

equals 19, times 4.3 equals 82 mm, which is the width of our columns (go ahead and try it).

“Marginalia” refers to notes, comments, and other writings on page margins. Notations by famous persons can add value to a book while those that you or I create probably will not. Computer programs such as Microsoft Word allow comments on the margins of pages and some even allow Web-sharing of this type of marginalia (called “shared annotations”). E-readers such as Amazon’s Kindle are capable of allowing marginalia and other annotations and go further by permitting you to share them with other readers via social networking programs. E-reader pages reproduce basically all aspects of paper, albeit at a higher cost and with increased difficulties when it comes down to marginalia (it is easier to scribble on the margin of a paper page than to type there by using the tiny physical or virtual keyboard found in E-readers).

E-readers try to give readers the same experience as print. (I often ask myself why. If I buy an E-reader, it is to have a completely different experience; if not, why not buy the book?) Of course, with digital books, space is no longer a consideration as it was with print and most have variable page and font sizes. Adobe PDFs also imitate the print experience as their software allows you to “leaf” through a document that simulates printed pages. Leafing is a feature found on the iPad (Apple, Cupertino, California) (something that I find anachronous and bothersome while I have heard others say it is cute). Your computer screen is basically a vertical never-ending virtual scroll in which the length of the text matters little. Paradoxically, as the capacity to store and display the written word increases, our attention spans decrease and make it impossible to take full advantage of these media.

The evolution of the page seems to have closed the circle: from clay tablets to computer tablets (witness the iPad), from ancient scrolls to scroll computer reading, from parchment pages to E-paper and E-readers. The capacity of the page no longer determines its contents. Margins are becoming superfluous as small screens must be completely filled with text to take maximum advantage of their viewing areas. Marginalia is no longer private with E-readers. I am not a fanatic of a specific medium, but as long as you are reading something, it will be contained within pages.

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EDITORIAL

Dramatically Reducing Imaging-to-Recanalization Time in Acute Ischemic Stroke: Making Choices

In the treatment of acute stroke, we are reasonably sure of certain issues. These are the following:

1) Dead brain is dead brain. Infarcted brain tissue cannot be salvaged.¹ So far, no attempts at neuroprotection have been successful.² These issues are relevant from the perspective of the detection of irreversibly damaged brain tissue. Various imaging methods have been shown to be reasonably good at detecting dead tissue (DWI,³ Alberta Stroke Program Early CT Score [ASPECTS] on NCCT,⁴ low CBV or very low CBF on CT/MR perfusion,⁵ and so forth). Of these, DWI is the most sensitive and specific, though not perfect.⁶

2) Hyperacute stroke is a dynamic process. In the absence of recanalization, it has been well demonstrated that for most strokes, the ischemic core grows to incorporate the penumbra with time.⁷ While exuberant collaterals might prolong the penumbral tissue survival, our ability to sustain these with medical intervention has not been successful.⁸

3) Recanalization helps. This has been the basis of not only IV thrombolytic therapy but also mechanical intra-arterial (IA) approaches.⁹

4) No form of intervention, chemical or mechanical, is without risk.¹⁰⁻¹²

5) Imaging is a snapshot in time of a dynamic process.

On the other hand, there are issues that we do not fully understand. The key ones are the following:

1) What is the rate of infarct progression? At what rate does penumbra turn into core? Which factors influence this rate? How much time does one have before recanalization becomes futile?

2) Do collaterals evolve with time and to what extent? Changes in the length and diameter of collaterals have been demonstrated in animal models, but this process is less well-understood in humans.

3) What is the role of spreading depression?¹³ This loss of electrical activity and the associated biochemical and structural alterations, classically described in migraine, may have a role in the ischemic core progression.¹⁴

4) How does selective vulnerability of neuronal tissue influence patient outcome? It is well-known that certain brain regions are more susceptible to ischemia than others, but the mechanisms underlying this vulnerability and their effect on infarct progression and patient outcome are not understood.¹⁵

5) What is the best measure of penumbra? This question assumes that the tissue measured conforms to the penumbra definition: nonfunctioning tissue that is currently viable but will die unless blood supply is resumed quickly (please note that in this definition, there is no mention of how much time there is before penumbra dies).¹⁶

Other relevant issues are related to the imaging technique that is the best, most appropriate, most widely available, and easiest to interpret. At one end of the spectrum is NCCT,

which is sufficient for triage and decision-making and has been extensively studied.¹⁷ Most large randomized controlled trials, including the National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group,¹⁸ European Cooperative Acute Stroke Study,¹⁹ and International Management of Stroke-III,²⁰ used NCCT. At the other end of the spectrum are DWI, perfusion, and MRA.⁶ MR imaging has been used in a number of trials including the Desmoteplase in Acute Ischemic Stroke Trial,^{21,22} the Echoplanar Imaging Thrombolytic Evaluation Trial,²³ the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study,²⁴ and the ongoing Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy trial.

These modalities have pros and cons, but most notably, NCCT has the big advantage of convenience (fast, available around the clock, no contraindications) and is supported by evidence from acute stroke trials, while MR imaging is sensitive to identifying the site and extent of early ischemic changes but requires screening for potential contraindications and requires patient cooperation (difficult in an acute stroke setting). In our opinion, the biggest limitation of the MR imaging-based approach is the amount of time it takes to perform the studies. Some centers have developed protocols lasting only 5–7 minutes,²⁵ but the total time required from when the test is ordered until all data are postprocessed can exceed 30 minutes.²⁶

Recently, there have been significant advances in mechanical IA therapy (the Merci retriever, Concentric Medical, Mountain View, California; the Penumbra System, Penumbra, Alameda, California; Solitaire, ev3, Irvine, California; and so forth).²⁷ Studies using these devices have consistently shown rates of recanalization approaching 90%.²⁸ These devices are being used in severe strokes and in proximal artery occlusions. However, these high recanalization rates are not reflected in the rate of functional recovery, which still lags behind.

Of all mentioned items, in our opinion, these are clear:

- 1) Most infarcts grow over time.
- 2) We are not good at determining their rate of growth.
- 3) Early recanalization prevents infarct growth and can lead to better patient prognosis.
- 4) We are reasonably good at determining the initial size of the infarct core.
- 5) Newer devices achieve high recanalization rates in patients with large-vessel occlusions.

If we accept these statements as true, we can infer that as soon as a patient is suspected of having an acute ischemic stroke with a small core and proximal vessel occlusion, every attempt should be made to minimize imaging-to-recanalization time because this affects infarct growth. Here, we suggest a protocol to achieve an imaging-to-recanalization time of <60 minutes. After a hemorrhage is excluded, the following steps could be taken:

- 1) CTA (5 minutes)
- 2) CT perfusion and postprocessing (15 minutes)
- 3) Brain MR imaging (45 minutes; this includes ruling out contraindications, doing necessary paperwork, taking the patient to MR imaging, achieving patient cooperation, performing the imaging, and postprocessing). Even though there would be some variability from center to center, in most cen-

ters, this protocol takes approximately 45 minutes, leaving only 15 minutes to achieve recanalization.

As soon as imaging is assessed, one must perform the following:

- 1) Start IV tPA if appropriate (10 minutes).
- 2) Obtain consent for IA therapy in case it will be necessary (10 minutes).
- 3) Plan for DSA.
- 4) Assess patient cooperation and involve anesthesia if necessary (20 minutes).
- 5) Prep the patient (10 minutes).
- 6) Obtain vascular access and perform DSA (10 minutes).
- 7) Achieve recanalization (10 minutes).

To achieve recanalization in <60 minutes, one must make choices and compromises. Is MR imaging really needed? It could be argued that without MR imaging, it is impossible to determine core size precisely. While this is correct, what degree of precision is required? The degree of core estimation on NCCT by using the ASPECTS methodology has been well-tested and validated.²⁹ Web sites are available to aid in becoming proficient at using this system (aspectsinstroke.com). Optimization of the newer CT scanners allows excellent gray-white differentiation without significant increases in radiation doses.³⁰

Is CTA really needed? We believe that it is worth the time spent. Overall, little additional time is needed if the patient is already on the CT table. While there are concerns regarding contrast-induced nephropathy, it has been shown that these are not significant.³¹ Benefits of CTA include the following: 1) confirming the presence of proximal occlusion, 2) core assessment on CTA source images,^{29,32} 3) collateral circulation assessment,³³ and 4) displaying arch anatomy that may facilitate DSA. Other benefits include ruling out possible contraindications to IA therapy, such as unstable aortic thrombus, and documenting the presence of arterial dissections.

Is CT perfusion really needed? While it helps to define core size, estimate penumbra presence and size, and determine the presence of collateral circulation, we suggest that it is not worth the time spent on it.³⁴ There is a lack of standardization of protocols and postprocessing techniques across vendors.³⁵ The best parameter to define penumbra is not clear,⁵ and there is no consensus about it. Perfusion does not answer the question of the rate of infarct progression.³⁶ Radiation dose may be an issue in younger patients, especially if whole-brain coverage is obtained.³⁷ Patient cooperation is important for image quality.

Is anesthesia really needed? This easily adds 20–25 minutes, leaving only 40–45 minutes to achieve recanalization. Additionally, a number of recent publications warn against the potential harm of general anesthesia.³⁸ While some interventionists think that performing these complex procedures without it may increase complication rates, this is not true in our experience in which conscious sedation is adequate.

Is a complete diagnostic DSA really needed? While it has merits (assessment of collaterals and so forth), it takes time, easily 10 minutes and, in our opinion, provides very little additional information. We favor going straight to the vessel of interest.

One could also argue that an IA treatment approach is not necessary. However, multiple studies have shown poor recan-

alization rates with IV tPA alone in proximal occlusions.⁹ It is difficult to precisely determine how long it takes to achieve recanalization with IV approaches. Moreover, if the aim is to achieve an imaging-to-recanalization time of <60 minutes, one may need to try multiple approaches simultaneously. Safety is paramount, and one should not gain efficiency at the expense of safety.

The issue of a well-informed consent in emergency situations still remains controversial.³⁹ While a stroke neurologist discusses the consent, the interventionist should proceed with preparation of materials, assuming that the consent will be obtained. Obtaining consent for inclusion in a trial can slow down the process, especially if the procedure itself is being tested.

Therefore, in our opinion, in patients with clinically large ischemic strokes, focusing on imaging-to-recanalization time makes the most sense. We think that spending time on CTA is worth the information it provides. MR imaging, while excellent at determining core, takes too long. The verdict on CT perfusion is not clear, but we favor avoiding it. General anesthesia may be avoided unless absolutely necessary, and a complete diagnostic angiogram may not be required. Mechanical approaches to recanalization may be preferable to systemic treatments.

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