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 intracerebral 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.5,8–11 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 unwitnessed and therefore unknown onset or 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 penumbra 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 dawning 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

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새로운 혈관내치료 시대의 혈혈뇌졸중 조직시간대

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혈혈뇌졸중은 시간, 잔여혈류 및 다른 인자들에 따라 경색 확장이 달라지는 역동적 과정이다. 시간은 쉽게 측정할 수 있지만 뇌졸중 발생 이후의 뇌의 생리 반응에는 부정확한 대리지표이다. 두개내동맥이 갑자기 막히면 뇌경색으로의 진행은 급속히 일어나며 몇 시간만 지나도 재관류 치료는 효과가 없다. 그러나 경색의 진행 속도는 상당한 범이 있어서 속련된 뇌졸중 전문의는 뇌영상을 이용하여 뇌졸중 발생 이후 시간이 별다른 후에도 재관류 치료가 유용할 수 있는 환자를 찾아낼 수 있다. 이런 영상을 이용한 선별적인 접근법은 최근의 무작위대조시험에서 효과가 입증되었다. 또한 뇌졸중 발병 후 짧은 시간만에 완전 경색이 되어 의료기관에 빨리 내원하여 신속한 치료를 받아도 재관류가 효과 없는 환자의 경우도 있을 수 있다. 시간을 뇌의 생리에 대한 대리지표로 사용하는 것은 역사적인 선례를 가지고 있다. 뇌혈관질환에서 비슷한 접근법을 사용하였는데, 시간의 이점은 쉽고 명확하게 측정할 수 있어 임상진료지침과 performance measurement에서 비교적 쉽게 널리 사용할 수 있다는 점이다.

뇌영상은 계속 발전하고 가장 쉽게 접근할 수 있으며 가장 유용한 뇌졸중의 생물표지자이다. 우리는 심장학의 동료들이 사용하는 도구와 비슷한 추가적인 도구를 가지고 있지 않다. 치료의 성공은 뇌징후로의 발달과 뇌혈관질환의 병리학적 이환에 따라 발생할 수 있는 점을 개발해야 한다. 그러나 급성혈혈뇌졸중에서의 뇌영상은 뇌혈관질환의 병리학적 이환을 쉽게 구분할 수 있고 허혈 중심의 범위를 추정할 수 있다는 점에서 혈관내치료 시대의 새로운 구준을 제시한다.

뇌혈관질환에 대한 치료 시간대는 뇌혈관질환의 발생에 대한 임상적, 관리학적 지표로 정의하며 입지로 정한 발병로부터 4.5시간 이내 6시간 또는 12시간 등의 단기적 시간대로 정의하지 아니한다. 우리는 지금까지 이 시간대를 두 개의 시간대로 나누는 것을 권고한다. 첫 시간은 뇌혈관질환의 발생과 혈관내치료 시대의 차이를 보여준다. 뇌혈관질환은 조명층에서 CT Scan의 첫 단변형성의 시간 또는 두 시간으로는 적합하지 않다.
공명을 사용한 경우 "localizer 영상의 단면영상의 시간으로 정의한다\(^{1}\). 뇌졸중 발생에서 영상활성까지의 시간은 영상 활성 후에 정의된 적합성의 가능성을 결정한다. 두 번째 단계는 영상활성에서 재관류까지의 시간이다. 재관류 시간은 영상활성을 시작한 시간에서 최종적으로 양호한 재관류\(^{2}\)가 될 경우 이 시간으로 정의한다 (Figure). 영상촬영에서 재관류까지의 시간은 치료에 적합하다고 결정한 화자만이 해당하며 허혈 중심이 너무 크지 않다는 증거가 있는 화자를 치료했을 때 좋은 결과를 얻을 가능성을 결정한 것이다. 각 시간대의 특정 시간 내에서 성공적 치료의 가능성은 화자의 임상적/검사적 특성, 영상결과, 재관류 성공 등에 따라 다를 수 있다.

급성혈뇌졸중 치료의 문제점을 이런 식으로 개념화하는 것은 해결책을 찾는데 도움이 되므로 유용하다. 지역사회의 관점에서 볼 때 적합한 화자를 적합한 의료진이 있는 적합한 병원으로 빨리 보내는 것은 치료에 적합한 환자 조건을 갖는 화자의 수를 늘리는 것이다. 이 관점은 재관류하는 병원 전체에서 증상 허혈뇌졸중 화자로 적합한 의료기관으로 이송하기 위한 분류를 재정립하는 것을 촉진시킬 수 있다. 이런 관점은 치료 성공에 대한 병원 기반의 성적표에 대한 분모 오류\(^{12}\)를 역학적으로 잘 설명한다. 응급실 도착에서 영상촬영까지의 시간을 이 시기에 포함하면 구급대가 응급실을 치료하지 않고 급하게 환자를 CT로 데려가도록 하는 해결책이 자명해진다. 마찬가지로 영상을 빨리 찍어내는 신파라다임은 영상활성을 시작한 시간의 기준으로 적합한 병원의 전단계를 개발하여 병원에 전달할 수 있는 방법을 개발한다. 그리고 마지막 단계로는 영상이 허혈을 가진 조직의 치료에 적합한지 판단하는 절차가 필요하다. 따라서는 발생에서 재관류까지의 시간을 공정하게 결정하는 것이 필요하다.

영상감사상 치료에 적합한 화자들은 영상활성에서 재관류까지의 시간을 단축하는 것에 집중하는 좋은 결과가 나올 가능성을 높일 수 있다. \(^{14}\) 우리는 영상감사의 첫 슬라이스를 시작 점으로 사용할 것을 권장하는데 이렇게 함으로써 환자가 허혈뇌졸중 화자로 간주하는 때 영상화학적 인자의 사용을 장려할 수 있기 때문이다. 우리는 영상화학적 인자의 사용에 따라 적합한 치료를 하는 데 있어서 병원 성적표를 개발할 수 있다. 마지막으로 뇌졸중 발생에서 재관류까지 걸리는 시간은 두 개의 시간으로 분리하는 중요한 이유는 최근의 혈관내치료시험에서 증명되었듯이 영상은 허혈뇌졸중 화자에서 유효한 생물표지자로, 임상적 결정 시점은 영상활성 직후이어야 함을 강조하고 싶다. 영상은 치료에 적합한 화자를 판단하는데 우리가 사용할 수 있는, 뇌생리용 신파라다임으로 확대된 영상소견이다. 경험적으로 급성혈뇌졸중 화자는 빨리 영상을 할수록 유호한 영상소견을 가질 통계적인 가능성이 높으며 재관류가 빨라질수록 예후가 더 좋을 가능성도 높기 때문에 영상소견이 악화될 수 있다. 시간이 지남에 따라 치료에 적합한 화자의 비율이 점차적으로 0에 접근하지만 24시간 또는 그보다 더 늦은 시간대에 도 치료할 수 있는 일부의 화자가 있을 수 있다. 영상은 비가역적 허혈조직손상의 정도를 생명 내에서 평가하여 조직-시간대를 결정한다.

**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 해소는 영상검사 상 적합성을 결과의 대표에 포함하여 사용하는 것으로 확인할 수 있는데, 이는 반응형의 감각에 급성기 치료의 결과로 사용될 수 있음을 의미한다. 허혈 중심의 증가를 막기 위한 새로운 치료약물—신경보호제(neuroprotectant)—의 효능은 반응형 영상을 이용하여 예비 연구의 효과 평가에 사용될 수 있다. 성공적인 약물은 발병에서 재관류 사이의 시간 중 어느 시점에서도 중심을 작게 할 수 있을 것이며 이론적으로 손상의 최소화와 회복을 도울 수 있을 것이다. 그로 전환법은 지역사회 병원이나 외래의 병원에서 삼가 의료기관으로 이용하는 시간이 긴 환자들에게 더욱 타당하다는 것이다. 영상을 이용해서 이런 약물이나 전략을 평가하는 것은 원리 중심성과 치료적합성에 대한 중요한 결정요인으로 인식하는 단계에서 자연스럽게 한 단계 더 나아가는 것이 될 것이다.

뇌졸중 및 영상의학계가 당장 당면한 숙제는 영상학적 적합성의 무엇이냐에 대한 그림을 어떻게 그리는 것이다. 최근의 무작위시험들은 이러한 논란의 많은 부분을 인도한다. 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.

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Key Words: brain infarction ■ neuroimaging ■ reperfusion ■ stroke ■ thrombectomy