Imaging-Based Selection of Stroke Patients: Physiology, Not Time

A review of the evidence supporting physiologic imaging versus strict time criteria in managing acute ischemic stroke.

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Traditionally, treatment for patients presenting with acute ischemic stroke (AIS) has been time based. A frequently cited study by Saver suggested that 1.9 million neurons die each minute when stroke is untreated.[1] Early studies evaluating the use of intravenous tissue plasminogen activator suggested its safety and efficacy only during the first 3 hours after symptom onset; this was later extended to 4.5 hours in subsequent analyses.[2-5] Later studies suggested that benefits of recanalization may persist as long as 6 or 8 hours after symptom onset.[6-9] Further, it is well known that better outcomes are associated with earlier and more complete revascularization.[10]

Unfortunately, many patients presenting with AIS do not meet the strict time criteria necessary for initiation of treatment. For instance, in most community settings, only about 5% of patients with AIS that would potentially be candidates for intravenous tissue plasminogen activator actually receive it.[11,12]

Over the last 2 decades, improvements in imaging capabilities with CT perfusion (CTP) imaging and diffusion-weighted MRI have transformed our ability to understand the ongoing status of infarcted versus ischemic tissues by interpreting regional blood flow and neuronal integrity.[13-15] This article reviews the available evidence supporting physiologic imaging as opposed to strict time criteria in the management of patients with AIS.

NEW GUIDELINES

Five major randomized controlled trials have now established intra-arterial therapies as the standard of care for patients presenting with anterior circulation emergent large vessel occlusions (ELVOs).[16-20] In response to these trials, the American Heart Association/American Stroke Association published updated thrombectomy guidelines in June 2015.[21] The guidelines provide a class I, level of evidence A recommendation that patients should receive endovascular therapy with a stent retriever if they have causative occlusion of the internal carotid artery or proximal middle cerebral artery (MCA), are aged ≥ 18 years, have a National Institutes of Health Stroke Scale of at least 6, and if treatment was initiated within 6 hours of symptom onset, among other criteria. Importantly, these guidelines reflect the evidence from the five trials based on trial inclusion criteria. Three of the five trials only enrolled patients with occlusions of the internal carotid artery or proximal MCA within 6 hours from symptom onset, while two trials used longer time criteria (8 and 12 hours).[16,20] Treating patients at time beyond 6 hours is a class IIB, level of evidence C recommendation.

THE IMPORTANCE OF COLLATERALS

There is an increasing body of evidence suggesting that certain patients with ELVOs may benefit from mechanical thrombectomy many hours after symptom onset. One major factor that may explain the variability in infarct progression in at-risk territories in patients with ELVO is the status of collateral blood supply. Data suggest that patients with better collateral blood supply to at-risk territories have better outcomes following mechanical thrombectomy.[22]

The relationship between collateral blood supply and outcomes is intuitive and logical. Consider a patient with an acute M1 occlusion and robust collateral supply from anterior cerebral artery and posterior cerebral artery territories. Some blood supply will be preserved to the watershed and cortical MCA regions from the anterior cerebral artery and posterior cerebral artery collaterals. At the time of presentation for thrombectomy, this patient may have core infarction, but a substantial amount of at-risk surrounding territory has yet to sustain irreparable neuronal loss. Revascularization of the occlusion may then restore ample blood supply to marginal and watershed zones, salvaging these tissues and resolving the associated neurologic deficits. In M1 occlusions, preserving these watershed territories from robust collateral supply may restore normal function of the contralateral arm or leg or language function—functions that may have been otherwise irreparably lost without sufficient collateral supply. As such, patients with robust collateral supply may benefit from revascularization many hours after acute ELVO. In contrast, patients with very poor collaterals may fail to receive any benefit from early thrombectomy if the entire at-risk territory has already infarcted. These observations suggest that time course may be less important in clinical decision making than an accurate, current, patient-specific assessment of the status of the territory at risk.

PHYSIOLOGIC IMAGING

Physiologic imaging techniques, such as CTP imaging and diffusion-weighted MRI, help guide physician decision making by capturing the integrity of the at-risk territories. At our institution, we employ noncontrast CT, CT angiography, and CTP imaging in sequence for all stroke patients. This strategy allows for the rapid evaluation for intracranial hemorrhage with noncontrast CT, with administration of intravenous thrombolytic with the patient still on the table. CT angiography and CTP images are then obtained in minutes. Mean transit time, cerebral blood flow, and cerebral blood volume maps are reconstructed from source images, and arterial input and venous outflow curves are reviewed to ensure complete data sets. We then qualitatively compare elevated mean transit time and decreased cerebral blood flow, which are markers of ischemic territory, to the regions of decreased cerebral blood volume, which indicate infarction. Using CTP imaging in this manner allows for a rapid and current understanding of which areas have already sustained infarction and which areas may be salvaged with revascularization (perfusion mismatch). Therefore, this individualized, patient-specific strategy minimizes the importance of time course in clinical decision making.

EVIDENCE FOR PHYSIOLOGIC IMAGING-BASED PATIENT SELECTION

We performed a multicenter retrospective study of 247 patients undergoing mechanical thrombectomy using CTP-based selection, regardless of time course.[23] All patients had a National Institutes of Health Stroke Scale score of at least 8 and underwent CT angiography and CTP on arrival. Patients were included if more than one-third of MCA territory completed infarction as assessed by cerebral blood volume maps or if they had > 50% salvageable penumbra in the territory at risk. The average time from the point in which the patient was seen as normal to groin puncture was 8.2 hours. One hundred seventy-three patients underwent groin puncture within 8 hours; 74 were treated after 8 hours. Interestingly, patients treated after 8 hours had no significant differences in functional outcome, revascularization, or intracranial hemorrhage compared to patients treated within 8 hours; 43% of patients treated within 8 hours had a modified Rankin score of 0 to 2 at 90 days as compared with 42% of patients treated after 8 hours.[23]

Other studies have provided further evidence supporting the utility of CTP-based selection. Abou-Chebl suggested that imaging-based selection could be performed safely, regardless of time, by showing similar outcomes after thrombectomy in patients undergoing imaging-based selection versus those treated within 6 hours of symptom onset.[24] Jovin and colleagues performed a similar multicenter retrospective study of 237 patients undergoing mechanical thrombectomy > 8 hours after symptom onset with anterior circulation ELVO. Forty-five percent of patients had good outcomes at 90 days, with 22% mortality.[25] Chalouhi and colleagues compared CTP- versus time-guided selection prior to thrombectomy in 132 patients. CTP-guided selection was associated with lower rates of mortality and intracranial hemorrhage compared to time-based selection, although outcomes did not differ.[26] Finally, two recent randomized controlled trials showed the benefit of mechanical thrombectomy in patients selected beyond 6 hours from symptom onset.[16,20] One of these trials, the ESCAPE trial, included patients with anterior circulation ELVO, small infarct cores on CT, and moderate-to-good collateral circulation on CT angiography presenting up to 12 hours after onset. Using these criteria, 53% of patients undergoing thrombectomy had good outcomes at 90 days. Although not CTP-based, the use of physiologic inclusion criteria (via collaterals) further supports a strategy that focuses less on time and more on understanding the status of the territory at risk.

We recently reviewed our experience using CTP-based selection at our institution over the last 3 years (unpublished data, 2016; submitted for publication). Of 173 consecutive patients with anterior and posterior circulation ELVO treated with a direct aspiration first pass technique, the average time from symptom onset to puncture was 7.6 hours. Fifty percent of patients had good outcomes at 90 days, as defined by a modified Rankin score of 0 to 2, with only 11% mortality. Importantly, more than half of these patients would not have been candidates for thrombectomy if the American Heart Association/American Stroke Association 6-hour time guideline was strictly followed and likely would have suffered worse outcomes without reperfusion. These data further support our strategy of using physiologic imaging as the primary determinant of candidacy for thrombectomy. We believe that restricting patient access to potentially life-saving therapies based on generalized, patient nonspecific time criteria is misguided.

This treatment strategy appears to be a gaining in popularity. There are two ongoing clinical randomized trials, POSITIVE and DAWN, which are evaluating patients beyond the currently recommended 6-hour time frame for thrombectomy. The POSITIVE and DAWN trials are randomizing patients between endovascular therapy and best medical management out to 12 and 24 hours, respectively. Although the American Heart Association/American Stroke Association guidelines support thrombectomy beyond 6 hours as a class IIB, level of evidence C recommendation, a recent survey of Society of NeuroInterventional Surgery physicians indicates that over 40% of physicians perform thrombectomy regardless of time course if imaging is favorable (unpublished data, 2016; submitted for publication).

CONCLUSION

Physiologic imaging, such as CTP, represents a means of rapidly and accurately understanding patient-specific anatomy in terms of occlusion location, infarct core, and penumbra. Using CTP-based patient selection for thrombectomy, our group and others have demonstrated excellent clinical outcomes regardless of time course. Subjecting highly variable patients to generalized time criteria may erroneously exclude patients from treatment when they would potentially receive significant benefit from endovascular revascularization. Therefore, we support a strategy of CTP-based patient selection for thrombectomy. ■

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