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.²⁻⁷ 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.⁵⁻¹¹ 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 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 prehospital arena is open for ideas on how to improve onset to imaging interpretation. The prehospital arena is open for ideas on how to improve onset to imaging interpretation. In doing so, we must not dismiss the critically important clinical information that is observed and obtained in the onset-to-imaging epoch. This must be incorporated into the clinical decision-making paradigm that culminates with imaging interpretation. The prehospital 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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References


Key Words: brain infarction ▪ neuroimaging ▪ stroke reperfusion ▪ stroke thrombectomy.
Ischemic Stroke Tissue-Window in the New Era of Endovascular Treatment
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혈관뇌졸중은 시간, 잔여혈류 및 다른 인자들에 따라 경색 확장이 달라지는 역동적 과정이다. 시간은 쉽게 측정할 수 있지만 뇌졸중 발병 이후의 뇌의 생리 반응에는 부정확한 대리지표이다. 두개내동맥이 갑자기 막히면 뇌경색으로의 진행은 급속히 일어나며 몇 시간만 지나도 재관류 치료는 효과가 없다. 그러나 경색의 진행 속도에는 상당한 범위가 있어서 속련된 뇌졸중 전문의는 뇌영상을 이용하여 뇌졸중 발생 이후 시간이 어느 정도 지난 후에도 재관류 치료가 유용할 수 있는 환자를 찾아낼 수 있다. 이는 영상을 이용한 선별적인 접근법은 최근의 무작위대조시험에서 입증되었다. 또한 뇌졸중 발생 후 짧은 시간만에 완전 경색이 되어 의료기관에 빨리 내원하여 신속한 치료를 받아도 재관류가 효과가 없는 경우도 있을 수 있다. 시간을 뇌의 생리에 대한 대리지표로 사용하는 것은 전신적인 접근법이ので서 비슷한 접근법을 사용하였다. 시간의 이점은 쉽게 측정할 수 있어 임상진료지침과 performance measurement에서 비교적 쉽게 널리 사용할 수 있다는 점이다.

뇌영상은 계속 발전하고 가장 쉽게 접근할 수 있는 뇌졸중의 생물표지자이다. 우리는 심장학의 동료들이 사용하는 도구와 비슷한 추가적인 도구를 가지고 있지 않다. 여러 흥미로운 성과를 보여준 CTA와 MRA 등에 대한 다양한 접근법을 사용하였다. 시간이 경과하는 노력을 통해서도 비슷한 접근법을 사용하였다. 시간의 이점은 쉽게 측정할 수 있어 임상진료지침과 performance measurement에서 비교적 쉽게 널리 사용할 수 있다는 점이다.

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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 영상활영 영역에 재관류의 첫 증거가 나타난 때까지의 시간으로 정의한다(Figure). 영상활영에서 재관류까지의 시기는 영상에 적합하다고 결정한 환자애가 해당하며 허혈 중심이 너무 크지 않다는 증거가 있는 환자를 치료했을 때 좋은 결과를 얻을 가능성을 결정한 것이다. 각 시간대의 특정 시간에서 성공적 치료의 가능성은 환자에 의한적/검사적 특성, 영상결과, 재관류 성공 등에 따라 다를 수 있다.

급성혈뇌졸중 치료의 문제점은 이런 식으로 개념화하는 것이다. 해결책을 찾는데 도움이 되므로 유용하다. 지역사회와의 관계에서 적합한 환자를 적합한 의료진이 있는 적합한 병원으로 빨리 보내는 것은 치료에 적합한 영상 소견을 가지는 환자의 수를 늘릴 것이다. 이 관점은 치료하는 병원의 선택에 대한 분모 오류(denominator fallacy)를 역학적으로 잘 설명한다.12 응급실 도착에서 영상촬영까지의 시간을 이 시기에 포함하면 구급대가 응급실을 거치지 않고 곧장 환자를 CT로 데려가는 해결책이 자명해진다. 마찬가지로 영상을 빠르게 촬영하게 하는 더 새롭고 더 공격적인 방식은 구급차에 CT 촬영기를 장착하는 것이나 이런 방법은 현재 몇몇 지역에서 시도 중이며 앞으로도 확산되기 어려울 것이다.13 초기의 병원내 및 병원전단계를 적합한 영상시간으로 하는 방식은 보건관리제공자의 역할과 업무방식에 대한 재고를 의미한다. 마지막으로 우리는 증상이 없었던 마지막 시간을 이용하여 보수적으로 추정하는 발생 시각에 의존하지 않고 뇌영상으로 정정하는 조치–시간대를 이용함으로서 목적자가 없고 발생 시각이 분명한 환자나 기상 시 증상을 알게 된 뇌졸중 환자들이 치료에 적합한지 판단할 수 있을 것이다. 이런 접근법의 장점에도 불구하고 지역인구에 대한 효과적인 혈관뇌졸중 치료를 위해서는 발생에서 재관류까지의 시간을 최대한 단축하는 것이 필요하다.

영상감사상 치료에 적합한 환자들은 영상활영에서 재관류까지 걸리는 시간을 단축하는 것에 집중하는 좋은 결과가 나올 가능성을 높일 수 있다.14 우리는 영상감사의 첫 슬라이스를 시각점으로 사용할 것을 권고하는데 이렇게 함으로써 결정에 필요한 최소한의 정보만을 제공하는 빠른 영상패러다임의 사용을 장려할 수 있기 때문이다. 우리는 영상프로세스의 작업과 환자 치료 그리고 마취가 필요한 소수의 환자에서 재관류가 지체되지 않도록 노력하면서 마취 치료를 하는 데 있어서 병렬적인 사고 방식 개발을 권장한다.

마지막으로 뇌졸중 발생에서 재관류까지 걸리는 시간을 두 개의 시기에 분리하는 중요한 이유는 최근의 혈관내치료시험에서 증명되었듯이 영상은 혈관뇌졸중에서 유용한 생물표지자이므로 임상적 결정 시점은 영상활영 직후이어야 함을 강조하고 싶다. 영상은 치료에 적합한지를 판단하는데 우리가 사용할 수 있는, 뇌뇌졸중 치료의 신시기로 활용할 수 있는 스냅사진이다. 경험적으로 급성혈뇌졸중 환자는 빨리 영상을 할수록 양호한 영상소견을 가질 가능성이 높고 재관류가 빠를수록 예후가 더 좋을 가능성이 높기에 시간은 앞으로도 병태생리에 대한 핵심적 often의 현장에서 중요한 역할을 한다. 시간이 지나면 치료에 적합한 환자의 비율은 점근적으로 0에 접근하지만 24시간 또는 그보다 더 늦은 시간대에도 치료할 수 있는 일부의 환자가 있을 수 있다. 영상은 비가역적인 허혈조직 손상의 정도를 생체 내에서 평가하여 조직–시간대를 규정한다.

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.13 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.
Adapting the time window to a tight window for the benefit of larger-scale data analysis and treatment analysis, we may find the optimal window for each case. However, this concept of time has been shown to improve outcomes in many patients to the maximum benefit. For example, in acute ischemic stroke treatment, new paradigms are emerging, and the latest guidelines are focusing on improving the time from diagnosis to reperfusion. It is important to understand that while imaging guidance can be used to improve outcomes, it must be used appropriately to avoid complications.

References


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