Time Is Brain: The Stroke Theory of Relativity

Camilo R. Gomez, MD, MBA*,†

Background: Since the introduction of the philosophical tenet "*Time is Brain!*," multiple lines of research have demonstrated that other factors contribute to the degree of ischemic injury at any one point in time, and it is now clear that the therapeutic window of acute ischemic stroke is more protracted than it was first suspected. To define a more realistic relationship between time and the ischemic process, we used computational modeling to assess how these 2 variables are affected by collateral circulatory competence. *Methods:* Starting from the premise that the expression "*Time = Brain*" is mathematically false, we reviewed the existing literature on the attributes of cerebral ischemia over time, with particular attention to relevant clinical parameters, and the effect of different variables, particularly collateral circulation, on the time–ischemia relationship. We used this information to construct a theoretical computational model and applied it to categorically different yet abnormal cerebral perfusion scenarios, allowing comparison of their behavior both overall (i.e., final infarct volume) and in real-time (i.e., instantaneous infarct growth rate). *Results:* Optimal collateral circulatory competence was predictably associated with slower infarct growth rates and prolongation of therapeutic window. Modeling of identifiable specific types of perfusion maps allows forecasting of the fate of the ischemic process over time. *Conclusions:* Distinct cerebral perfusion map patterns can be readily identified in patients with acute ischemic stroke. These patterns have inherently different behaviors relative to the time–ischemia construct, allowing the possibility of improving parsing and treatment allocation. It is clearly evident that the effect of time on the ischemic process is relative. **Key Words:** Ischemia—time—intervention—acute—treatment—assessment—thrombectomy.

Introduction

Nearly a quarter of a century has elapsed since the original introduction of the concept that *Time is Brain!*[1] It began as a simple exhortation to prioritize the efforts of expediting acute ischemic stroke (AIS) treatment, acknowledging the deleterious effect of the passage of time on the fate of ischemic brain tissue. The decade that followed witnessed major advances in the treatment of AIS, notably the completion of a pivotal study demonstrating the effectiveness of intravenous (IV) tissue plasminogen activator within 3 hours of symptom onset.[2] As a result, alteplase (Activase; Genentech, Inc., South San Francisco, CA) was quickly approved by the Food and Drug Administration, and a supplement to the prevailing guidelines for AIS treatment was published in haste.[3] It seemed clear that, if patients could be treated with IV alteplase within a 3-hour *therapeutic window*, their overall outcome could be consistently improved. Curiously, the next salvo of information from pooled data of subsequent trials suggested that the 3-hour limit may not be as rigid as originally thought, and that some patients could be effectively treated within intervals between 3 and 6 hours from onset.[4] This

From the *Department of Neurology; and †Department of Neurological Surgery, Loyola University Chicago—Stritch School of Medicine, Maywood, Illinois.

Received March 14, 2018; accepted April 4, 2018.

Address correspondence to Camilo R. Gomez, MD, MBA, Department of Neurology, Loyola University Chicago—Stritch School of Medicine, 2160 First Avenue South Maguire 2713, Maywood, IL 60153. E-mail: crgomez@lumc.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.04.001

was confirmed about a decade later, expanding the therapeutic window for treatment with IV alteplase to 4.5 hours (270 minutes) and further refining the recommendations for thrombolytic treatment of AIS beyond the first 3 hours, although only in "selected patients."[5-7]

Still, despite the allure of a more protracted therapeutic window, the negative effect of elapsed time from onset was palpable in the results of every clinical study of AIS treatment.[4,8] In fact, in the midst of active discussions about therapeutic window prolongation, Saver[9] elegantly provided a theoretical quantification of the damaging effect of ischemia on brain tissue *per unit of time!* And so, 2 competing and seemingly incompatible ideologies became juxtaposed and appeared to create an insurmountable paradox of AIS treatment: "*Time is of the essence!*" and "*There is more time than expected. . ..*" Interest in using imaging parameters instead of just time from onset to select patients for treatment rapidly grew, some suggesting that such an approach should replace the concept of a therapeutic time window per se.[10-12] More recently, the incorporation of imaging of the ischemic penumbra as a criterion for patient selection for neuroendovascular rescue, specifically thrombectomy, added a more tangible dimension to this discussion in the context of treatment of infarction from large arterial occlusion (LAO). The data have consistently demonstrated that certain patterns of ischemia are associated with a greater chance of neurologic improvement even if therapeutic reperfusion is achieved more than 12 hours after the estimated time of onset (ETO).[13-19] Despite these findings, the inexorable effect of time delays continues to be consistently evident in the same datasets, individually or when examined in the aggregate.[13-20]

In light of this apparent contradiction, it seemed reasonable to re-examine the relationship between time passage and the ischemic process, looking to identify to what degree they each influence the effective therapeutic window for patients with AIS, and how their interaction could potentially shape future management decisions. It seems fair to begin our analysis by acknowledging that, although philosophically sound, the statement "*Time is Brain!*" is *mathematically false* (see the Appendix) as it would otherwise be impossible to provide a logical construct to the concepts we will introduce.

Background Rationale

Fundamental Considerations

Estimating the likelihood of therapeutic success in the care of patients with AIS at any one point along the time continuum requires having information about the difference between the volume of already infarcted tissue (i.e., beyond recovery) and the volume of tissue remaining at risk of progressing to infarction (i.e., salvageable). This dichotomy is of particular importance in the context of LAO as the former has been repeatedly shown to directly correlate with mortality, poor outcome, and therapeutic complications (e.g., hemorrhagic transformation).[21-25] It follows that, in practice, we should ideally estimate those 2 parameters for any element x of the set T, defined as

$$T = \{x \in \mathbb{N} : 1 \leq x \leq 720\},$$

where x represents the time interval in minutes (min) from the stroke ETO, and to which we have assigned a maximum of $x = 720$ to match the most recent prospective thrombectomy studies, which reported approximate median times of 12 hours between last known well time and clinical evaluation (i.e., randomization).[17,18]

As to the actual parameters, it has traditionally been suggested that ischemia affects the brain steadily, creating physiologic derangements that depend on the severity of the blood flow insufficiency, and that morphologically appear as concentric volumes (Fig 1).[26-29] As such, the most centrally located component (i.e., the "ischemic core") corresponds to the severest blood flow reduction, has been conventionally thought to represent irreversibly damaged brain tissue, and seems to be typically surrounded by an area of lesser flow reduction considered potentially viable (i.e., the "ischemic penumbra").[26-30] The latter is further surrounded by a third concentric volume with only mild reduction in blood flow (i.e., the "benign oligemia")[9,26,31] whose relevance will be worthy of consideration further along in our analysis and discussion. First, however, we should focus on the 2 principles that seem to govern the behavior of this system: (1) as time elapses, the ischemic penumbra progressively fails at a certain rate, and it is replaced by a centrifugal expansion of the ischemic core, whose volume is inversely proportional to a good clinical outcome,[32,33] and (2) the difference in volume (i.e., "ischemic mismatch") between the ischemic core and the overall area of reduced tissue perfusion generally corresponds to the surrounding ischemic penumbra, and is directly proportional to the opportunity for intervention and good clinical outcome.[10,27,34-36] Although axiomatic, these 2 postulates are subject to influences that affect their expression along the time continuum, such that the impact of the ischemic process for any value of x is *relative* to the weighted effect of different variables, including the specific vascular occlusion site, the robustness of the collateral blood supply, the intrinsic tissue susceptibility to ischemia, and other patient-specific variables (e.g., blood pressure, intravascular volume, and blood glucose).[27,29,30,35,37] Moreover, although the progressive increase of the value of x is associated with less effectiveness of treatment,[13-16,20] for any value of x, the ischemic core and ischemic penumbra volumes show considerable variability between patients, the former more so (i.e., 3- to 4-fold) than the latter (i.e., 2- to 2.5-fold).[28,30] These findings underscore the *relative* impact of any value of x for the purpose of making