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Collateral lessons from recent acute ischemic stroke trials

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Abstract

Numerous acute ischemic stroke trials have recently published detailed results, providing an opportunity to consider the role of collaterals in stroke pathophysiology and their influential effect on patient outcomes. Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS), the largest randomized controlled trial of device therapy to date, tested the potential augmentation of collateral perfusion. SYNTHESIS Expansion, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE), and Interventional Management of Stroke (IMS) III chronicled the saga of endovascular therapy trialed against medical treatment for acute ischemic stroke. These recent randomized studies, however, largely neglect current device technology available for endovascular therapy as advanced by the TREVO2 and SOLITAIRE™ FR With the Intention For Thrombectomy (SWIFT) studies. Such exhaustive efforts in recent trials have failed to introduce a new treatment for stroke that unequivocally improves patient outcomes. Collateral perfusion is widely recognized to vary across individuals in any population and exerts a dramatic effect on baseline variables including the time course of ischemic injury, stroke severity, imaging findings, and therapeutic opportunities. Similarly, collaterals have been recognized to influence recanalization, reperfusion, hemorrhagic transformation, and subsequent neurological outcomes after stroke. Collateral lessons may be gleaned from these trials, to expand consideration of overall study results and perhaps most importantly, alter ongoing and new trials in development. Detailed analyses of available information on collaterals from these trials demonstrate that collaterals may be more influential than the choice of treatment modality or intervention.

Keywords

Stroke; Ischemia; Collateral; Neuroprotection; Reperfusion

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Ethics approval None.

Introduction

Numerous acute ischemic stroke trials have recently published detailed results, providing an opportunity to consider the role of collaterals in stroke pathophysiology and their influential effect on patient outcomes. This much-anticipated influx of phase III clinical trial endpoints measuring the impact of diverse acute stroke treatments yielded somewhat disappointing primary conclusions, yet these trials generated expansive data regarding many clinical variables. Almost all of these trials testing novel therapeutic strategies placed marginal emphasis on imaging variables, yet the resultant datasets of routine diagnostic evaluation with imaging and angiography provide valuable information on collateral perfusion, patterns of ischemic injury and the relationship with revascularization or reperfusion of downstream tissue in the brain.[1]

The Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS) trial, the largest randomized controlled trial of device therapy to date, tested the potential augmentation of collateral perfusion.[2] The SYNTHESIS Expansion study, The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial, and the Interventional Management of Stroke (IMS) III trial chronicled the saga of endovascular therapy studied against medical treatment for acute ischemic stroke.[3-5] These three randomized studies, however, largely neglect current device technology now available for endovascular therapy as advanced in the Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO2) and Solitaire flow restoration device versus the Merci Retriever in patients with acute ischemic stroke (SWIFT) studies.[6,7] Such exhaustive efforts in recent trials have failed to introduce a new treatment for stroke that unequivocally improves patient outcomes, yet these investigators have gleaned precious findings on the pivotal pathophysiology of collateral flow.

Collateral perfusion is widely recognized to vary across individuals in any population and exerts a dramatic effect on baseline variables including the time course of ischemic injury, stroke severity, imaging findings, and therapeutic opportunities. Similarly, collaterals have been recognized to influence recanalization, reperfusion, hemorrhagic transformation, and subsequent neurological outcomes after stroke.[8-11] Individual variability, however, has eluded simplistic algorithms based on isolated variables such as age or National Institutes of Health Stroke Scale (NIHSS) alone to predict the subsequent clinical course of a stroke patient. The recent advent of precision medicine, however, underscores the critical value of individual data such as the constellation of key clinical variables, imaging, or other biomarkers to discern influential determinants of outcome. Precision medicine utilizes detailed patient-specific data to inform clinicians regarding the expected course of an individual patient rather than the traditional extrapolation from population-based studies. Recent work on collateral perfusion has incorporated this approach to focus on predictors of clinical outcome in a given patient rather than using simplistic selection criteria across a population of heterogeneous stroke patients.

In this article, we focus on the role of collateral circulation and the potential impact on outcomes of patients in this comprehensive and authoritative series of recent stroke trials.

Collaterals are specifically defined and then analyzed within these studies, to explain potential differences in subject outcomes. The impact of collaterals is considered with respect to angiographic endpoints, and more importantly, with respect to clinical outcomes. Finally, the role of collaterals is considered in light of novel stentriever device technology and adjunctive hemodynamic interventions. Collateral lessons are gleaned from these trials, to expand consideration of overall study results and perhaps most importantly, alter ongoing and new trials in development. Such lessons regarding collateral pathophysiology are relevant beyond the realm of trials as such analyses may also guide next steps to improve the outcome of stroke patients treated daily in routine practice worldwide.

Defining Collaterals

Consideration of collateral pathophysiology requires an understanding of the specific cerebrovascular anatomical routes involved in delivering collateral perfusion to the territory at risk of ischemic injury. For any given vascular occlusion, there are potential corresponding collateral flow routes that may compensate to preserve blood flow.[12] Although all segments of the cerebral circulation, from arterial inflow routes to the microcirculation and the downstream venous channels are involved in sustaining collateral perfusion, arterial anastomoses provide alternative routes to rapidly shunt flow around an arterial occlusion. In ischemic stroke, occlusion or stenosis of an arterial segment may diminish blood flow to the downstream territory. Decreased intraluminal pressure in distal or downstream arterial branches beyond the occlusion allows collateral blood flow to arrive via adjacent territories. The potential extent of collateral blood flow may be minimal, as in end arteriolar circuits such as the lenticulostriate branches of the anterior circulation or robust enough to completely compensate for a proximal middle cerebral artery (MCA) occlusion because of rich anastomoses with neighboring cortical arterial branches. In general, two distinct systems of arterial collaterals in the brain have been described. These include the relatively short arterial segments that form the circle of Willis to instantaneously re-route arterial blood flow due to pressure alterations and the substantially more complex leptomeningeal or pial collateral routes at the surface of the cerebrum and cerebellum (Fig. 1). These small, serpiginous arterial connections between distal branches of the principal arterial territories in the brain are able to send flow in retrograde or reverse fashion into the branches downstream from an occlusion.[13] These diminutive, yet pivotal segments are barely discernible even at conventional or digital subtraction angiography but the corresponding flow patterns are readily seen (Fig. 2). The downstream resistance of the microcirculation may be increased due to evolving infarction or ischemic tissue in the parenchyma thereby offsetting the maximal vasodilatory response of the arterial circulation. At the same time, nearby venous segments allow pooling of cerebral blood volume to provide the maximal degree of oxygen and nutrients.[14]

Collaterals in acute ischemic stroke are typically measured by the extent of arterial flow at angiography but it should be remembered that such inflow routes are heavily influenced by the corresponding downstream microcirculation and venous segments. In fact, the principal scale used to date for measuring collaterals at conventional angiography, the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System, is substantially weighted by

arterial phenomena.[15] This five-point grading system has been used to score the extent of collaterals in numerous endovascular trials and studies, including those elaborated below. It is imperative that angiographic runs or injection of potential collateral routes are provided in order to properly grade collateral extent. In brief, grade 0 or 1 collaterals signifies only marginal flow and grades 3 and 4 imply varying rates but complete filling of the occluded arterial territory via collaterals. The intermediate grade 2 collaterals signifies only partial filling of the ischemic territory. Alternative angiographic collateral scales have been proposed, yet the complexity of some of these scales has limited routine use.

Noninvasive markers or features of collateral flow are abundant, notable on almost every form of diagnostic imaging from ultrasound techniques including carotid Duplex studies and transcranial Doppler ultrasonography to cross-sectional modalities such as multimodal CT and MRI. For instance, the extent of ischemic changes noted by the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) system in the presence of a known MCA occlusion may be seen as a marker of collateral flow.[16] Some stroke patients with poor collateral flow exhibit extensive ischemic changes (low ASPECTS) whereas those with more robust collaterals may reveal only marginal or no changes (high ASPECTS). On MRI, fluid-attenuated inversion recovery (FLAIR) sequences reveal slow, reverse collateral flow in arterial segments beyond an occlusion, a reliable marker for the presence of collateral flow.[17,18] Although such noninvasive markers of collateral flow have been correlated with proven collateral grade at DSA in several studies, systematic evaluation of collaterals in recent trials is largely dependent on the nature of imaging included in these studies. In the future, noninvasive collateral grading systems will be critical, as many stroke patients do not undergo DSA and ideally, even those enrolled in endovascular trials would be screened with noninvasive imaging.

Recent Trials in Acute Ischemia

Throughout the last half-century, numerous clinical trials have attempted to broaden the potential treatment options for stroke patients, culminating in a recent burst of study results in the last couple of years. Importantly, these recent formative trials have secondarily provided key findings related to collateral flow despite the ongoing elusive quest to prove that any of the studied interventions is superior to routine medical care of the stroke patient.

Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke was the first randomized controlled trial in stroke studying the effect of a device to potentially increase collateral blood flow to the brain.[2] This seminal study was actually the largest device trial in acute stroke when completed. A total of 515 acute stroke patients between 0 and 14 hours after symptom onset were randomized to partial aortic occlusion or standard care. The trial failed to meet the pre-specified primary efficacy endpoint, yet safety of this novel treatment was confirmed and the optional imaging provided some interesting findings. Specifically, patients with a favorable vascular profile on multimodal imaging were noted to benefit from this approach, suggesting that specific collateral anatomy may be key to therapeutic response with such a treatment strategy.[19] In other words, potential collaterals must be available to realize augmentation of collateral perfusion. Perhaps the most interesting secondary finding of the study relates to the relative benefit of collateral augmentation in the

older cohort of patients above 70 years of age.[20] This older subgroup of patients demonstrated a favorable response to this novel collateral treatment. Prior studies have suggested that older patients may harbor worse collaterals and therefore these SENTIS subgroup results may suggest that older patients with relatively worse collaterals may benefit the most from this alternative treatment strategy.

The SYNTHESIS Expansion trial compared the outcomes of 362 stroke patients randomized to either intravenous (IV) or intra-arterial (IA) therapy in acute ischemic stroke.[4] This relatively simple, yet pragmatic design revealed that the IA approach yielded higher recanalization rates. Despite the higher recanalization rates, the clinical outcomes were similar between the IV and IA arms. This finding once again raises the issue of whether the specific treatment approach is critical to outcomes or alternatively, it is the nature of the patients enrolled. Variability in collateral pathophysiology across patients may be an important aspect to consider in future studies.

In MR RESCUE, 118 eligible patients were randomized in a nested trial design to test the impact of imaging patterns and endovascular therapy compared with standard medical treatment.[5] This population with a mean age of 65.5 years and a mean trial enrollment of 5.5 hours exhibited a favorable penumbral pattern on multimodal CT or MRI in 58% of cases. Although this small trial also failed to demonstrate the benefit of endovascular therapy, it was noted that those with a favorable penumbral pattern on imaging showed improved outcomes, smaller infarct volumes, and attenuated infarct growth, compared with those with a nonpenumbral pattern, regardless of treatment assignment.[21] Once again, the focus moves from treatment assignment to patient-specific pathophysiology such as collateral flow patterns that determine penumbral extent.

During 2006–2012, collaterals were systematically evaluated on angiography acquired prior to endovascular therapy in the IMS III trial.[22] Adequate views of collateral circulation to the ischemic territory were available in 276/331 (83%) subjects. Collateral grade was strongly related to both recanalization of the occluded arterial segment ($P = 0.0016$) and downstream reperfusion ($P < 0.0001$). Multivariable analyses confirmed that robust angiographic collateral grade was a significant predictor of good clinical outcome (modified Rankin Score (mRs) ≤ 2) at 90 days ($P = 0.0353$), adjusted for age, history of diabetes, NIHSS strata, and ASPECTS.

In the SWIFT trial, collateral grade was strongly related to ASPECTS at baseline and at 24 hours.[7] Better collaterals were associated with less ischemic change on CT prior to treatment and the response to endovascular therapy was also strongly influenced by collaterals. Better collaterals were linked with greater reperfusion ($P = 0.019$), better median NIHSS at Day 7/ discharge ($P < 0.001$), and better Day 90 mRS ($P < 0.001$). Conversely, worse collaterals were associated with symptomatic hemorrhage ($P = 0.075$).

Similar results were noted in the TREVO2 study that proved the superiority of the novel stentriever device over standard thrombectomy.[6] The degree of collaterals was a potent predictor of outcome. Specifically, the odds ratio for good clinical outcome at Day 90 mRS was 1.85 for those with better collaterals ($P = 0.003$).

Impact of Collaterals

These analyses of collaterals in recent trials have also been replicated in single center experience with treatment of acute ischemic stroke. At UCLA, serial MRIs before and after thrombectomy has revealed important aspects of collateral perfusion. Analyses of angiographic details regarding collaterals in concert with these intensive imaging datasets has demonstrated that the degree of collateral flow in a specific patient may strongly influence their outcome. In a consecutive series of 117 MCA occlusions, collateral grade was associated with smaller strokes on baseline DWI (*b* 0.025, $P = 0.001$) and greater extent of reperfusion, with higher TICI rates (rho 0.191, $P = 0.043$). Additionally, patients with more robust collaterals had lower hemorrhagic transformation rates (rho 0.229, $P = 0.015$). Furthermore, better collaterals were associated with better clinical outcomes, measured as lower mRS at discharge (rho 0.317, $P = 0.001$). This simultaneous look at how collaterals influenced all these parameters was underscored by the finding that when patients are matched based on duration and degree of cerebral ischemia, the degree of collateral flow has a causal relationship with ultimate clinical outcome.

Clinical Outcomes Ultimately Trump Angiographic Endpoints

These multicenter and single center analyses of collateral flow confirm that collateral perfusion may be heterogeneous and vary from case to case, yet there is a dramatic effect of collaterals with respect to the time course of ischemic injury, stroke severity, imaging findings, recanalization, reperfusion, hemorrhagic transformation, and the subsequent neurological outcomes after stroke. Importantly, it is the clinical outcome and not necessarily the angiographic results after revascularization that is paramount. This point is at the center of current research in endovascular therapy, where revascularization rates have recently improved significantly, yet the clinical outcomes that would prove this therapeutic approach, remain elusive. Recent redefinitions of successful reperfusion to include lower thresholds for the TICI score with respect to the extent of perfusion restoration in the ischemic bed will only make it increasingly important to consider the effects of such reperfusion.[23,24] The degree of collateral flow at baseline may also impact tissue response in the downstream bed, whether it relates to hemorrhagic transformation or other forms of ischemia-reperfusion injury.

Stentrievers and Collaterals

The consistent relationship between the degree of collateral flow at baseline and the likelihood and extent of revascularization after treatment may change in coming years. Until now, the better collaterals have been associated with greater recanalization, yet the potent and rapid effect of stentriever device technology on opening arteries in acute stroke may change this relationship.[9] In other words, endovascular therapy with stentriever device technology may lead to greater recanalization rates, irrespective of baseline collateral flow. Stentriever technical success in revascularization may obliterate the effect of collaterals. This intriguing implication may result from higher rates of revascularization achieved with this class of endovascular devices. In other words, such devices may make it easier to achieve recanalization, due to mechanical forces at the site of occlusion and irrespective of

the influence of collaterals. Easier reperfusion of patients with poor collaterals, however, may be associated with increased dissociation of clinical and angiographic outcomes, more reperfusion injury and possibly more occurrences of hemorrhagic transformation.

Adjunctive Hemodynamics

This shift in focus toward baseline collateral pathophysiology of a patient and the individual propensity for various outcomes due to collateral status suggests that dedicated hemodynamic interventions may be warranted to improve collateral perfusion.[25] A variety of hemodynamic interventions may be applied in routine clinical practice and specifically studied in future clinical trials. For instance, dependent head positioning may improve cerebral perfusion. Hypervolemia with aggressive administration of IV fluids may increase cerebral blood volume and the resultant hemodilution may offset venous congestion. Finally, induced hypertension in select cases may be studied with respect to availability of specific collateral inflow routes. These adjunctive hemodynamic interventions require further study in context of possible alterations in intracranial pressure that may accompany subacute infarct evolution.

Collateral Lessons

This consideration of recent stroke trials from the collateral perspective yields important insight despite the extremely limited results of these negative randomized trials. These collateral lessons suggest ways to alter ongoing and new trials in development. For instance, targeting earlier and more severe stroke patients without imaging selection may result in the enrichment of a trial with subjects that have poor collateral status and therefore, worse outcomes in general. At the other extreme, selection of later and milder stroke patients with imaging identification of robust collaterals may yield only a modest therapeutic benefit for any given treatment. Overall, it is important to recognize the denominator population or extremes of collateral status that influence our selection strategies. Furthermore, consideration of collaterals underscores the need to consider how an individual patient differs with respect to a larger population. The continued focus on therapeutic impact of a specific treatment may also be misleading, as the ‘benefit’ may be inherently tied to differences in patient pathophysiology or collateral status at baseline.

Conclusions

Recent stroke trials are rife with collateral lessons that may be used to enhance our approach to treat stroke worldwide and to refine future trial design. Detailed analyses of available information on collaterals from these trials demonstrate that collaterals may actually be more influential than the choice of treatment modality or studied intervention.

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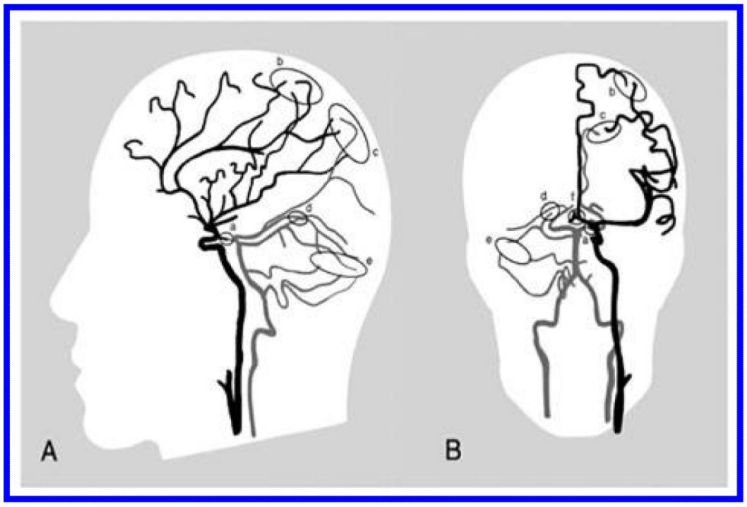

Figure 1.

Schematic of collateral anastomoses in the arterial circulation of the brain: (A) lateral; (B) frontal. Specific collateral segments include (a) the posterior communicating artery, (b) anterior-middle cerebral artery pial collaterals, (c) posterior-middle cerebral artery pial collaterals, (d) superior cerebellar arterial anastomoses, (e) connections with other cerebellar anastomoses, and (f) the anterior communicating artery. The gray shading indicates the posterior circulation and the black shading corresponds to the anterior circulation.

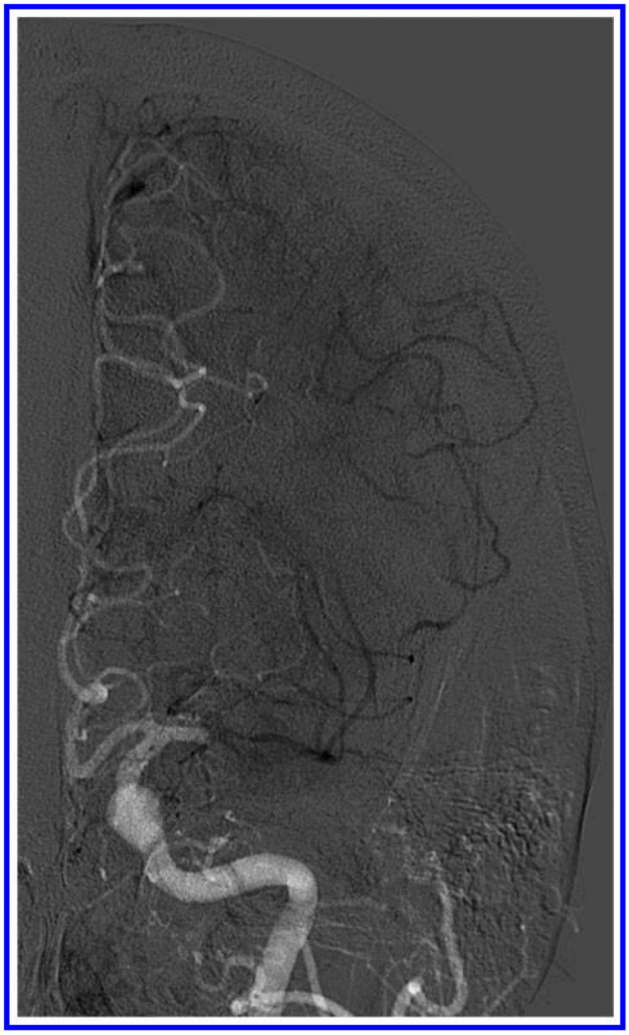

Figure 2.
Angiography of an MCA occlusion in acute ischemic stroke reveals antegrade flow (white) and retrograde leptomeningeal collateral perfusion (black).