EDITORIAL

The complex dynamics of stroke onset and progression

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Purpose of review

The aim of this article is to discuss the dynamic nature of cerebrovascular ischemia.

Recent findings

Acute risk factors are superimposed on chronic risk factors to precipitate plaque rupture in myocardial infarction. The interaction between external triggers, such as stress, with internal triggers, such as vasoconstriction, is mediated to a large part by the autonomic nervous system. Numerous algorithms have been developed to describe physiological time-series data, for example heartbeat variability, and reveal complex structure that has diagnostic and prognostic significance. Much of this structure is mediated by the autonomic nervous system. Recent data on stroke triggers, carotid stenosis, transient ischemic attack, and infarct expansion suggest a similar need for detailed physiological measurement and non-linear dynamics in order to understand stroke onset and progression.

Summary

The picture emerging is that stroke arises as a result of multiple processes with different time constants. The nature and timing of interventions should be tailored to these complex interacting processes. This will require more frequent and varied physiological measurement accompanied by non-linear analytical methods. This new approach, which stresses complex within-subject measurements, will likely make 'one size fits all' solutions to stroke care untenable.

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Abbreviations

MI myocardial infarction
TIA transient ischemic attack

1350-7540

Introduction

The concept of stroke is derived from the Greek word *apoplexia*, which means to suddenly strike to earth, to knock down. The word stroke is thought to derive from an Old English word, *strac*, a hard blow. Thus the etymological details make it clear that it is the out-of-the-blue quality of cerebrovascular ischemia that led it to be called stroke. Despite this defining feature, however, it is remarkable how little attention has been paid to why a stroke occurs today rather than yesterday or tomorrow. Instead the emphasis has been on risk factors and their relationship to stroke occurrence over a prolonged time period. While the study of risk factors is very important, it does not tell us why a patient can have multiple risk factors but be stroke-free 99.9% of the time.

What can we learn from cardiology?

Questions about the causes of an acute vascular event have been addressed more in the cardiology than in the stroke literature. In the case of myocardial infarction, 'triggers' are thought to increase the chance of the precipitant event, which is rupture of a vulnerable plaque (usually one that causes only mild-to-moderate stenosis). Thus plaque rupture is not just a stochastic event, i.e. an event with a fixed chance of occurrence, but instead a trigger increases the chances of rupture. In an excellent recent review, a framework has been outlined with regard to acute risk factors for myocardial infarction (MI) [1]. The idea is that chronic risk factors lead to the slow formation of a vulnerable plaque and then acute risk factors, acting in a much shorter time frame, superimpose a triggering mechanism. Acute risk factors can be thought of as the external triggers that increase the intensity of internal triggers, which then directly precipitate plaque rupture. The three main internal triggers are posited to be vasoconstrictive, prothrombotic, and biomechanical. Identified external triggers include physical and mental stress, alcohol, caffeine and drug use, sexual activity and cold exposure. Acute inflammation is also being shown to be a significant trigger, as have circadian rhythms. The connection between external and internal triggers is the autonomic nervous system. Increased sympathetic tone augments internal triggers by promoting vasoconstriction, increasing platelet aggregation, decreasing fibrinolysis, and increasing pulse and blood pressures. The sympathetic nervous system is activated by physical exertion, emotional stress, and, unfortunately, good coffee. The parasympathetic nervous system is also

thought to play a role, albeit less than the sympathetic, in MI. In particular, reduced arterial pressure and cardiac output might increase the risk of thrombosis due to sluggish flow and arterial wall collapse. This framework, which links external triggers, the sympathetic nervous system, and internal triggers can explain why events sometimes occur in the absence of chronic risk factors. In such cases these factors might be severe enough to induce electrical and thrombotic events without the need for vulnerable plaques. At the current time there is no way to determine which coronary lesion in an individual will rupture and result in an MI. A number of new screening approaches, however, are under development in an attempt to remedy this situation. For example, high-resolution intracoronary ultrasound has shown some promise in defining 'high risk' lesions [2]. There is also active investigation to identify inflammatory markers, such as high sensitivity C-reactive protein, and genetic testing. The utility of the latter two approaches for directing treatment of individuals is questionable however [3].

What do we know about stroke onset?

What is known about analogous triggers for stroke onset? Neurology lags behind cardiology here but this is explainable by the marked heterogeneity of stroke compared to myocardial infarction. In this issue of *Current Opinion in Neurology*, Mitchell Elkind (pp. 51–57) provides the first thorough review of what is currently known about stroke triggers and shows that a change in perspective is on the way. Although less is known about acute risk factors for stroke compared to chronic risk factors, there appears to be considerable overlap with findings in the cardiology literature. The importance of infection and inflammation in the weeks leading up to a stroke is becoming increasingly apparent. The role of the autonomic nervous system is also likely to be of major importance as both emotional stressors and sympathomimetic drugs have been associated with stroke [4]. It is ironic that, so far, cardiologists seem to be more interested than neurologists in the interaction between the nervous system and atherosclerosis. Important differences between cerebrovascular and cardiac disease are certain to be discovered as research in this area continues, differences that will no doubt reflect the much greater heterogeneity of stroke as compared to myocardial infarction. For example, although it is likely that the concept of unstable plaque will apply to carotid disease [5], it remains unclear whether it will apply to intracranial disease and it is very unlikely to be relevant to lacunar infarction or embolism.

Carotid stenosis as a model for stroke onset

Unlike coronary arteries, the carotid arteries are easily accessible. With carotid stenosis, unlike coronary artery disease, the lesion is essentially always in the same place and there are several noninvasive ways to study it. This makes carotid disease a good model system for the study of plaque dynamics. At the current time, treatment of asymptomatic carotid stenosis remains controversial. Carotid endarterectomy has only marginal benefit in this patient population and the jury is still out for angioplasty and stenting. Thus effective risk stratification is urgently needed. J. Redgrave and P. Rothwell (pp. 58–64) provide an exhaustive and rigorous review of current evidence and thinking on this topic. The difficulty that clinicians face is that every symptomatic plaque was at some point an asymptomatic plaque and therefore must have been unstable or transitioned to instability. The importance of identifying instability is reinforced by recent studies that show that when a carotid stenosis becomes symptomatic it is important to treat it within weeks [6]. This means that processes that had moved slowly suddenly begin to move fast. The underlying message is that infrequent static measurements, like degree of stenosis, fail to capture the dynamics of the disease. How do we catch the transition to instability? Dynamics refers to a change in the state of a system over time. A system is nonlinear when it does not obey rules of proportionality and superposition. For example, the voltage across a cell membrane with only passive conductance is a linear function of the current through it. Once active conductances are present, however, the relationship between voltage (output) and current (input) no longer scales: this is what allows an action potential to occur. Systems that display nonlinear dynamics are called complex systems. The language and methods of complex system analysis are unfamiliar to the majority of physicians, although they have begun to be applied in the areas of intensive care monitoring and in the measurement of heart rate variability [7,8]. Usually when physicians collect and measure physiological data, it is single values at fixed time intervals. Even when a value is continuously measured, physicians will often do no more than calculate the mean or give a range; on rounds it is common to hear a statement to the effect that, in any given time period, the systolic blood pressure ranged between, say, 150 and 180. The data, however, have far more structure than this: structure that has prognostic and predictive significance. For example, it has been shown that the approximate entropy and short-term fractal exponent (both nonlinear measures) of heart rate variability data predict the onset of spontaneous atrial fibrillation in the absence of structural heart disease [9]. The core idea is that a loss of variability and complexity in physiological measurements is an indicator of pathology and incipient worsening.

Nonlinear effects are almost certainly occurring with carotid stenosis and cerebrovascular disease in general. A patient with an asymptomatic over 70% stenosis has a

2% risk of stroke per year [10]. In contrast, a patient with the same degree of stenosis who has recently suffered a hemispheric transient ischemic attack (TIA) in the vessel's territory has approximately 20–30% risk in the next month [10]. Why this very large difference in risk for the same degree of stenosis? Although differences in plaque morphology, rather than just degree of stenosis, may be found to correlate with these differences in risk, it is still a static single measurement. Instead, it can be envisaged that more elaborate time-series analysis of physiologic measurements that detect changes in plaque behavior and flow dynamics will be more informative. Analysis of heart rate variability would provide a measure of the status of the autonomic nervous system and similar nonlinear analytical methods could be applied to blood flow data. Another example is provided by recent studies with transcranial Doppler (TCD), which suggest that the presence of microembolic signals in patients with recently symptomatic carotid stenosis are at higher risk of recurrent stroke [11]. It could be conjectured that additional structure might be found in the data if more than just the total number of micro-embolic signals in unit time were computed. There is also evidence that inflammation may play a role in making a carotid plaque unstable [12]. Recent studies show that turbulent flow patterns through stenosed vessels can be successfully simulated [13,14]. Similarly, studies have also modeled dynamic platelet accumulation distal to an occluded middle cerebral artery and shown how this is associated with resistance to fibrinolysis and with further ischemia [15]. Is it far-fetched to imagine a carotid equivalent of a Holter monitor, which would collect continuous data over 24 h or longer, the data then being subjected to complex time series analysis?

Stroke progression

The review by Shyam Prabhakaran (pp. 65–70) summarizes a similar shift in thinking with respect to TIA and other forms of reversible ischemia. In this new framework, the biology of plaque and vessel instability, with associated changes in flow dynamics, may be similar whether it precedes stroke or TIA, or when stroke fluctuates and progresses. Intracranial atherosclerosis has a high rate of stroke recurrence [16], which suggests that the lesions are highly dynamic. It is also known that infarcts evolve after stroke. Almost half of patients who present with an acute hemispheric stroke show a greater than 20% increase in infarct size in the first week after stroke onset [17]. Data suggest that this is mainly due to the ischemic penumbra progressing to completed infarction, a process driven by both hemodynamic (status of collaterals) and nonhemodynamic factors (inflammatory mediators). As outlined in the review by M. Elkind (pp. 51–57), inflammation also plays a role in the week leading up to stroke onset. It can therefore be conjectured that similar mechanisms are operative in the week before and the week after certain kinds of stroke.

The future

With full awareness that prediction of the future is foolhardy, speculation is offered on how the treatment of acute cerebrovascular disease will evolve over the next 5–10 years. Patients with TIA or stroke will be admitted to units with the capacity for extensive and continuous physiological measurement. Sophisticated time series analysis of hemodynamic, hemorheological, and inflammatory marker data will identify variables associated with the stroke-prone state: the term used to describe those patients at maximal risk for imminent stroke occurrence, recurrence and progression. It is to be hoped that a loss of complexity in these physiological data will be detectable hours or even days before the ictal event and allow for intervention. If stroke onset and progression share similar mechanisms then physiological studies of the stroke-prone state may help direct secondary prevention trials. An expected consequence of such a flow of information is that clinical trials will become more homogenous with respect to putative stroke mechanism. This is because carotid disease, intracranial atherosclerosis, and lacunar infarction are almost certainly going to differ in terms of their physiological dynamics and will require different interventions in the acute setting.

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