Ischemic Stroke Tissue-Window in the New Era of Endovascular Treatment

Michael D. Hill, MD, MSc; Mayank Goyal, MD; Andrew M. Demchuk, MD; Marc Fisher, MD, PhD

Ischemic stroke is a dynamic process of infarct expansion that varies as a function of time, residual blood flow, and other factors. Time can be measured easily but is an imprecise surrogate marker for brain physiology after stroke onset. After sudden intracranial artery occlusion, progression to brain infarction occurs quickly and on average, reperfusion therapies are not effective after several hours.1–4 However, there is enough variance in the rate of infarct development that experienced stroke physicians can identify individual cases using brain imaging where reperfusion will be useful in later time windows after stroke onset. This imaging selective approach has proven effective in recent randomized controlled trials.5–7 Furthermore, the opposite situation also occurs, where the infarction is completed in a short time after stroke onset and reperfusion is futile despite early presentation to medical attention and rapid treatment. The use of time as a surrogate marker for brain physiology has historical precedent with a similar approach having been used in cardiology and in the trials of intravenous thrombolysis for stroke. Time’s advantage is that it is easily and definitively measurable resulting in relative ease of widespread use for guidelines and performance measurement.

Brain imaging has advanced and is the most readily available and valuable biomarker for stroke. We do not have additional tools akin to those available to our colleagues in Cardiology. The brain equivalents of the ECG and serum troponin levels have yet to be discovered. However, brain imaging in acute ischemic stroke has many advantages over serum markers because primary intracranial hemorrhage can be readily identified and an estimation of the extent of the ischemic core and penumbra provided. Because the brain is immobile in real time, detailed noninvasive imaging of the brain parenchyma, neurovascular anatomy, and perfusion is possible and relatively easy to obtain.

The recent endovascular treatment trials provide proof of efficacy of reperfusion.5–8 The principle of fast reperfusion is now firmly established. In each of these trials, eligibility criteria were deliberate and specific. This therapy only applies to an imaging-defined subset of patients with ischemic stroke; neurovascular imaging was the key physiological marker in each of these trials. In 3 of the 4 trials, a small ischemic core as identified by the Alberta Stroke Program Early CT Score (ASPECTS) on plain computed tomography (CT) or CT perfusion was required for inclusion after CT angiography (CTA) was used to demonstrate the presence of a large vessel occlusion amenable to endovascular therapy. In the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial, multiphase CTA was also used to evaluate the extent of collateral flow and only patients with good or excellent collaterals were included. In each case, the key time point is at imaging because for both medical and endovascular treatments, the decisions about treatment take place immediately after neurovascular imaging.

We propose a new conception of interval times in stroke treatment with imaging at the center.

The full treatment time window for stroke is defined by the stroke onset to successful reperfusion time, and not by an arbitrary 4.5-hour or 6-hour or even 12-hour time window after onset. We recommend dividing this time window into 2 epochs with imaging time as the dividing instrument. The first epoch is the stroke-onset-to-imaging time. Imaging time is defined as the time of the first slice of the noncontrast CT scan, or less commonly if magnetic resonance is used, the time of first slice of the localizer image (Figure). The stroke-onset-to-imaging time defines the probability of imaging-defined eligibility for endovascular or reperfusion therapies. The second epoch is the imaging-to-reperfusion time. Reperfusion time is defined as the time from the beginning of imaging to the first
evidence of reflow into the affected vascular territory, with the presumption that good final reperfusion (Thrombolysis in Cerebral Ischemia 2b/3) will follow (Figure). The imaging-to-reperfusion time epoch only applies to eligible patients and will define the probability of a good outcome among treated patients who have evidence of an ischemic core that is not too large. The probability of successful treatment at any given time in each epoch will be modified by patient clinical/laboratory characteristics, imaging results, and reperfusion success.

Conceptualizing the problem of acute ischemic stroke treatment in this manner is helpful because it immediately points toward solutions. From a population perspective, getting the right patient to the right hospital with the right team faster will result in a greater number of patients with a favorable imaging profile who are therefore eligible for treatment. Regional decisions to redefine the prehospital phase of triaging major ischemic stroke to the correct center will be facilitated by taking this perspective. The denominator fallacy, inherent in hospital- or center-based report cards on treatment success, is well explained epidemiologically by taking this perspective. By including the door-to-imaging time in this epoch, the solution of taking patients directly to CT by the paramedics and bypassing the Emergency room becomes self-evident. Similarly, the newer and more aggressive approach to early imaging is the availability of an ambulance equipped with a CT scanner, but this approach is currently only occurring in a few selected locales and will likely remain limited. The principle of merging the early in-hospital and prehospital phases of care into one that ends with the imaging time means rethinking the roles of healthcare providers and workflow. Finally, we can begin to consider patients with untreated stroke-on-awakening as eligible for therapy, not based on their conservatively presumed onset time defined by the last time known well, but instead by the tissue-window defined by their brain imaging. Despite the potential of this approach, effective ischemic stroke treatment for the population is going to require the shortest possible onset-to-reperfusion time.

Among imaging-defined patients eligible for treatment, a focus on shortening imaging-to-reperfusion time would increase the likelihood of good outcomes in these patients. Optimization strategies have been published. We recommend using the first slice of the imaging study as the starting point, because in doing so we encourage the use of fast imaging paradigms that provide the minimum discriminatory information necessary for decision-making. We encourage the development of parallel thinking in angiography suite processing and patient management and in the small proportion who need it, anesthesia management focusing on minimizing delays to reperfusion.

Finally, we would like to emphasize that the key reason to split the stroke onset to reperfusion time into 2 epochs in this manner is that the clinical decision-making point is immediately after imaging, exactly because imaging is a useful biomarker in ischemic stroke as was documented in the recent endovascular trials. Imaging is the brain physiology snap shot in time that we can use to define eligibility for therapy. Time will always remain a reasonable surrogate for the pathophysiology because empirically, patients with acute ischemic stroke are statistically likely to have favorable imaging profiles at early time points and they will also do better if reperfusion is faster. As time elapses the proportion of eligible patients asymptotically approaches zero, but there will likely be subsets of patients that can be treated in late time windows extended out to 24 hours or longer. Imaging defines the tissue window by providing an in vivo assessment of the extent of irreversible ischemic tissue injury.

Innovation to increase the proportion of eligibility patients could be defined by a surrogate outcome of imaging eligibility, meaning that the volume of penumbra could be used as outcome for early phase trials. Novel therapeutic agents—neuroprotectants—to freeze the core could be assessed for preliminary efficacy by imaging the penumbra. A successful agent would result in a smaller core at all times from onset to reperfusion, and theoretically minimize damage and aid recovery. Such an approach would be particularly relevant for patient who will have long transport times from their communities or from outlying hospitals to the tertiary center. Assessing these compounds or strategies using imaging would...
be natural evolution of this recognition of stroke imaging as the key determinant of eligibility for treatment.

An immediate challenge for the stroke and imaging community is to work out how to draw the line on what imaging eligibility means. Much of this debate can be informed by the recent randomized trials. It is clear that we can select patients with high specificity for successful treatment using multimodal imaging. However, given the large effect size observed in recent trials, we may have been overly specific. We have to determine the best balance of sensitivity and specificity, whereas simultaneously maximizing speed. Assessment of the intracranial collaterals is similar to assessment of the perfusion abnormality. There is high concordance between the degree of the perfusion deficit and the status of collaterals on CTA. Thus, although some recent trials used CTA only to assess collaterals and others used CTP to assess for a penumbral pattern, fundamentally both techniques are measuring the underlying blood flow. A focus on the principles of blocked artery and adequate collaterals/penumbral tissue, knowing that each of these 3 are highly inter-related, will likely lead to the right imaging schema for determining treatment eligibility in the shortest amount of time.

We can and should begin to move away from rigid decision-making based on time windows. In doing so, we must not dismiss the critically important clinical information that is obtained and observed in the onset-to-imaging epoch. This must be incorporated into the clinical decision-making paradigm that culminates with imaging interpretation. The pre-hospital arena is open for ideas on how to improve onset to imaging (at the mothership hospital capable of endovascular treatment) times and in hospital our stroke and neurointervention teams must move as one to improve imaging to reperfusion times. A new era of acute ischemic stroke therapy is treatment) times and in hospital our stroke and neurointervention teams must move as one to improve imaging to reperfusion times. A new era of acute ischemic stroke therapy is dawnning and to maximally benefit as many patients as possible time from onset-to-imaging and imaging-to-reperfusion must be as used as efficiently as possible.

Disclosures

Dr Hill, Dr Goyal, and Dr Demchuk were coprincipal investigators of the ESCAPE trial. The ESCAPE was sponsored in part by a grant to the University of Calgary from Covidien/Medtronic. Dr Fischer is the current editor of Stroke. Dr Demchuk has received honouraria from Medtronic. Dr Hill has an ownership position (stock) in Calgary Scientific Inc, an imaging software company.

References


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New Era of Endovascular Treatment

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Ischemic stroke is a dynamic process that is time-dependent. The brain's response to ischemia is affected by both the time of ischemia and the collateral blood flow. The tissue-timing window is a period during which reperfusion therapy may be beneficial. The tissue-timing window is defined as the time from the onset of symptoms to the time when the brain has been adequately reperfused. This window is critical for determining which patients are candidates for reperfusion therapy. The tissue-timing window is defined as the time from the onset of symptoms to the time when the brain has been adequately reperfused. This window is critical for determining which patients are candidates for reperfusion therapy.

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공명을 사용한 경우 localizer 영상의 첫 단면영상의 시간으로 정의한다(Figure). 뇌졸중 발생에서 영상촬영까지의 시간은 영상으로 정의된 적합성의 가능성을 결정한다. 두 번째 시기는 영상촬영에서 재관류까지의 시간이다. 재관류 시간은 영상촬영을 시작한 시간에서 최종적으로 양호한 재관류(Thrombolysis in Cerebral Ischemia 2b/3)가 될 것이라는 추정하에 해당 혈관영역에 재관류의 첫 증가가 나타난 때까지의 시간으로 정의한다(Figure). 영상촬영에서 재관류까지의 시간은 치료에 적합하다고 결정한 환자에서 해당하며 허혈 중성이 너무 크지 않다는 증가가 있는 환자를 치료 했을 때 좋은 결과를 얻을 가능성을 결정한 것이다. 각 시간대의 특정 시간에서 성공적 치료의 가능성을 환자 의 임상적/검사적 특성, 영상결과, 재관류 성공 등에 따라 다를 수 있다.

급성혈뇌졸중 치료의 문제점을 이런 식으로 개요화하는 것은 해결책 찾는데 도움이 되므로 유용하다. 지역사회의 관점에서 볼 때 적합한 환자를 적합한 의료진이 있는 적합한병원으로 빠르게 보내는 것은 치료에 적합한 영상소견을 가지는 환자의 수를 늘릴 것이다. 이 관점을 차용하는 것은 혈관조절에서 중요하다는 이유로 기존의 의료기관으로 이송하기 위한 분류를 재정립하는 것을 촉진시킬 수 있다. 이는 지속적 관리에 대한 병원 기반의 성적표에 내재하는 분모 오류(denominator fallacy)를 역학적으로 잘 설명한다.12 응급실 도착에서 영상촬영까지의 시간을 이 시기에 포함하면 구급대가 응급실을 거치지 않고 환자를 CT로 데려가도록 하는 해결책이 자명해진다. 마찬가지로 영상촬영에서 재관류까지의 시간은 치료에 적합한 환자를 올바르게 조치하는데 유용한 방법이다.13 초기의 병원내 및 병원전단계를 하나로 통합한 방식은 보건관리자에게 보다 기대할 수 있는 결과를 보장할 수 있다. 마지막으로 우리는 증상이 없었던 마지막 시각을 보수적으로 추정하는 발병 시각에 의존하지 않고 능상적으로 규정하는 조직-시간대를 이용함으로써 목적자가 없고 발생 시점이 불분명한 환자나 기상 시 증상을 알게 된 뇌졸중 환자들이 치료에 적합한지 판단할 수 있을 것이다. 이런 점에의한 잠재적 장점으로 병원인력에 대한 효과적인 혈관조절의 필요성을 위해서는 발생에서 재관류까지의 시간을 총대한 단축하는 것이 필요하다.

영상감상사 시점에 적합한 환자들은 영상촬영에서 재관류까지의 시간을 단축하는 것이 중요하다는 결론이 나을 가능성을 높일 수 있다.14 우리는 영상감상의 첫 슬라이스를 시각 점으로 사용할 것을 권장하는데 이렇게 함으로써 결론에 필요한 최소한의 정보만을 제공하는 데 동영상의 장점을 장려할 수 있기 때문이다. 우리는 혈관조절에서의 작업과 환자 치료 그리고 이후의 병원내 치료에서 재관류가 지체되지 않도록 노력하면서 마치 치료를 하는 데 있어서 병원내 치료를 개발할 것을 권장한다.

마지막으로 뇌졸중 발생에서 재관류까지 걸리는 시간을 두 개의 시기에 분리하는 중요한 이유는 최근 혈관조절사시의 과정에서 중요한 영상소견의 유용성이나 재관류의 중요성을 강조하고 있다. 영상소견은 치료에 적합한지를 판단하는데 유용한 정보이다.12 영상소견은 치료에 적합한지 판단하는 데에 있어서 발생에서 재관류까지의 시간을 단축하는 데에 있어서 병원내 치료의 역할을 강조한다. 영상소견은 치료에 적합한지를 판단하는데 유용한 정보이다.12 영상소견은 치료에 적합한지 판단하는 데에 있어서 발생에서 재관류까지의 시간을 단축하는 데에 있어서 병원내 치료의 역할을 강조한다.

Figure. Interval times in acute ischemic stroke. Epoch 1 represents time from stroke onset to first imaging. As time elapses, the proportion of treatment-eligible patients will decline because irreversible brain infarction will occur. The actual shape of the line remains to be determined. Epoch 2 represents imaging to reperfusion time. Similarly, as time elapses, the proportion of patients who do well will decline asymptotically to zero. The shape of this relationship is better known and is relatively linear. We note that the shape of the curve in both Epoch 1 and Epoch 2 are likely to show high inter-individual variance. This has important implications because if the initial slope in Epoch 1 for a specific group of patients is relatively shallow, this would identify a group that could be transported over longer distances and remain eligible for endovascular treatment. Research is strongly encouraged to define and better understand the shape of the curve in both time epochs.
적합한 환자 비율을 높이기 위한 해선은 영상검사 상 적합성을 결과의 대리표자로 사용하는 것으로 확인할 수 있는데, 이는 반응영의 크기가 급성기 치료의 결과로 사용될 수 있음을 의미한다. 혈관중상의 증가를 막기 위한 새로운 치료약물—신경보호제(neuroprotectant)—의 효능은 반응영 영상을 이용하여 예비 연구의 효과 평가에 사용될 수 있다. 

뇌졸중 및 뇌졸중의학가가 당장 당면한 숙제는 영상학적 적합성 이 무엇이냐에 대한 그림을 어떻게 그리는가이다. 최근의 무작위시험들이 이런 논란의 많은 부분을 인도한다.

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최적의 영상 절차를 만들 수 있는 것은 이 세 가지가 서로 연관되어 있다는 것을 이해한다는 것이다. 막힌 혈관과 충분한 곁순환 및 반음영 조직의 원칙에 집중했지만 본질적으로 두 가지 기법은 모두 혈류를 측정하는 것이었다. 최근의 몇 개의 임상시험들은 곁순환을 평가하기 위해서 CTP를 이용했고 나머지는 반음영 상태를 평가하기 위해서 CTA를 이용했다. 최근의 몇 개의 임상시험들은 곁순환을 평가하기 위해서 CTP를 이용했고 나머지는 반음영 상태를 평가하기 위해서 CTA를 이용했다. 최근의 몇 개의 임상시험들은 곁순환을 평가하기 위해서 CTP를 이용했고 나머지는 반음영 상태를 평가하기 위해서 CTA를 이용했다.

Disclosures

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