Neurosurgical Forum

LETTERS TO THE EDITOR

Radiosurgery for cerebral cavernous malformations: a word of caution

TO THE EDITOR: We read with great interest two articles by Nagy et al.^{13,14} highlighting their use of stereotactic radiosurgery for the treatment of superficial and deep-seated cerebral cavernous malformations (CCMs) (Nagy G, Burkitt W, Stokes SS, et al: Contemporary radiosurgery of cerebral cavernous malformations: Part 1. Treatment outcome for critically located hemorrhagic lesions. *J Neurosurg* [epub ahead of print July 27, 2018. DOI: 10.3171/2017.5.JNS17776]; Nagy G, Stokes SS, Eröss LG, et al: Contemporary radiosurgery of cerebral cavernous malformations: Part 2. Treatment outcome for hemispheric lesions. *J Neurosurg* [epub ahead of print July 27, 2018. DOI: 10.3171/2018.2.JNS171267]). These articles address the controversial question of whether radiosurgery provides an improvement over the natural history of CCMs and whether this treatment modality can serve as an alternative to surgery for select patients. The future implications of these papers are significant. Therefore, we address each article separately with the hope of facilitating an open dialogue on this important issue.

In the first article on the use of radiosurgery for the treatment of patients with hemispheric lesions,¹⁴ the authors first tackled the question of alterations in natural history caused by radiosurgery. In this cohort, they noted that in the subset of patients without a hemorrhagic presentation treated with radiosurgery, the annual rate of bleeding was 0.4% per lesion; the rate was 2.5% in those with a single prior hemorrhage, and for those with multiple bleeds, this rate was 3.85% for the first 2 years after treatment and 1.3% in long-term follow-up. Several retrospective natural history studies have addressed the rate of hemorrhage of CCMs in superficial locations using a similar methodology to that used by Nagy et al. These studies cited a natural history rate of annual hemorrhage ranging between 0.25% and 2.3% per patient per year.^{5,9} Prospective studies have cited a higher hemorrhage rate, especially for individuals with a history of a hemorrhage. In these studies, incidental lesions had a hemorrhagic rate of 0.6% per year compared to those with a history of hemorrhage (4.5% per year) and those with a history of seizures (0.4% per year).^{5,9} In sum, the rates of hemorrhage when treated with radiosurgery versus when not treated with radiosurgery do not appear to be significantly different.

A large recent meta-analysis of 1620 patients demon-

strated a 5-year risk of hemorrhage of 3.8% in patients with nonbrainstem CCMs who did not present with intracerebral hemorrhage (ICH) or a focal neurological deficit (FND), or roughly a 0.7% per-year risk of hemorrhage.⁸ Although there are many statistical nuances associated with the calculation of hemorrhage rates, the rate of bleeding after radiosurgery does not appear to be different from what is known to be the natural tendency of these lesions to bleed and for bleeding episodes to cluster. Not only does radiosurgery provide no protection over the natural history of CCMs, but the series noted 8 treatment failures associated with radiosurgery, with a posttreatment hemorrhage complication associated with a permanent deficit of 4.3% and with radiation toxicity in 2% of patients. The combined posttreatment morbidity rate under this paradigm is therefore 6.3%. Compare this with surgery, in which the rate of permanent deficits after the resection of a cortical lesion has been reported to range between 1.3% and 3.2%.^{2–4,6} Surgery, therefore, provides a definite cure of CCMs with a more favorable morbidity rate in both the short and long term for superficial lesions. Perhaps most alarming is the finding that in this cohort, pediatric patients had the highest rate of treatment failure. The use of radiosurgery in this context would unnecessarily place the population at highest risk for radiation side effects and with the highest life expectancy at the greatest risk. Further along the same line of discussion, radiosurgery has been shown to lead to the formation of CCMs in a delayed fashion.¹² The use of radiation to treat patients at risk for formation of additional lesions, such as familial cases of CCM, may lead to a further increase in disease burden in at-risk populations.

A separate but critical issue addressed by Nagy and colleagues is the question of radiosurgery's efficacy in seizure control. The authors noted a seizure control rate of 78%–87% for patients with a variety of epileptic presentations, with or without hemorrhage, but they did not provide enough detail for readers to parse out the subtleties required to attribute a role for radiosurgery for seizure control. The reported rates for seizure control in this paper are comparable to those in surgical series.

The second article by Nagy et al.¹³ addressed a cohort of 210 patients with lesions located in the brainstem, basal ganglia, or thalamus treated with radiosurgery. The authors asserted that radiosurgery results in a decrease in the tendency of deep-seated lesions to bleed. The results of this paper warrant an independent discussion. The natural history of untreated CCMs in deep locations has been

the topic of several recent publications. Tian et al. recently reported on the outcome of untreated thalamic CCMs,¹⁶ noting an annual hemorrhage rate of 9.7% in this population. The highest rate was observed in patients who presented with hemorrhage and neurological deficits (14.1%), and the lowest annual hemorrhage rate was in those in whom the lesion was identified incidentally (1.2%). Therefore, the natural history of annual hemorrhage in thalamic lesions rests between 1.2% and 14.1%. The natural history of untreated brainstem cavernous malformations has been the topic of two recent studies. Li et al. reviewed the Beijing Tiantan Hospital experience in both pediatric patients and all comers.^{10,11} In the larger study of 331 patients, they noted that the annual risks of hemorrhage in patients with or without FNDs were 15.9% and 12.4%, respectively. The rate of hemorrhage in patients with incidentally identified lesions was 8.7%. In their pediatric cohort, they noted an annual hemorrhage rate of 11.7%, and they observed a significant decline in rate of hemorrhage 2 years after the initial hemorrhage. Based on a recent large meta-analysis, the estimated 5-year risk of hemorrhage in patients with brainstem CCM presenting with ICH or FND was 30.8%, whereas that for brainstem CCMs without ICH or FND was 8.0%. Therefore, the rate of hemorrhage based on this meta-analysis on a per-year basis is between 1.6% and 6.1%. Nagy et al. cited a lifetime annual hemorrhage rate of 2.4% per lesion for patients with a single hemorrhage. The rate appears to stabilize at 1.1% after an initial increase to 4.3% during the first 2 years after radiosurgery, suggesting that the radiation treatment itself may exacerbate the bleeding risk for a short period. Their annual pretreatment hemorrhage rate was 2.8% for lesions with multiple bleeds prior to radiosurgery, with a pretreatment rebleeding rate of 20.7% (although it is not clear over what period of time), a decrease within the first 5 years, and plateau at 11.5%. They noted that the rebleeding rate fell to 7.9% for the first 2 years after radiosurgery, and it declined to 1.3% thereafter. The rates noted are within the range reported in the literature for risk of rebleeding and fit with what is known about the natural history of lesions followed in the long term: some go on to be dormant. Further troubling is the fact that the conclusions of the authors as to the long-term hemorrhage-free rate in this cohort are based on a single patient using Kaplan-Meier analysis.

The common shortcoming of these natural history studies is their preselection at surgical centers where readily accessible lesions are operated on. Nonetheless, these data support the notion that brainstem CCMs have a higher annual hemorrhage rate than their cortical counterparts; the rate of rehemorrhage is higher; there exists a wide range in the risk of hemorrhage by these lesions and factors leading to hemorrhage are ill-defined; the risk of hemorrhage decreases significantly after the initial period of hemorrhage, but this natural history is not well delineated; and the existing natural history data are heavily influenced by surgical centers and their patient selection criteria.¹⁵

Nagy et al. stated that their treatment paradigm consisted of an “early intention to treat paradigm” given that repeated hemorrhages resulted in a significant rate of deficit. However, review of the paper shows that the median age at presentation in this cohort was 37 years but that the medi-

an age at treatment was 43 years. This significant discrepancy between ages at presentation and treatment begs the question of whether the patients were truly treated early or if they were treated after a cool-down period, when the risk of hemorrhage from these lesions had decreased. The use of radiosurgery as a treatment option was associated with 11 failures: 5 treated with surgery and 6 requiring retreatment with radiosurgery. Posttreatment hemorrhage was associated with morbidity in 7.4% of patients and radiation-related complications in another 7.2%, for a combined morbidity/complication rate of 14.6%. The mortality rate was 1%. These data compare with a 10%–14% permanent morbidity rate (although the transient morbidity rate is higher) and 1% mortality rate observed with surgery for similar lesions.^{6,7} Furthermore, surgery is associated with a 2% risk of rehemorrhage per patient¹ and, for most lesions, results in a cure, whereas in this study radiosurgery was associated with a significantly higher risk of rebleeding than surgery, a comparable risk of complications, and no apparent alteration in the natural history of brainstem cavernous malformations.

In the search for the ideal treatment for patients with CCMs, practitioners must weigh the risks of their intervention against the natural history of the disease. If the treatment offers no improvement over the natural history, or differently stated, if the risks of complications outweigh the natural history of the disease, one must urge caution with the use of the treatment. The two papers by Nagy et al. reignite discussion on the role of radiosurgery for CCMs. Radiosurgery is thought to obliterate arteriovenous malformations through a sclerosing action on arteries and arterioles, inducing endothelial cell loss and stimulation of smooth muscle cells. CCMs lack these arterial elements, and therefore they lack the biological basis of radiosurgery's action. With long life expectancies, patients with CCMs should be treated with modalities that offer definitive and durable treatment effects on their lesions. Based on the data from the two papers by Nagy et al. and a review of the existing literature, it does not appear that radiosurgery a) significantly alters the natural history of CCMs; b) offers a “cure” rate comparable with that of surgery; or c) offers a morbidity profile that is better than surgical options, definitely for hemispheric lesions, and most likely for deep-seated lesions; but it does seem that radiosurgery d) provides a higher failure rate than surgery in pediatric patients who are at most risk from radiation and have the longest life expectancy and are therefore at highest risk long-term. We urge caution in interpreting the results of these papers that suggest that radiosurgery is an alternate to surgery or even to observation for patients harboring these lesions.

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Disclosures

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Response

Radiosurgery for cavernous malformations (CMs) has been controversial since its introduction. Not only the fact that there is no reliable radiological measure available to indicate cure after radiosurgery, but also the high morbidity associated with the pioneering efforts and ambiguous reports on natural history, has discouraged the neurosurgical community from accepting radiosurgery as a real treatment alternative for a long time. However, while the controversy has lived on, treatments have continued, and at the same time radiosurgery has made technical and perceptual progress, and the natural history and real-life surgical outcomes of patients have become better understood. In this context, we felt it mandatory to analyze data accumulated during the last 2 decades, particularly in light of our current knowledge concerning the natural history and different treatment modalities. The aim of writing our two papers on CM radiosurgery was not only to revisit our increasing pool of data but also to reflect on our current knowledge and to promote open discussion in this context. Therefore, we were happy to read the commentary by Kalani et al. on our papers. While we agree with the authors on some observations, there are strong arguments against some others, and we also have to point out the limitations of our current knowledge that may help us to define future directions.

To start with the weaker part of the CM radiosurgery story, we intentionally wrote a separate paper on hemispheric CMs. As we pointed out in the introduction, hemispheric CMs are not often considered for radiosurgery, because their natural history is less aggressive⁷ and microsurgical resection is usually safe and effective.⁴ Moreover, our data suggest that rehemorrhage in this anatomical location does not lead to significantly increased cumulative morbidity. Clearly, for a benign lesion with a 5-year estimated bleeding risk of 3.8% without and 18.4% with prior hemorrhage⁷ (an annual first-ever hemorrhage rate of 0.6% and rehemorrhage rate of 4.5%),⁸ the statistical power to detect a significant benefit on hemorrhage rate after radiosurgery remains low. Therefore, even if the radiosurgery-related morbidity is low (6%, all modified Rankin Scale [mRS] score of 1), its role in the prevention of hemorrhage and neurological consequences can rightly be questioned. Ours is an honest paper, clearly pointing out the current limitations of our knowledge in this field, and based on our data, we would strictly reserve radiosurgery for a small group of selected patients harboring proven-aggressive CMs in eloquent locations not amenable to safe resection. There is no doubt that microsurgery is the treatment of choice for most hemispheric hemorrhagic CMs, and we counsel our patients with this knowledge in mind. It should be also stressed, however, that even if the patients are well informed, some would still be reluctant to undergo craniotomy. More importantly, our current paper, together with few prior publications,¹⁰ demonstrates that radiosurgery leads to good seizure control similar to microsurgery. Outcomes after both microsurgery and radiosurgery appear to be superior to the natural history or medical therapy alone.³ Thus, as a noninvasive option, radiosurgery can be confidently considered as part of our armamentarium to prevent seizures associated with CMs,

especially if the lesion is eloquent, in a patient reluctant to undergo open surgery. It is with this sentiment that we felt it important to bring our results into the public domain.

The second issue is the natural history of deep-seated CMs and the question of whether outcome after radiosurgery is superior to observation in the long term? The most conservative estimate of the 5-year risk of rebleeding from brainstem CMs with a hemorrhagic presentation is 30.8%.⁷ However, other series give an estimated median hemorrhage-free survival time of 55 months with and 67 months without FNDs of hemorrhagic brainstem CMs,⁹ and only 55% of thalamic CMs were hemorrhage free at 5 years after presentation.¹³ Our data suggest a far superior long-term outcome after radiosurgery: the 5-year hemorrhage-free survival is 90% (numbers at risk: 113), falling only to 83% at 10 years (numbers at risk: 43). We accept the argument that our prediction for longer-term outcome becomes uncertain (only 1 patient), but we have to stress that we cannot even provide a prediction of median hemorrhage-free survival after radiosurgery because our data suggest it far later than our observation period (20 years), contrary to the natural history studies. Clearly, more data and a longer follow-up period are needed, but available long-term data are promising.

With regard to the quoted median age at presentation of 37 years and the median age at treatment of 43 years, it is not a real discrepancy between our early intention to treat and our real practice. We would call it, rather, a statistical “illusion” as we state later in the text that the median time between the presenting bleed and radiosurgery was 1 year in the single-bleed group and 3 years in the multiple-bleed group, and the median time between the first and second bleeds was 2 years in the latter group. At first, this may seem paradoxical, but the statistical reason is that the older half of our patients was treated sooner after presentation. In other words, younger patients were relatively older at treatment, which shifted the median time at treatment to older age. In fact, 70% of the single-bleed cohort was treated not later than 1 year after the bleed and 87% within 2 years. From a strict point view, analyzing those single-bleed lesions that were treated within the 1st year after bleed, the annual rate of rebleed was 6% within the first 2 years after radiosurgery and 1% thereafter. These data do not support the “cooling down” theory as a bias. Based on the most conservative estimate, the annual rebleed rate is 15% during the 1st year, 8% during the 2nd year, and 4% thereafter in untreated hemorrhagic brainstem CMs.⁷ Our data are in line with this trend if we assume a partial protection of radiation during the first 2 years after radiosurgery and a more likely protection thereafter. Moreover, due to partial removal of a significant proportion of surgical cases, the long-term annual rebleed risk is 2% after microsurgery,¹ which is clearly not superior to our 1% annual long-term rebleed rate.

The next controversial issue is the morbidity of microsurgery and radiosurgery. It is important to stress that the indications for surgery are restricted, even in the opinion of most experienced surgeons. To quote Dr. Spetzler: “... those that are symptomatic, those that cause mass effect, or those that abut a pial surface” are surgical candidates, and “those with mild symptoms and/or deep-seated CMs

were observed until further bleeding episodes made the lesions more amenable to intervention (that is, the pial surface could be reached via the hemorrhagic cavity).”²² This leaves, from our point of view, a broad spectrum of indications for radiosurgery: patients who are without symptoms or with only minimal symptoms and those with deeper-seated, small lesions. If left untreated, only 30% of the patients harboring brainstem lesions recovered fully,⁹ and only 38% of those with thalamic CMs remained independent.¹³ We disagree with the policy of waiting until a further bleed destroys enough of the brainstem or thalamus/basal ganglia to become amenable for resection, because it means additional morbidity that is higher than the morbidity of radiosurgery. The rate of functional independence (mRS score of 0 or 1) was 84% before radiosurgery in our cohort of patients with CMs and single hemorrhage, and it remained 78% after radiosurgery, whereas it was 69% and 62% in the multiple bleed group, respectively. Keeping in mind that we are not talking about identical groups of patients, we should point out the dark and not always apparent side of surgery for deep-seated CMs. The authors quote a 36% rate of permanent new deficits with their impressive 260-patient experience in their earlier report of surgical outcome of patients with brainstem CMs,¹ while a meta-analysis of 1390 patients indicated only 16% worsening after surgery.⁶ One wonders about the discrepancy between surgical outcomes in one of the most experienced centers and the rest of the published literature and wonders whether the meta-analysis of the published results is only a reflection of the shiny tip of the iceberg. Admittedly, surgeons do not like to publish their poor results, and our personal perception of the real outcomes of brainstem and thalamic CM surgery (at least in our countries) is certainly closer to (may even be worse than) the 36% surgical morbidity rate of one of the most experienced brainstem surgeons in the world. Moreover, strictly speaking on the shiny published results, 12% of the surgical patients required tracheostomies or gastrostomies, 1.8% of whom required them permanently.⁶ Even if one does not need them permanently, this is a significant morbidity. We should also consider the socioeconomic costs of microsurgery (including shorter or longer ICU stay) and that nearly half of the microsurgical patients were discharged to an in-patient rehabilitation unit and not home.¹ Unfortunately, little information can be found in the literature about the severity of surgical morbidity (in mRS scores), but it is important to stress that the 14.6% overall morbidity rate of radiosurgery indicates an increase of 1 in mRS score in 13.1% of the patients, which means independent life. It is also important to stress that radiosurgery is independent of the operator as it is well standardized even in the case of CMs today. Outcomes are well reproducible all over the world, as it was shown in a recent review of ours: adverse radiation effects of 4.2% and posttreatment hemorrhages of 5.3%.¹⁰ From this perspective, one might even consider our present results “poor” in comparison to the radiosurgical literature, but our definition of morbidity was strict and therefore sensitive, and we are still talking about rare minor symptoms in independent patients.

Finally, the authors claim that “radiosurgery is thought to obliterate arteriovenous malformations through a sele-

rosing action on arteries and arterioles, inducing endothelial cell loss and stimulation of smooth muscle cells,” and CMs “lack these arterial elements, and therefore they lack the biological basis of radiosurgery’s action.” Several histopathological reports demonstrate a “scarring” effect of radiosurgery in CMs¹¹ in parallel to the decreasing rebleed rate, which is not identical to the effect of radiosurgery on arteriovenous malformations.¹⁴ It is important to note that these studies were based on specimens from symptomatic patients who underwent surgery after radiosurgery, and therefore it is likely that the histopathological view reflects a partial response in these studies. Nevertheless, the effect of radiosurgery on CMs is already well documented histopathologically.

In conclusion, we agree that CM radiosurgery is still controversial, and there are several concerns to be answered. However, over the last 3 decades the radiosurgical community has been able to define a safe treatment protocol that reduced the initial high morbidity rate seen in the experimental phase, which was the main basis for the early skepticism.⁵ Moreover, during the last decade, accumulation of extensive population-based data also led to a better understanding of the natural history of CMs, shifting the debate surrounding radiosurgery from a speculative¹² to a data- and observation-based foundation. This debate remains ongoing until more data with a higher number of patients and longer follow-up times are available, but we hope that with our present pair of papers we were able to add important pieces of mosaics to the whole picture, and we believe that the current debate will be stimulating for the neurosurgical community.

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The treatment of cerebral cavernous malformation-related hemorrhage using β -blocker medication

TO THE EDITOR: We read with great interest the article by Goldberg et al.² regarding the treatment of cerebral cavernous malformation (CCM)-related hemorrhage using β -blocker medication (Goldberg J, Jaeggi C, Schoeni D, et al: Bleeding risk of cerebral cavernous malformations in patients on β -blocker medication: a cohort study. *J Neurosurg* [epub ahead of print June 15, 2018. DOI: 10.3171/2017.12.JNS172404]). In this article, the authors performed a retrospective cohort study to investigate whether β -blocker medication can lower the risk for CCM-related hemorrhage. They found that β -blocker medication does not seem to be associated with a decreased risk of CCM-related hemorrhage at presentation or during follow-up. This is an excellent retrospective cohort study, focusing on the role of β -blocker medication in CCM-related hemorrhage. However, the topic is still controversial, and some issues need to be discussed.

This research included almost every type of β -blocker medication but only two patients were under treatment with propranolol. The proportion of patients with hypertension was 36%, and the proportion of patients with hypertension under the treatment of a β -blocker was 92.5%. It has been

reported by Zabramski et al. that propranolol reduced the size of CCMs and recurrent hemorrhages.⁸ However, these two patients did not present with hypertension. Another study by Reinhard et al. indicated that propranolol stopped progressive multiple CCMs in a 22-year-old man.⁷ Notably, this patient did not present with hypertension. It has been recently reported that the level of plasma acetylcholine was lower in patients with intracerebral hemorrhage (ICH) compared with the healthy controls. However, serum norepinephrine and cortisol were higher in patients with ICH. Namely, ICH can lead to sympathetic nervous system activation.⁹ In addition, the cholinergic antiinflammatory pathway has been suggested to be critical in attenuating inflammation after stroke.¹ In hypertensive patients, the sympathetic nervous system has already been activated, and it will be further activated after ICH onset. As a result, the parasympathetic nervous system is strongly inhibited, facilitating inflammation around hemorrhagic brain tissue. Therefore, hypertension might interfere with the effect of β -blocker medication, and hypertension might be a critical factor in the effect of β -blocker medication on the CCM-related hemorrhage. We suggest that the authors investigate the effect of β -blocker medication on CCM-related hemorrhage in patients without hypertension.

Additionally, the effect of propranolol has been confirmed in infantile brain cavernoma⁶ and cutaneous hemangiomas.^{3,5} In this retrospective cohort study, the patients were mainly middle aged and elderly. Age might be another important factor that affects the effect of propranolol. The mechanisms of propranolol involve vasoconstriction, apoptosis of capillary endothelial cells, and decreased expression of vascular endothelial and basic fibroblast growth factor genes.⁴ With increasing age, dysfunction of the β -2 receptor in the blood vessels will occur, and there might be a decrease in the expression of β -2 receptor. Consequently, the efficacy of propranolol will be decreased.

In summary, further clinical research is needed to confirm the efficacy of β -blocker medication, which might be determined by hypertension and age. We, therefore, suggest that attention should be paid to these two factors when designing clinical trials.

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Disclosures

The author reports no conflict of interest.

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Response

We thank Dr. Zhao for his thoughtful letter and response to our article. The issues raised by the author focus on the inclusion of all types of long-term β -blocker medications in our study, the high rate of underlying arterial hypertension, and the age in the subgroup of patients treated with β -blocker medication.

Like the author, we have been impressed by the published case series observing size reduction or stabilization of CCMs in terms of the likelihood of hemorrhage after treatment with propranolol.^{1,6,7,9,10} We agree that the results provided by our study are limited and cannot be generalized regarding exclusive propranolol medication. However, the underlying mechanisms for the effects of propranolol are not yet completely elucidated, and the β 1-selective β -blocker atenolol also showed positive effects for infantile cutaneous hemangiomas.^{2,8} This is why the decision was made to investigate the effects of all types of β -blockers. All in all, we could not find an association between CCM-related hemorrhage and any type of β -blocker medication at presentation or during follow-up in our cohort.

We agree that most of the patients in our β -blocker cohort suffered from arterial hypertension. This is inherent to the retrospective design of the study. Dr. Zhao suggests that this might influence the effects of β -blocker medication. The activity of the sympathetic nervous system may be increased in patients suffering from arterial hypertension and ICH, this being responsible for an inhibition of the protective effects of the parasympathetic nervous system on brain inflammation. This thought is interesting but still highly speculative. The authors of the studies provided analyzed primary basal ganglia ICH¹¹ and stroke in general.³ To our knowledge, it is unclear whether these results can be generalized to CCM-related hemorrhage. The question of whether arterial hypertension is influencing the possible effects of propranolol in CCMs can only be answered in the setting of a prospective comparative trial.

We agree that age is an important factor concerning CCM-related hemorrhage. Further studies are needed in order to assess whether this, together with other factors

(and possibly including genetic ones), influences the effect of propranolol on the disease. The average age at diagnosis of CCM was reported to range from 42.7 to 45 years in recent meta-analyses.^{4,5} Patients in the β -blocker cohort of our study were on average 62.5 years, whereas the age available in the reported case series ranges from newborns to 58 years.^{1,6,7,9,10}

The questions and controversies raised by the author, by the reported case series, and by the present cohort study highlight the need for a prospective multicenter trial, powered enough to determine which subgroups of patients could potentially benefit from β -blocker medication.

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Intracranial stenting in acute stroke

TO THE EDITOR: We read with great interest the ar-

ticle from Kang et al.³ (Kang DH, Yoon W, Kim SK, et al: Endovascular treatment for emergent large vessel occlusion due to severe intracranial atherosclerotic stenosis. *J Neurosurg* [epub ahead of print June 22, 2018. DOI: 10.3171/2018.1.JNS172350]). As an institution with significant interest and more than a decade of experience with intracranial stenting in the setting of acute large vessel occlusion (LVO), we found the results of this study quite remarkable. In the spirit of advancing the care of acute stroke, we were extremely impressed by the outcomes. Should these results be extrapolated to the general stroke population, a quantum leap in outcomes could very well be observed.

The authors present data from a cohort of 72 patients treated with intracranial stenting after thrombectomy in the setting of severe intracranial atherosclerotic disease. The rate of symptomatic hemorrhage was 1.4%, mortality was 9.7%, and a modified Rankin Scale (mRS) score 0–2 was recorded at 90 days in 57%. Comparatively, in a cohort of 68 patients treated with the infusion of tirofiban after thrombectomy instead of stenting, the rate of symptomatic hemorrhage was 0%, mortality was 5.9%, and an mRS score 0–2 was found at 90 days in 63%. The authors concluded that both approaches are safe and effective.³

The HERMES collaboration pooled patient-level data from five randomized trials on thrombectomy and reported a 4.4% symptomatic hemorrhage rate, 15% mortality, and an mRS score 0–2 in 46% at 90 days.² Obviously, the results of Kang and colleagues are significantly better. This is remarkable given that Kang et al. performed thrombectomy and subsequent intracranial stenting or tirofiban infusion. Most would agree that an average thrombectomy harbors less risk than performing intracranial angioplasty/stenting. Nevertheless, outcomes in their study were better for the compound procedure than the published results for thrombectomy alone.

Although one can perhaps partially account for this in the stenting cohort in the context of lower National Institutes of Health Stroke Scale (NIHSS) scores among presenting patients (median 11 for stented cohort in Kang study vs 17 in HERMES study); in the tirofiban cohort, the median presenting NIHSS score was similar to those in the intervention groups in the HERMES study. It is thus remarkable that despite the added administration of tirofiban, the symptomatic hemorrhage rate was, in fact, less than that in the HERMES collaboration (0% vs 4.4%).^{2,3} It is also important to emphasize, considering the results in the SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis),¹ that patients with medically managed severe symptomatic intracranial stenosis harbor a 6% risk of recurrent transient ischemic attack (TIA) or stroke in 30 days. Thus, it is remarkable that, despite this compounded risk, 63% of patients had an mRS score 0–2 at 90 days.³

In our hands, and as recently reported by Kasab et al.,⁴ we have found symptomatic hemorrhage rates to be higher after acute stenting for LVO caused by severe intracranial atherosclerotic disease, a result some might consider intuitive. Consistent with other groups as well, we have found clinical outcomes among this cohort to be generally worse

and worthy of more precise quantification. Although we have not utilized tirofiban after recanalization of LVO due to intrinsic disease, it is important to emphasize the significant risk of acute vessel re-occlusion in the setting of recent recanalization. We have often seen the vessel re-occlude on interval angiography in the process of preparing to stent.

Kang et al.'s results are remarkably superior to those seen in the HERMES collaborative data. It is obvious that these discrepant results are worthy of discussion. Specifically, an explanation for the discrepancy may shed invaluable light on an ability to improve stroke outcomes. Do the authors believe the discrepancy is attributable to a pre-intervention process? A technical aspect of intervention? Posttreatment care? Highlighting the specifics would be of particular use to those treating this challenging disease process as some might otherwise endorse a more guarded prognosis for patients with LVO secondary to severe atherosclerotic disease.

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Response

We greatly appreciate the interest in our study. As suggested by Gross et al., it would be beneficial to readers to provide further discussion on the possible factors associ-

ated with the better treatment outcomes after the endovascular therapy in our patient population in comparison to those in the HERMES collaborative data.¹

First, most of the patients included in our study underwent preoperative MRI including a gradient-recalled echo (GRE) sequence, which may be helpful in predicting the underlying intracranial atherosclerotic stenosis (ICAS) before the procedure. Prediction of the underlying ICAS before commencing the endovascular therapy is of particular importance because it can minimize the unnecessary passage of thrombectomy devices through a severely stenotic artery. Therefore, it allows a significant reduction in procedure time and leads us to perform the rescue therapy with more confidence as early as possible, all of which collectively could contribute to procedural success in this patient population. One of the ways to predict the underlying ICAS in patients with LVO is by observing a susceptibility vessel sign (SVS) on GRE or susceptibility-weighted sequences. We previously reported that the absence of an SVS (negative SVS) on GRE MRI was significantly associated with the underlying ICAS in patients with an acute middle cerebral artery occlusion.⁴ The negative SVS in patients with ICAS may be due to a component of clots (fibrin and platelet dominant) as well as a small clot burden.

Second, we tried to achieve optimal angiographic results (defined as < 50% residual stenosis on the final angiogram) as much as possible when performing angioplasty or stenting. We previously investigated the predictors of acute re-occlusion in patients undergoing emergent angioplasty with or without stenting for the treatment of LVO due to severe ICAS.² In this study, acute re-occlusion occurred more frequently in patients with a suboptimal result than in those with an optimal result (71.4% vs 2.6%). In addition, acute re-occlusion was significantly associated with a poor 90-day outcome. These results suggest that sufficient dilatation of the stenosis should be obtained to prevent the acute re-occlusion and thus achieve favorable outcomes in patients who are undergoing emergent angioplasty or stenting for severe ICAS.

Third, we could achieve a very high rate (95%) of successful reperfusion with our treatment strategies compared to those in the five randomized controlled trials (58.7%–88%). A very high rate of successful reperfusion in our patient cohort may be attributed to the following factors: 1) patients with underlying ICAS have no apparent clot burden or a very small clot burden;^{4–7} and 2) these patients have an excellent pre-existing collateral circulation before the onset of acute arterial occlusion.³

In summary, the use of an MRI vessel sign to predict the underlying ICAS before endovascular therapy, a maximal effort to restore adequate luminal patency during angioplasty or stenting, the achievement of a very high rate of successful reperfusion with effective rescue approaches, and intrinsic factors related to the ICAS itself, such as a small clot burden and good collateral circulation, may have contributed to better treatment outcomes in our study.

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Reducing EVD-related infections

TO THE EDITOR: We read with great interest the paper from Champey et al.¹ (Champey J, Mourey C, Francony G, et al: Strategies to reduce external ventricular drain–related infections: a multicenter retrospective study. *J Neurosurg* [epub ahead of print June 22, 2018. DOI: 10.3171/2018.1.JNS172486]). We congratulate the authors on this large study, which tackles an ever-present challenge in neurosurgical practice. It raised some interesting issues, and we would like to respectfully offer some interpretation and ask some questions of this study.

The authors state that this study examines the impact of two aspects of external ventricular drain (EVD) care, namely, daily samples and intraventricular antibiotics prior to EVD removal, but it is shown in the article that the response to positive cultures differs between the three units (Grenoble, Saint-Etienne, and Marseille). Grenoble has a policy of distal EVD replacement at suspicion of coloniza-

tion or infection, while the other two units will only intervene once infection is confirmed. Do the authors feel that the lower infection rate at the Grenoble site, despite the same proportion of positive cultures, is generated through this third aspect of practice?

In Grenoble, the threshold for EVD removal did not reach confirmed infection. It is not stated whether it was sufficient to exclude the re-inserted EVD (assuming one was re-inserted) from the study as a marker of pre-existing CSF infection. The potential problem from this omission is patients developing confirmed infections in EVDs no longer included in the study.

The criteria for confirmed infection attribute much value to clinical deterioration with multiple cultures, and fever in its absence being classified as colonization. However, is the intensive care population the most sensitive group for these criteria to be applied, as a clinical deterioration is difficult to detect in the patient undergoing intubation and ventilation, and as such may be misclassified due to the obscured clinical state?

The omission of intraventricular antibiotics in the 3 patients who developed ventriculitis can be interpreted in different ways; is it confirmed that the remaining 218 patients all received the antibiotics or were these 3 patients part of a larger group of Grenoble patients without pre-removal antibiotics? This is understandably a constraint of retrospective research, but these two scenarios greatly alter the perceived impact of the intraventricular antibiotics, as the lack of administration can be interpreted as a significant contributor to development of ventriculitis or a chance finding in a heterogeneous group.

Daily sampling behind the collector in Grenoble not showing an increase in positive cultures is an interesting finding, demonstrating a level of safety despite such frequent access.

This study appears to successfully demonstrate variety in practice, but a unity in approach between 3 units, achieving similar results in positive cultures through the use of standardized care plans. We commend the authors for providing this important message for those managing patients with EVDs.

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Disclosures

The authors report no conflict of interest.

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Response

We warmly thank Dr. Dapaah and colleagues for their constructive comments on our article. They addressed three important issues concerning the bundle of care resulting in a lower incidence of EVD-related infections in the Grenoble site compared to the two other sites.

Was this low incidence explained by an early EVD removal prior to the development of CSF infection in Grenoble? This could have artificially impacted the incidence of CSF infections. In fact, 1 of the 21 patients with positive CSF cultures underwent EVD removal for suspicion of infection. For the rest of the Grenoble cohort, EVD removal was performed because of neurological improvement or EVD dysfunction with no associated CSF infection.

How to diagnose ventriculitis in sedated patients? This could have misclassified confirmed EVD-related infection in patients with neurological deterioration. This comment is obviously correct and reminds us of the importance to clinically assess brain-injured patients without interference of sedatives to detect neurological complications. In sedated patients, such detection relies on changes from indirect measurements such as pupil size, cerebral imaging, transcranial Doppler ultrasonography, intracranial pressure, and/or extracranial variables. In the present study, the development of each case of ventriculitis was delayed in the 3 cohorts, typically occurring after 1-week duration of EVD drainage in which patients were no longer sedated. As mentioned in the Supplemental Material, the 3 patients who developed ventriculitis in Grenoble were awake and able to be examined neurologically at the time of diagnosis.

What was the role of pre-removal administration of intraventricular antibiotics in preventing EVD-related infections? Although intraventricular administration of amikacin prior to EVD removal was one specific measure of our EVD bundle of care, it was unfortunately not possible to establish a causal link between the absence of this measure and the development of ventriculitis in our 3 patients. This was due to a number of missing data regarding this action in the 218 other patients. The prophylactic effectiveness of such a measure needs to be confirmed.

It should be kept in mind that the EVD bundle of care at Grenoble may help physicians to be more reactive when biological changes occur in daily CSF samples prior to the development of ventriculitis. This strategy may also limit the overtreatment of patients with positive CSF cultures.

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Ketamine sedation for the suppression of spreading depolarizations

TO THE EDITOR: We wish to congratulate Carlson et al.¹ on their important study demonstrating the effect of ketamine sedation to suppress injurious spreading depolarizations (SDs) during intensive care after severe brain injury (Carlson AP, Abbas M, Alunday RL, et al: Spreading depolarization in acute brain injury inhibited by ketamine: a prospective, randomized, multiple crossover trial. *J Neurosurg* [epub ahead of print May 25, 2018; DOI: 10.3171/2017.12.JNS171665]). SDs have been intensively studied as a causative mechanism of lesion development and excitotoxicity in animal models,⁶ and translational studies have demonstrated even greater relevance to human brain injury.^{3,5} A hurdle to broader application—and patient benefit—has been identification of effective approaches to prevent SDs through pharmacology or amelioration of tissue conditions that trigger them. The multicenter study of Hertle et al.⁸ showed a strong effect of ketamine on decreasing SD incidence, yet the study suffered from having a retrospective and nonrandomized design in which case mix, factors leading to sedation choice, and natural SD time course^{4,7} were possibly confounding. Carlson et al. addressed these concerns with a randomized, multiple-crossover design in which ketamine, dosed to the patient's sedative needs, was alternated with dexmedetomidine and either propofol or midazolam every 6 hours. Thus, the effects of injury type/severity and SD timing were balanced between the alternating regimes. The authors found that periods with no or low-dose ketamine (< 1.5 mg/kg/hr) had increased risk of SD compared to periods of ketamine dosage > 1.5 mg/kg/hr, with an impressive odds ratio of 13.8.

We noted that effects in this trial were not significant in a per-subject analysis and suspect this was due to a relatively low overall rate of SDs when patients were off ketamine. Toward this point, we wish to communicate a case of severe brain trauma with a high baseline rate of SDs that were strikingly suppressed with a 1.5-mg/kg ketamine bolus (see Fig. 1 for details). From the start of electrocorticography after emergency neurosurgery, SDs (n = 55) recurred continuously in the injured hemisphere at regular intervals of 20 ± 6 minutes for 18 hours. After the ketamine bolus was given, the next expected SD did not occur, and SDs remained suppressed for 2 hours. Subsequently, they resumed at regular intervals of 23 ± 6 minutes, totaling 50 SDs in the following 19 hours. The potency of this effect was particularly noteworthy given the injury severity and the refractory rise of intracranial pressure (ICP). Ketamine was not continued due to a family decision to withdraw care. It is provocative to wonder whether the patient's course might have been different had he received sustained ketamine sedation from the start.

There has been resistance to ketamine use for sedation in brain-injured patients due to historical fears that it may cause ICP elevation. However, these views have been refuted in randomized studies, and in some centers ketamine

FIG. 1. Ketamine bolus suppresses SDs in a case of severe brain trauma. A 49-year-old man fell 30 feet from a ladder. Upon arrival to our Level I trauma center, he was withdrawing his upper extremities. Head CT scan (left) showed a large subdural hematoma, and the patient was taken emergently to the operating room for hemicraniectomy and hematoma evacuation. A subdural electrode strip was placed on the left inferior frontal gyrus, ICP and tissue oxygen (PtiO₂) probes were placed through a bolt in the contralateral hemisphere, and scalp electroencephalography (EEG) monitoring was performed. In the 1st day of postoperative neurointensive care, ICP became progressively refractory to standard treatment, while SDs occurred continuously at electrodes 4–6 of the subdural strip. In order to maximize sedation while preserving arterial pressure, a 1.5-mg/kg intravenous bolus of racemic ketamine was given. The traces (right) show a 9-hour period around this time. *Upper trace:* Recordings from electrode 5 of the subdural strip show SDs evidenced by the negative deflections (asterisks) in the direct-current electrocorticography (ECoG) study and simultaneous depressions of spontaneous ECoG activity (0.5–50 Hz; second trace). *Center trace:* EEG study from the C3–P3 channel shows amplitude fluctuations reflecting the depression periods of SD. Similar fluctuations were present in other ipsilateral EEG channels. Note that both ECoG and EEG studies show a dramatic recovery of spontaneous brain activity after ketamine administration, which persists continuously for 2 hours until SDs resume. ICP increased progressively from 55 to 75 mm Hg over the period shown, and mean arterial pressure was maintained at 100–110 mm Hg. Due to the patient's poor neurological examination results and lack of improvement, the family elected to withdraw care, and the patient died the next day.

is now routinely used in conjunction with other anesthetics for sedation when patients are mechanically ventilated.² The randomized study by Carlson et al. has now provided a conclusive demonstration that sedative doses of racemic ketamine are not only safe regarding ICP effects, but also effective in suppressing SDs. We agree that multicenter trials of ketamine for neuroprotection are now warranted and note that SD monitoring in such a trial would allow a novel precision medicine approach through selective patient inclusion and mechanistic targeting.⁷

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Disclosures

The authors report no conflicts of interest.

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Response

We appreciate the comments from this very experienced and pioneering group regarding the role of SDs in brain injury. The case presented provides a very dramatic illustration of the “on/off” effect of ketamine on SDs, and we thank authors for sharing this very interesting case. We agree that this example strengthens our data regarding an effect that can be quite dramatic in some patients.

We also appreciate the comments regarding ketamine and ICP, which we agree add to the large body of literature supporting the safety from an ICP perspective. Finally,

we strongly agree that the observational, retrospective, and now prospective pilot data that have been amassed regarding the potential benefits of monitoring for SDs and administering targeted therapy (such as ketamine) are adequate to warrant prospective multicenter trials.

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