

The Time Man Has Cometh to Brain Tick . . . Death . . . Tick . . . Death

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See related article, pages 263–266.

The stroke community has been chanting the qualitative battlecry of “time is brain” for 12 years¹ and has been able to act directly on it for a decade.² Now, Saver³ has thoughtfully and critically synthesized a quantitative face on one of the most important aspects of acute stroke care: getting an eligible patient treated with intravenous tissue plasminogen activator as soon as possible because each minute that ticks away without treatment equates to about an additional 2 million neurons lost.

Developing a quantitative approach to time-specific ischemic brain damage in humans is an elegant concept with tremendous implications for treatment and future clinical trial design. Saver systematically modeled a typical supratentorial, large artery infarct volume over time using various, readily available, neuroanatomic and physiological data. This allowed the first detailed analysis of how much brain substance is lost (with coefficients of variation) over various units of time based on the best available (albeit, at times, incomplete) information. He then performed sensitivity analyses to address the robustness of the model.

One implication from Saver’s analysis is that true and pure transient ischemic attacks may be much rarer than believed because even after a few seconds of the focal cerebral ischemic process, tens of thousands of neurons and hundreds of millions of synapses are lost - if the time function is linear. Are these very brief episodes really then “microstrokes” (invisible to the neurological examination or current imaging modalities) with very subtle, if any detectable parenchymal or functional change?

Based on Saver’s initial analyses it is clear we need to better understand the shape of the time function for the course of irreversible damage—is it front-end loaded, back-end loaded, predominantly linear, or is it more complex? Only well-designed studies in humans will be able to directly

address this question. Some help may also come from theoreticians.

One potential limitation of the analysis is the relative lack of data addressing the shape (morphology) of the growth function of a typical stroke—or even the degree of heterogeneity of the growth and time function from stroke to stroke, from vessel to vessel, and from occlusive mechanism to occlusive mechanism. Saver’s data are extrapolated from rodent brain where the shape is model specific. The high degree of variability of human stroke (are any 2 exactly alike?) suggests that additional sensitivity analyses with broader ranges may help refine the results.

To the degree multimodal computed tomography, magnetic resonance, and positron emission tomography studies in acute stroke (that also collect data on final infarct volume) can coregister hyperacute and multiple, serial tissue imaging at well-defined time points, an estimate of growth per unit time can be obtained.⁴ With a large enough dataset, there could be modeling for the effects of timing, occurrence, and degree of reperfusion, serum glucose, and other potentially important factors that could independently impact growth rate and time course to final infarct volume. The penumbra’s time course to death is likely slower than the core’s.⁵

Saver is to be congratulated for providing a unique, quantifiable aspect to the importance of stopping the clock from ticking ischemic brain away. The gauntlet has been dropped to refine these estimates and use them in our battle to minimize acute stroke damage.

Acknowledgments

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