear is the tempo of BBB disruption and development of hemorrhagic

transformation. DWI-MR imaging is often considered the best available modality for estimating the extent and location of the infarct; however, there remains no true imaging-based reference standard for tissue death as established by comparison with neuropathologic findings [45]. If reperfusion is quickly achieved, for example, DWI reversal may occur, followed by sustained normal tissue appearance, minor FLAIR abnormality, or late reappearance of marked FLAIR abnormality [33, 46]. Sustained DWI reversal is associated with higher ADC values [47, 48]. However, animal studies have shown that even brief periods of diffusion restriction with complete, permanent normalization can be associated with neuronal loss [49]. DWI hyperintensity, therefore, is not fully predictive of tissue that is destined to die. Rather, it is plausible that a continuum of infarct severity exists that is more granular than the imaging based binary approach commonly used (i.e., tissue that is radiologically abnormal is uniformly damaged, while tissue that is radiologically normal is uniformly preserved) [46]. Conversely, if reperfusion is not achieved or is achieved late, infarct growth can continue beyond the 24-h period, leading 24-h scans to substantially underestimate final infarct size [50, 51]. These dynamic changes in tissue state, potentially influenceable by distinct cerebroprotective agents, can only be visualized with serial imaging. The single snapshot in time of a 24-h imaging is only a small piece of the puzzle.

Suggested imaging toolbox for cerebroprotection trials

The advantages of CT are its feasibility (even during EVT as cone beam CT), its widespread use, and the complementary information provided by NCCT, CT-angiography, and CT perfusion imaging. Further, the advent of novel imaging biomarkers, such as net water uptake, allows us to determine the time window for thrombolysis eligibility with comparable accuracy to MRI [53], as well as identify patients who may be "fast progressors" and thus likely to experience poor outcomes despite successful recanalization [54]. However, CT has several limitations, including the ability to probe the ischemic core only indirectly via perfusion imaging and constraints on use of contrast in patients with renal impairment. In addition, for monitoring the serial evolution of neurovascular state, radiation exposure limits its repeated use. New technical developments such as dual source CT and photon-counting detector technology may reduce this risk, though not entirely remove it.

While MRI also has its limitations, it is currently the best non-invasive option available in clinical routine. An MRI imaging protocol including DWI, T2-fluid attenuated inversion recovery (FLAIR), susceptibility-weighted imaging/gradient echo, and perfusion sequences, together with antero-posterior and final lateral angiogram runs registered to axial MR images, can provide a reasonable estimate of the extent and nature of tissue damage at baseline and technical treatment success of EVT. Dependent on the access to MRI scanners with fast gradients and the ability to generate complex radiofrequency pulses for acceleration purposes, e.g., simultaneous multislice technique (SMS) [55], anatomical and classical contrast will likely be augmented by pathophysiological or metabolic contrasts. Modeled capillary transit time heterogeneity (CTH) and the relative heterogeneity of transit times, i.e., the CTH:MTT (mean transit time) ratio, appear to capture microvascular perfusion disturbances closely associated with progression to infarct [56].

Serial MRI offers the best current approach to delineating evolving tissue state and mechanisms of cerebroprotective action in human ischemic stroke. Ideally, the sequence would start with MR as the initial baseline imaging modality on arrival (foregoing CT). However, while MR as first imaging is used regularly at some centers, particularly in France, Germany, and South Korea, and can be conducted with speedy workflows in optimized care systems [57], it is less common, and a more pragmatic approach would also permit CT as the first imaging modality. The baseline study would then be followed by serial multimodal MR scans at 4 timepoints: immediately, 24 h, 3–5 days, and 60–90 days after reperfusion (Table 4). The morphological changes between each stage could then be correlated to known mechanisms of action and pathophysiological processes following treatment (Fig. 1, Tables 1 and 4). For example, the extent of infarct growth between the time of complete reperfusion and 24 h could be determined. If a cerebroprotectant active against reperfusion injury was administered prior to or at the moment of reperfusion and was effective, one would expect minimal infarct growth after the immediate post-procedure imaging. However, if the cerebroprotectant is ineffective, neuronal cell loss/injury would continue, resulting in ongoing infarct progression. In such scenarios, a variety of determining factors affecting growth curve dynamics would come into play, including not only reperfusion status, but also collaterals, time from symptom onset, and factors known to play a role in infarct progression such as blood glucose levels, comorbidities, and patient age [58].

In the stage between 24 h and 3 to 5 days, further processes could be observed, such as potential onset of brain swelling and subsequent midline shift, the level of FLAIR demarcation, and presence of hemorrhage. Serial MRI scans could capture infarct growth patterns and edema evolution in this time interval, which may, in turn, be influenced by cerebroprotective agents (Tables 1 and 4). For example, one could imagine a cerebroprotectant that reduces brain edema and whose effect could be measured by signal intensity/disturbance in brain volume increase on serial imaging between 24 h and 5 days compared to placebo.

Table 4 Suggested timing of post-EVT imaging protocol and key imaging features to be captured

Angiography	Immediate (< 1 h)	24 h	3 to 5 days	60 to 90 days
• eTICI grade • Perfusion angiography: status of peripheral vessels/ signs of microcirculatory arrest	• Delineate regional reperfusion • Assessment of continued mismatch for possible reintervention • Early prediction of hemorrhagic changes	• Presence of hemorrhage (PH)/BBB breakdown • Swelling and midline shift • Infarct growth/ reversal • Extent of FLAIR demarcation	• Degree of white vs. grey matter involvement • Presence of hemorrhage (HI)/BBB breakdown • Final infarct volume • Determination of selective neuronal loss	• Degree of atrophy/gliosis true volume loss • Wallerian degeneration • Cortical necrosis/ mineralization

EVT, endovascular treatment; e*TICI*, expanded thrombolysis in cerebral infarction scale; *PH*, parenchymal hematoma; *BBB*, blood–brain-barrier; *FLAIR*, fluid-attenuated inversion recovery; *HI*, hemorrhagic infarction

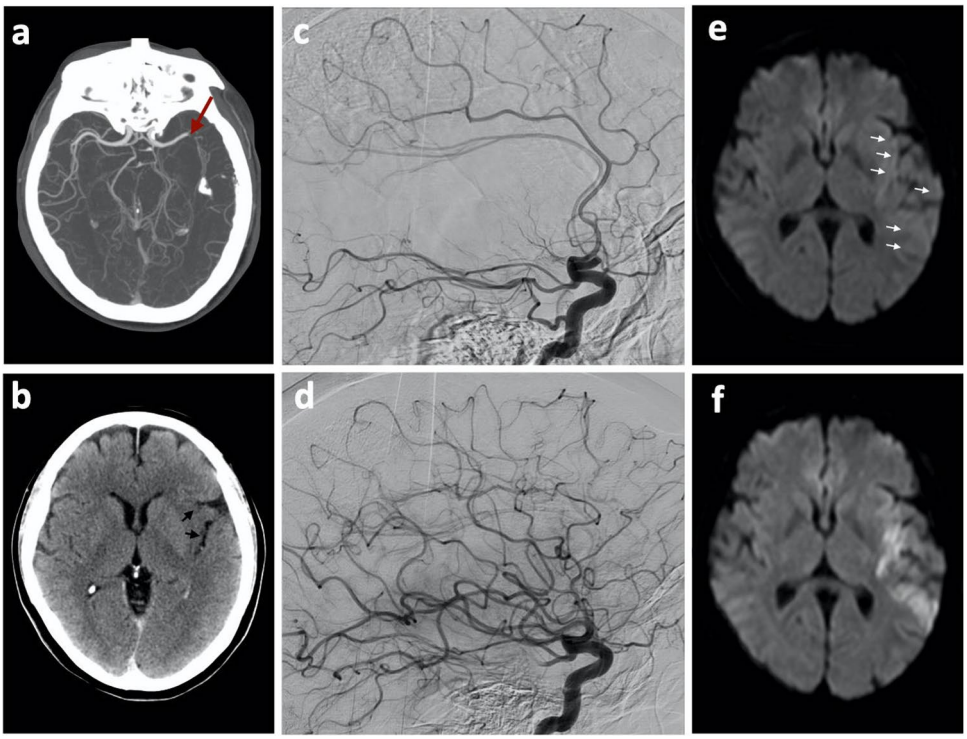

Fig. 1 Illustrative case: patient with left M1 occlusion (**A**, red arrow) and subtle early ischemic changes (**B**, black arrows), achieved eTICI 3 reperfusion 200 min after symptom onset (first intracranial angiogram prior to EVT (**C**), final intracranial angiogram after EVT (**D**)). In the early (2 h) post-EVT DWI-MRI, subtle hyperintensity of the ipsilateral insula and M2/3 regions was seen (**E**, white arrows), which was much more pronounced at the 24-h timepoint (**F**). (For images of the entire infarcted region on DWI-MRI, see Online Resource 1). In this scenario, various mechanisms of late secondary injury may have been initiated, including cellular/molecular cascades that led to apoptosis of cells within the penumbral tissue or neuronal necrosis due to energy failure. Additional activation of the inflammatory system (ROS, excitotoxicity) may have led to reperfusion injury. *EVT, endovascular treatment; DWI-MRI, diffusion-weighted imaging magnetic resonance imaging; ROS, reactive oxygen species*

Finally, changes in imaging profiles between the 5- and 90-day period could provide valuable information regarding the degree of atrophy, gliosis, and volume loss due to infarction, as well as other sequelae such as Wallerian degeneration, cortical necrosis, and/or mineralization (Table 4).

There will likely be other techniques and/or sequences that could be added to the "toolbox" to enhance our understanding further. Diffusion tensor imaging, for example, could be used to determine the effects of treatment on grey vs. white matter, while quantitative blood oxygenation level-dependent imaging or spectroscopy could monitor tissue metabolism. If contrast is to be avoided, arterial spin labeling (ASL) perfusion techniques could be employed. In all instances, the protocol should be as efficient and safe as

possible while providing the maximum amount of information to enhance our understanding.

Of course, there are obstacles in implementing such a serial MRI protocol. For patients in the (post) acute setting, motion artifacts can lead to poor image quality. However, recent advances with accelerated sequences and thus short scan times may partially offset this issue [59, 60]. There is also the question of cost which will vary regionally and according to local healthcare and insurance policies. In some jurisdictions, such as France and Korea, MRI is the preferred modality for stroke imaging (even in the acute setting), suggesting that such paradigms are economically feasible at least in some regions of the world. Finally, and despite this, CT remains the most widely available imaging strategy, which will at least initially influence the broad implementation of our suggested protocol.

Nevertheless, due to the high-level of detail MRI provides on brain tissue viability, perfusion, and vascular integrity compared to other neuroimaging techniques, it remains the best option for providing comprehensive information on ischemic tissue damage mechanisms and their temporal evolution. Once we have established a comprehensive, standardized imaging protocol within the framework of the temporary ischemia model of EVT, we may not only be able to substantially expand our knowledge on the mechanisms of action of existing cerebroprotective agents, but also identify new therapeutic targets that could guide the development of additional, novel cerebroprotectants [61].

Conclusion

A standardized protocol of serial post-treatment MR imaging or, at the very least, an immediate post-procedure and one delayed-timepoint MRI would provide valuable information regarding tissue damage immediately after EVT, the quality of reperfusion, infarct growth dynamics, and patient prognosis. Furthermore, it could help us to better understand the mechanisms of action of cerebroprotectants and may even allow us to use imaging markers as surrogate outcomes in cerebroprotectant trials. Hopefully, this will accelerate the translation of cerebroprotective agents from bench to bedside, with the ultimate goal of improved patient outcome.

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Declarations

Conflict of interest Drs. McDonough, McTaggart, Roozenbeek, Luijten, Wiest, and Lundberg report no conflicts. Dr. Ospel reports being a consultant for NICOLab. Dr. Saver reports being an employee of the University of California; serving as an unpaid site investigator in multicenter trials run by Medtronic and Stryker for which the University of California Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled; and receiving funding for services as a scientific consultant regarding trial design and conduct to Medtronic, Stryker, Cerenovus and Rapid Medical. The UC Regents have patent rights in endovascular retrievers. Dr. Hill reports unrestricted grant funding for the ESCAPE trial to University of Calgary from Covidien/Medtronic, and active/in-kind support consortium of public/charitable sources (Heart and Stroke Foundation, Alberta Innovates Health Solutions, Alberta Health Services) and the University of Calgary (Hotchkiss Brain Institute, Departments of Clinical Neurosciences and Radiology, and Calgary Stroke Program); grant funding from Boehringer Ingelheim, NoNo, Inc, and Stryker. Personal fees from Merck, nonfinancial support from Hoffmann-La Roche Canada. In addition, Dr Hill has a submitted patent for triaging systems in ischemic stroke and owns stock in Calgary Scientific, a company that focuses on medical imaging software. Dr. Goyal reports receiving an unrestricted institutional grant from Medtronic; he received a grant from Stryker and consulting fees from Stryker, MicroVention, Mentice; he holds patent rights in systems and methods for acute stroke diagnosis with GE Healthcare. Dr. Van der Lugt reports unrestricted grants from Stryker, Penumbra, Medtronic, Cerenovus, Thrombolytic Science, LLC, Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organization for Health Research and Development, and Health Holland Top Sector Life Sciences & Health for research, paid to institution. Dr. Tymianski is the CEO of NoNO Inc., a biotechnology company that has sponsored the ENACT, ESCAPE-NA1, and ESCAPE-NEXT trials. Dr. von Kummer is the Editor-in-Chief of *Neuroradiology*.

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