Reborn Workhorse, CT, Pulls the Wagon Toward Thrombolysis Beyond 3 Hours

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Computed tomography (CT) is the time-honored workhorse of every emergency room and has revolutionized the speed and accuracy of the diagnosis of stroke. It is used to select patients for thrombolysis, the only approved drug treatment for ischemic brain infarction. However, the criteria for eligibility are very restrictive, notably with respect to the accepted 3-hour window. Only in a few centers >10% of ischemic stroke patients will receive thrombolysis, although it has been estimated that if all patients arrived within 3 hours from the onset of symptoms, 45% could be eligible for thrombolysis. However, there probably is no absolute time window of tissue viability. More likely, brain tissue viability includes 4 factors: a time factor, a hemodynamic factor, a tissue factor, and an intervention factor. How to know when to provide thrombolysis after the 3-hour window is an enigma. Dynamic perfusion CT may be an answer because it wins on accessibility, speed, and low cost. Other imaging methods such as positron-emission tomography, functional MRI, and single-photon emission computed tomography are not available in busy emergency rooms, but every stroke center has the needed hardware, CT. Only new software is needed to be able to perform perfusion CT.

Dynamic Perfusion Computed Tomography Technology

Dynamic perfusion CT is a functional CT that allows accurate quantitative assessment of regional blood flow (rCBF) and regional blood volume (rCBV) in a single slice of brain, but with multislice technology it is possible to cover a wider part of brain. Perfusion CT can be completed within minutes and involves the sequential acquisition of CT images performed in cine mode during the intravenous administration of iodinated contrast material. A modern helical CT scanner images faster than 1 brain slice per second. At this speed, CT scanners can trace the entry and washout of a bolus of contrast dye injected into a large arm vein. Contrast dye behaves as an intravascular tracer and the CT scanner as a detector of cerebral blood flow. The change in signal intensity in Hounsfield units is proportional to the concentration of the contrast dye in the pixel imaged. The dye-related change in signal intensity in pixels located within an artery enables calculation of dye concentration in the arterial blood. During the first pass of the bolus through the brain, these data allow calculation of rCBV and rCBF maps. An advantage of the perfusion CT methodology over gadolinium-based magnetic resonance (MR) perfusion imaging is the linear relationship between dye concentration and signal intensity, which allows quantitative measurements of rCBV and rCBF. Wintemark and coworkers specified ischemic region as one with a >34% decrease in rCBF compared with the corresponding region in the contralateral healthy hemisphere. In this ischemic region, which includes both infarction and penumbra around it, 2.5 mL per 100 g was chosen as the rCBV threshold of infarction, which predicts that cerebral parenchyma below this rCBV is highly likely to die. These thresholds were selected in agreement with the values reported in the literature.

What Is New?

In their landmark study, Wintemark and coworkers were able to show that perfusion CT could with reasonable accuracy predict the final cerebral infarct size in acute stroke patients at the time of emergency evaluation. Furthermore, perfusion CT provided information about the extent of the ischemic penumbra, ie, about what the size of saved brain tissue would be, if the artery could be recanalized with thrombolysis (Figure). Fast recanalization allowed the penumbra to be salvaged with a proportional improvement in clinical condition. In patients with persistent occluded cerebral artery, the brain infarction gradually evolved over the ischemic penumbra and finally completely replaced it, which was reflected in a poorer clinical condition. The penumbra, as described by perfusion CT, has been shown to be accurate in comparison with acute12,13 and delayed diffusion/perfusion-weighted MRI (DWI/PWI). The authors introduced a new parameter, potential recupera
tion ratio (PRR), which can be calculated using the following equation: PRR = penumbra size/penumbra size + infarct size. The higher the ratio is, the bigger the size of penumbra and the smaller the size of infarct at that point of time, predicting that if the occluded artery is rapidly recanalized with thrombolysis, the more the patient will gain irrespective of how much time has elapsed from the onset of symptoms of stroke. The ratio also tells that the smaller it is, the less the patient will gain, even if the occluded artery can be recanalized. When the penumbra has vanished and the sizes of ischemic area and infarct area are identical, thrombolysis can no longer improve the outcome of the
patient. Yet it may induce intracerebral hemorrhage. Accordingly, it may not be appropriate to provide recombinant tissue plasminogen activator (rtPA), even within 3 hours from stroke onset if the infarction has matured to the full. Perfusion CT may help identify patients who arrive late and still are candidates for thrombolysis. It may also detect those arriving early but who, in spite of their early admission, are no longer good candidates for thrombolysis. At present, a few emergency rooms have functional MRI available 24 hours a day, 7 days a week. In most of them the clinical decisions have to be made based on time from the onset of symptoms and ordinary CT data, but new postprocessing software for perfusion CT may revolutionize the way stroke is treated.

Why Is the Study of Wintermark and Coworkers So Important?
Thrombolysis with rtPA has been approved within the 3-hour window. The pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA trials suggests that treatment with rtPA may be safe and effective up to 4½ hours from the onset of symptoms. When PWI and DWI mismatch is used in selecting patients for thrombolysis, desmoteplase may be safe and effective up to 9 hours. The problem is that functional MRI is not widely available at busy emergency rooms and is not suitable for uncooperative patients without sedation and intubation, whereas CT is available everywhere, where such treatment decisions must be made. It is possible to perform perfusion CT in critically ill or uncooperative patients due to the enormous reduction in examination time. The only investment needed for the CT is software allowing rapid construction of validated, color-coded, “infarcted (red) and penumbra (green) maps” on a patient’s brain slice. Such prognostic maps will serve busy emergency rooms well and help in making the decision whether or not a stroke patient should be treated with rtPA. As opposed to MRI, every emergency room should be able to complete this form of imaging within minutes of the patient’s arrival. Contrast CT angiography (CTA) is able to reveal occluded arteries in acute stroke patients. This data together with perfusion CT data may help in the selection of patients for thrombolysis. The extra time needed for CTA is reasonable and does not preclude patients from receiving thrombolysis.

What Could the Benefits Be?
Thrombolysis within 3 hours is safe for selected patients. It is also cost-effective. It has been estimated that treating 1000 patients with rtPA in the United States will save $4.5 million US dollars, in Canada $3.8 million Canadian dollars and in Finland 6.5 million euros. Based on systematic reviews, rtPA in acute ischemic stroke seems to be 3 times more effective during the first 3 hours and twice as effective up to 6 hours than in acute myocardial infarction. However, these systematic reviews had different end points: the end point in AMI trials was death, whereas the end point in the acute stroke trials was combined death and disability. While the reanalysis of the NINDS rt-PA trial database definitely eliminated any suspicions of the effectiveness of rtPA in acute stroke trials, the quicker rtPA is given to stroke patients, the greater the benefit. A major problem both at present and in the future will be how to educate lay people that stroke is an emergency and needs fast admission to hospital and how to organize stroke management in the way the triage for AMI or trauma has been organized. The challenge is formidable. Perfusion CT, the newly updated version of the workhorse of emergency rooms, may turn out to be of great value in deciding which patients may benefit from thrombolysis and when it is already too late. Whether this holds true needs to be assessed in future trials.
Conclusions

Even in the future, many patients will arrive beyond the 3-hour window in the emergency room and yet quite many of them might benefit from thrombolysis. Any additional time over 3 hours would increase the target population for stroke thrombolysis. Modern perfusion CT technique could be one possibility for enlarging the target population, but it may also help exclude those who have nothing to gain from thrombolysis. Perfusion CT is not time consuming, suits critically ill or uncooperative patients, and is widely available and accessible. It may change the way acute stroke patients are treated in the future, but the results of Wintermark and coworkers need to be confirmed in larger studies.

References

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