Silent Cerebral Infarction
Are We Listening?
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See related article, pages 2929–2935.

The clinical event of stroke is not always a good guide to the existence of cerebral infarction. The advent of widespread neuroimaging has made this clear: up to one-third of patients with TIA and no physical examination changes have infarcts on scans.1 These patients are at even higher risk for subsequent stroke as are other patients with silent cerebral infarction.2 In consequence, silent cerebral ischemia is recognized as part of a spectrum of cerebrovascular disease, which also includes TIA to stroke. In this issue of Stroke, Das et al3 contribute to our understanding of silent cerebral infarction by evaluating its prevalence and correlates infarcts in the Framingham Offspring study. They report a prevalence of 10.7% among >2000 mid-life (mean age, 61 years), community-dwelling people who were clinically stroke-free. Das et al3 propose that only some vascular risk factors are linked to silent cerebral infarction.

The strengths of the Framingham data are well-known, and this report from the Offspring study joins what are literally generations of others from that impressive investigation in building a better understanding of the interplay between vascular risk factors and adverse events. Inevitably, the results raise additional questions. Some, such as understanding the impact of silent cerebral infarction on outcomes in this sample—ie, what difference did these silent infarcts make to those who had them?—accept the premises of the study. But there is merit, too, in pursuing other questions that arise from these data, even when these questions reflect uncertainty about the starting assumptions that first motivated the inquiry reported here.

To begin, what makes cerebral infarction silent? The Framingham data collection protocol used a time-based definition of stroke as “rapidly developing signs of focal neurological symptoms if they do not have corresponding stroke symptoms.8 Those vascular dementia criteria that ignore imaged ischemic lesions if they do not have corresponding stroke symptoms.8

The claim by Das et al that only some vascular risk factors are important in silent cerebral infarction is of interest, and they make that case for atrial fibrillation, left ventricular hypertrophy, and elevated homocysteine in addition to hypertension (the last of which has also been found in another recent study).9 But does this conclusion arise because it is what the data say, or does it, too, reflect how we listen?

Here, the investigators considered some vascular risk factors separately and others in combination, with the latter being in the Framingham Stroke Risk Profile, which includes age, SBP, antihypertensive therapy, DM, cigarette smoking, cardiovascular disease, atrial fibrillation, and electrocardiographic evidence of left ventricular hypertrophy. Increasing levels of the aggregate Framingham Stroke Risk Profile scores were associated with higher odds of silent cerebral infarction. In addition, echocardiographic measurement of left ventricular mass, sonographic carotid artery measurements, various cholesterol, and homocysteine levels were studied, but not all reached statistical significance in the age-and sex-adjusted logistic regression model.

An important question in understanding these results is the extent to which we are prepared to believe that the various vascular risk factors are independent, ie, that they do not co-vary
across their range, or in interactions. Independence of factors is assumed in multivariable models that aim to tease out effects of one versus another, but is the assumption reasonable? An alternative, which does not require that assumption, which, in fact, violates it, is to count risks in an index variable, as is performed with the Framingham Stroke Risk Profile or in other vascular risk factor index variables. 

So, instead of evaluating hypertension and dyslipidemia each in relation to stroke, we can consider “vascular risk factor burden,” with factors combined in an index variable, in relation to stroke.

Of course, traditional multivariable analyses can also show that risk factors are cumulative. But it is not at all common for traditional analyses to deal with interactions. The reason is simple: interactions increase exponentially, so that even with a few variables, sample size requirements become unmanageable. A related issue is what mathematicians call “computational intractability,” ie, that there are too many interactions to take into account. For example, with just 4 variables, eg, hypertension, dyslipidemia, diabetes, and dysrhythmia, the interactions are not just the doubles of hypertension–diabetes, diabetes–dyslipidemia, etc, but the triples of hypertension–diabetes–dysrhythmia, diabetes–dysrhythmia–dyslipidemia, and so forth. It may well be the interactions that are important in allowing individually small, biologically meaningful, clinically relevant effects to be expressed and that these interactions, if not accounted for, mean that small, additive effects are masked. In other words, the effect of studying risk factors independently is that we “know more and more about less and less.” What we know more is the myriad ways that individual factors might be associated with adverse outcomes. What is lost is a good understanding of how the factors work together. In contrast, working with index variables of several risk factors can be a more parsimonious model, with greater explanatory power, than traditional multivariable models. The ability to focus on the impact of individual factors is of course lessened, but the importance attached to that loss again is the question of the independence of the various factors.

Perhaps more important than the question of independence (after all, individual items from a risk factor index can be isolated in relation to the rest of the index) is that index variables can themselves be the object of useful inquiry. For example, it is possible to evaluate by what patterns mean levels of the index variables accumulate, eg, linear or non-linear. How do the index variables change over time, or with treatment? Is there a limit to risk factor accumulation? If so, is it expressed in a simple quantitative count—are there just so many risk factors that an individual can have before an adverse outcome occurs?—or must they be expressed in a time function (eg, how many factors can be present for what period of time)? Will multi-component interventions (eg, exercise) affect some variables more than others, or will they affect the count most of all?

The view of the brain as a dynamic organ of, at a minimum, complex circuitry encourages its more complex, dynamical evaluation. It may be that for some issues as complex as why some strokes are expressed in traditional ways whereas others are not, we need access to an apparatus that can consider the full scope of the question. Too often in medicine we use the word “complex” simply as a synonym for “complicated” and do not take advantage of the mathematical tools that allow complexity to be evaluated. Index variables can themselves be the objects of study, ie, they can offer considerably more illumination than showing graded risk. After all, who would doubt that the more risk factors a person has, the more likely that person is to have a stroke? Complex systems analyses used to evaluate changes in the index variables can allow more than gradations of risk to be explored.

Just as recent generations of investigators and, later, practitioners have come to grips with molecular genetics and the magnetization of hydrogen molecules in radiofrequency fields, a new crop of investigators is embracing the complexity of networks and systems approaches to brain function. If the brain is speaking to us in mathematical terms, perhaps cerebral silence is less the problem than that of listener deafness.

Sources of Funding

K.R. receives career support from the Dalhousie Medical Research Foundation as the Kathryn Allen Weldon Professor of Alzheimer Research, and operating grant support from the Canadian Institutes of Health Research.

Disclosures

None.

References


Keywords: cognitive impairment ■ silent ischemia ■ complexity
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Stroke. 2008;39:2919-2920; originally published online June 26, 2008; doi: 10.1161/STROKEAHA.108.523803
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/11/2919

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