

Editorial

Assessing the constancy of intracranial aneurysm growth rates

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Despite ongoing natural history studies,^{1,2} the natural history of unruptured cerebral aneurysms, including patterns of growth, remains undefined. Elucidating this growth pattern may allow physicians to determine if specific periods of risk occur or if the risk to the patient is constant. Two possibilities exist for the pattern of aneurysm growth: linear (constant) or episodic with periods of growth separated by periods without. Linear growth would theoretically be associated with a constant predictable risk based on the growth rate, which occasionally could be rapid,^{5,16} whereas episodic growth might be associated with periods of unpredictable increased or decreased risk. It has been assumed that cerebral aneurysms have linear growth, and the authors of the proceeding article have tested this hypothesis by evaluating the plausibility of a constant growth rate for intracranial aneurysms via mathematical modeling. They tested the plausibility of a constant growth rate by comparing hypothetical cohorts of patients with different initial mean constant lesion growth rates and the population-based incidence of subarachnoid hemorrhage (SAH). The authors found that even within a hypothetical cohort with a growth rate that most closely resembled the incidence rates in the actual population, the specific incidence rates in the model differed substantially from those in the observed population data. They therefore concluded that the actual growth process must be episodic. This conclusion should be interpreted with caution as biological behavior is seldom accurately predicted with mathematical modeling. An aneurysm is a complex active biological structure and not simply a balloon that obeys the LaPlace Law. Constant biological changes are occurring at all times within the aneurysm wall and can be related to flow⁶ or molecular changes¹¹ that are not clearly understood. Not all aneurysms are equal and some may indeed have constant slow growth whereas others may be more unstable and associated with episodic growth based on factors that are currently unknown.

Regarding the limitations of the paper by Koffijberg and colleagues, as with other mathematical modeling studies, assumptions are made that can hinder a conclusive argument. This is particularly true if multiple

assumptions are made despite the authors' arguments to the contrary. The first assumption to be addressed concerns the multiplicity of aneurysms not influencing the results. Although the authors stated that the International Study of Unruptured Intracranial Aneurysms did not show an increased risk of SAH with multiple aneurysms,³ which was also demonstrated by Juvola et al.,⁴ and therefore will not affect the results of their own study, it must be remembered that many other studies have shown that multiple aneurysms do increase the risk of SAH in patients. In 1974 Mount and Brisman⁷ reviewed 158 cases of unruptured multiple aneurysms and found a bleeding rate of at least 10% per year in patients with multiple aneurysms. Wiebers and associates¹³ have also noted that unruptured lesions that are part of multiple aneurysm constellations can have a greater propensity to rupture than solitary aneurysms, and this hypothesis was supported by data from Winn et al.¹⁴ The Finnish data also support the concept that patients with multiple aneurysms have a higher likelihood of rupture of an unruptured intracranial aneurysm. Heiskanen and Marttila² have reported on 84 patients with multiple aneurysms in whom a ruptured lesion was definitely identified and treated at surgery. Of these 84 patients, 8 had a recurrent hemorrhage from the unruptured aneurysm during follow-up periods ranging from 4 months to 11 years with a rupture rate of > 1%/year. Heiskanen¹ has also reported on a 10-year follow-up in 61 patients with unruptured intracranial aneurysms who had undergone surgery for a prior ruptured aneurysm and with a lesion rupture rate of > 1%/year. Japanese data also support an increased risk of hemorrhage in patients with multiple aneurysms, with Yasui and associates¹⁷ demonstrating an annual rupture rate of 6.8% for multiple aneurysms and 1.9% for single ones. Therefore, if the latter argument holds true, it would significantly change the results of the study by Koffijberg et al., as up to 30% of patients have multiple aneurysms.

The second assumption that must be addressed is in regards to ignoring the age-related mortality rate and its insignificance. This factor may not be as insignificant as the authors suggest. In the recent International Study of Unruptured Intracranial Aneurysms data,¹² a patient's age was especially important because, although it does not affect rupture rates, it has a substantial effect on surgical morbidity and mortality rates, which would significantly affect the results of their analysis. The third assumption that needs to be addressed regards ignoring the association between growth and rupture risk. This factor is significant as growth does not always equal rupture, and there are no direct clinical data that prove that growth really equates with rupture. Insufficient data

exist in the literature to conclusively document a relationship between aneurysm growth and risk of rupture, and therefore, any speculation of its minimal effects on the modeling must be considered with caution. In regards to the fourth assumption of a decreasing aneurysm size affecting the results, we agree with the authors that the effect of a decreasing aneurysm size is probably negligible, although it is interesting that in bed-rested patients, cerebral angiograms obtained 6 months after aneurysmal SAH revealed a decrease in the size of ruptured aneurysms in 30%.¹⁵ Moreover, the authors failed to highlight another significant assumption: they compared simulation with population-based data on SAH incidence rates and assumed that these were correct data. Population-based data are often significantly flawed, and therefore, the foundation of the comparison may be flawed.^{8,10}

In summary, Koffijberg and associates have demonstrated mathematically that aneurysms appear to have episodic growth and rupture rather than constant growth; however, as delineated above, the conclusions must be taken with reservations as mathematics is not biology. The truth is probably that each aneurysm is different based on the genetic makeup of an individual,⁹ specific flow dynamics to the aneurysm and a specific cascade of inflammatory and molecular changes occurring in the aneurysm wall that are related to flow and genetics and cause some aneurysms to remain stable, others to have linear growth, and others to have episodic growth.

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Response

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We appreciate the thoughtful and detailed comments on our article. Furthermore, we fully agree with Drs. Britz and Winn that not all intracranial aneurysms are equal. Some aneurysms can exhibit constant growth, whereas others display episodic growth, possibly at different growth rates. In fact, the main point of our article is a constant growth rate for (all) intracranial aneurysms, in general, is unlikely. The actual growth process is likely to be episodic, at least for some aneurysms.

The main critique of Drs. Britz and Winn focuses on several assumptions in our model. Although we agree that assumptions may hinder a conclusive argument and that each additional assumption may weaken the overall conclusion to an unknown degree, there are several points on which we disagree with the commentators. With respect to the first assumption—a multiplicity of aneurysms does not influence the results—we can only conclude that it is currently unclear whether multiple aneurysms increase the risk of SAH in patients. Evidence for and against this notion can be found in the literature, as indicated by Drs. Britz and Winn. Moreover, the effect of a multiplicity can vary between regions and populations, which would partially explain the diverse findings reported in the literature. The results by Yasui and associates⁵ may well be valid in Akita, Japan, but are unlikely to be valid worldwide. As Yasui and associates have stated in their discussion: “the higher incidence of

rupture of unruptured aneurysms may be related to the differences in race or other environmental conditions.” A substantial increase in the risk of SAH due to multiple aneurysms in some regions may therefore be counterbalanced by no or a small increase in the risk of SAH due to multiple aneurysms in other regions, resulting in no substantial overall increase in risk. Concerning the second assumption, that is, on ignoring the relation between age and the surgical morbidity and mortality rate, we want to emphasize that surgical morbidity and death play (fortunately!) only a minor role in the eventual outcome of patients with SAH and in our model. If patients in the model become disabled as a consequence of aneurysm treatment, new aneurysms can still develop, which in turn can rupture and cause SAH. Thus, the risk of surgical morbidity does not affect our results on the incidence of SAH in any way. The risk of surgery-related death does affect our results, as new aneurysms do not develop and SAH does not recur in patients who die due to aneurysm treatment. However, our analysis focuses on SAH incidence rates, which are primarily determined by the number of patients with a first-ever SAH. Only a small fraction of patients surviving the initial SAH will, later in life, experience a recurrent episode of SAH from a new aneurysm.³ Furthermore, the age category containing the oldest patients in our model ranges from 60 to 64 years. Any recurrent SAH in individuals in this age category implies that the initial (first) episode of SAH occurred at an even younger age, that is, before the age of 55 years, because in our model the risk of recurrent SAH within a few years of the initial SAH is very small. In patients 55 years of age the increase in the surgical mortality rate is probably very low compared with that in patients 40–49 years old.⁴ Thus, we do not believe that the increased risk of surgical morbidity and death has influenced to a measurable extent our results on the incidence of SAH. With respect to the third assumption—not taking into account a direct relation between aneurysm growth and risk of rupture—we agree with Drs. Britz and Winn that such a relation is insufficiently documented in the literature. We mentioned this matter in our paper when we discussed a potential shift in the results that would be caused by a risk of rupture partially dependent on aneurysm growth rates. Rapidly growing aneurysms would rupture earlier than in our present model because of both their growth rate and large size, which would cause the SAH incidence rates at young ages to increase. As these incidence rates are already too high and incompatible with the observed population-based incidence rates, the model results and the observed incidence rates would be even further apart.

Although we agree with Drs. Britz and Winn that population-based data can be flawed, we argue that the quality of the particular data used in our study is suf-

ficiently high.¹ Interestingly, in the study of Tolonen and associates² mentioned by Drs. Britz and Winn, the accuracy of the stroke diagnoses in the Finnish Hospital Discharge Register and Causes of Death Register was assessed by comparing these data with the population-based FINSTROKE register, which was assumed to represent the gold standard. This register is a continuation of the FINMONICA Stroke Register, which was part of the World Health Organization multinational monitoring of trends and determinants in cardiovascular disease (WHO MONICA) project that we used for the assumptions in our model.¹ Thus, there are probably few population-based data sets with quality as high as that of the WHO MONICA data used in our model.

We are aware that our model has its limitations, but we are confident that they have not affected our results to a significant extent. Furthermore, we fully concur with Drs. Britz and Winn that mathematics is not biology. All biological factors listed by them emphasize that on a population level a constant growth rate of aneurysms is implausible. Thus, in this case mathematics and biology concur. From a biological perspective each aneurysm is different, with different sizes, locations, shapes, and growth rates. Drs. Britz and Winn may be right that in real life some aneurysms remain stable, others have a linear growth rate, and others have an episodic growth rate. As long as we cannot tell which aneurysm follows which type of growth, we cannot assume a stable growth rate for an individual patient in our clinic. Thus, although we differ in opinion on the validity of some of the assumptions made in the model, we agree in the final conclusion that for individual patients and for analyses of screening and intervention strategies for intracranial aneurysms, accounting for variation in aneurysm growth rates, as well as episodic growth, is not optional but crucial. (DOI: 10.3171/JNS/2008/109/8/0173)

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