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INVITED COMMENTARY

Collateral Status, Reperfusion, and Cerebral Edema After Thrombectomy for Stroke

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Endovascular thrombectomy has revolutionized the landscape for those with acute ischemic stroke. Patients' functional outcomes can be dramatically improved by reperfusion of large vessel occlusion (LVO) in both the anterior and posterior circulations [1–3]. However, a major concern that remains, despite these advances, is that despite successful recanalization of occluded vessels and apparent reperfusion of ischemic brain tissue, up to half of patients still do not regain functional independence. Several reasons for this discrepancy, termed futile recanalization or clinically ineffective reperfusion, have been proposed [4, 5]: one hypothesis is that patients with LVO can still experience severe brain edema and hemorrhagic complications (i.e., reperfusion injury), which threaten loss of life and secondary brain injury, thereby imperiling recovery [6]. Experimental data and some human studies have suggested that reperfusion could exacerbate brain edema, especially when it occurs late and/or in the setting of large ischemic volumes [7, 8]. However, early clinical data from thrombectomy trials and registries instead suggested that reperfusion reduces edema, measured using midline shift [9, 10]. Additionally, two recent mediation analyses have suggested that a substantial proportion of the improvement in outcome observed in studies of endovascular reperfusion is mediated by a reduction in brain edema and not just final infarct volume [11, 12].

However, these analyses were all from studies of patients with stroke presenting with relatively small ischemic cores. A more recent retrospective analysis of the HERMES (Highly Effective Reperfusion using Multiple Endovascular Devices) collaborative imaging data raised the concern that those with large cores at baseline could have even greater midline shift after reperfusion [13]. Although the recent success of large core thrombectomy trials may have tempered these concerns, some suggested higher rates of brain edema in the intervention arm (although more detailed edema-focused data are still pending) [14–16]. Regardless of this emerging data, we will inevitably see a rise in the frequency and scope of thrombectomy to include those with larger strokes and delayed presentations, making an evaluation of brain edema a key part of postreperfusion care in the neurological intensive care unit and stroke unit. A deeper understanding of which of these patients undergoing thrombectomy are at particular risk of malignant brain edema (MBE) would allow better risk stratification, triage, monitoring, and early interventions to mitigate secondary brain injury.

The study by Chen and colleagues [17] from Beijing evaluated more than 600 patients with anterior circulation LVO, of whom one third had large infarct size (assessed by ASPECTS [Alberta Stroke Program Early CT Score] < 6). They hypothesized that an elevated hypoperfusion intensity ratio (HIR), a marker of impaired tissue-level collateral status, would predict a greater risk of MBE, defined as clinical deterioration associated in most cases with midline shift. MBE, which developed in 15% of this cohort, conferred a very poor chance of recovery; almost half those with MBE died, and the median modified Rankin Scale score was 5. As expected, higher NIHSS (National Institutes of Health Stroke Scale) score, lower ASPECTS, and proximal occlusion were associated with risk of MBE, as was unsuccessful recanalization. Independent of these known predictive variables, higher HIR was also associated with MBE (as well as, separately, a higher risk of parenchymal hematoma, suggesting a

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shared risk profile for both, possibly stemming from reperfusion injury); HIR was also an important predictor of edema in the subset who experienced successful recanalization.

Poor angiographic collateral status has long been associated with multiple poor outcomes after LVO stroke, including faster infarct progression and more early brain edema formation [18, 19]. Tissue-level metrics, such as HIR may provide complementary information on collateral status, have also been associated with early edema formation [20]. Although HIR has been associated with risk of MBE in a prior study, that study focused only on those with unsuccessful reperfusion after thrombectomy [21]. A recent study evaluated collaterals and MBE, demonstrating that combining multiple measures of poor collateral status (including HIR, angiographic assessment, and venous outflow impairment) correlated not only with MBE but also with greater edema growth over time, measured by using a quantitative edema biomarker [22]. Several groups are currently investigating whether collateral measures, along with other parameters such as blood pressure trajectories, correlate with hemorrhagic transformation, edema growth, and MBE, as measured using quantitative biomarkers that assess the full spectrum of these complications and their impact on recovery [23, 24].

There appears to be a relevant interaction between larger baseline infarct size (although core volume was not part of this article's primary analysis, it was included in a supplementary analysis) and poor collateral status; although poor collaterals contribute to early infarct growth [25], it appears that both likely also contribute to higher risk of progressive malignant edema formation. It will be interesting to see if this is borne out in post hoc analyses from the large core thrombectomy studies, which allow comparison of such patients with those not undergoing thrombectomy, which was not possible in this retrospective study. This will allow us to evaluate whether there are subgroups of those with large infarcts on presentation (who usually have poor collaterals) who are at such a high risk of developing brain edema that the benefits of intervening are negated.

It is likely that the focus on the collateral circulation will only continue to advance within stroke research, as we seek to advance the precision care of these patients who present with complex evolving cerebrovascular physiologies [26]. Previously, patients were lumped into crude buckets by time from symptom onset and treated with unified protocols, but advanced imaging now allows us to assess how much tissue is injured and how much remains vulnerable as well as evaluate interacting physiologic factors such as collateral status and early edema formation. This will enable more precise selection of patients for reperfusion therapies, identification of some patients who may be at particular risk from these interventions, and identification of which patients are at the highest risk of complications and which patients may benefit from emerging neuroprotective and antiedema interventions. Indeed, the therapeutic induction and manipulation of collateral flow itself may provide additional means of limiting ischemic brain injury, which itself will inevitably lead to less brain swelling and better stroke outcomes [27].

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Conflicts of interest
The author has nothing to disclose.

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