matters of interpretation regarding the relative extent that aPC affects different parts of the coagulation system.

First, they highlight our use of D-dimers rather than a specific fibrin degradation marker and state that the high level of D-dimer must simply be a reflection of high thrombin generation. Our extensive reading of the literature and our understanding of fibrinogen and fibrin cleavage is that these processes are not linear and that no specific test differentiates between the different ways in which they are broken down. Indeed, they themselves say that D-dimers represent ongoing fibrin degradation. In either case, we have shown that products of fibrin/fibrinogen breakdown are dramatically higher in patients with ATC and that blocking aPC (with thrombomodulin knock-in mice) essentially abolishes this response (despite equivalent markers of thrombin generation).

Second and central to their concerns is our finding that, although factor V levels are affected by aPC, this does not appear to have a large effect on overall functional measures of anticoagulant activity. Conversely, they state that there is a general reduction in all procoagulant factors and therefore the factor V effect is of minimal relevance. In our patient and mouse data there are clear differential reductions in factor V levels in patients with ATC to a greater extent than the procoagulant proteases. It is true that our endogenous thrombin potential assay may have missed subtle effects of factor V inhibition, and the correspondents are right to highlight that lower levels of tissue factor may reveal these effects. We absolutely did not say that there was no effect of aPC on the anticoagulant pathways. However, from patient functional assays and from our mechanistic data, these aspects of aPC activation seem to have less of an impact on overall hemostatic function than fibrinolysis and possibly fibrinogenolysis.

Finally, the authors discuss our findings in the context of our previous work, which included elevations of thrombin activatable fibrinolysis inhibitor (TAFI) activity levels. Much of this part of their argument is conjecture, and we believe that they are missing the differential effects of TAFI within a formed clot and that found in the systemic circulation. All of this requires additional study, because our previous data were very preliminary, and we have not explored TAFI activity in this mechanistic model. Throughout the correspondence we believe that their interpretation of our findings is based primarily on *in vitro* hemostasis biology being applied to the circulating plasma samples obtained from our trauma patients who will have multiple derangements in blood and endothelial function. Although we fully agree that high thrombin generation is required to generate aPC, we believe that our mechanistic data fully support a central role for this dysregulated aPC generation in the overactivation of systemic fibrinolysis and fibrinogenolysis rather than this being a purely consumptive phenomenon. We fully agree that this mechanism may drive other clinical coagulopathies, and additional studies in these areas are warranted.

Competing Interests

The authors declare no competing interests.

Karim Brohi, M.D., Ross A. Davenport, Ph.D. Queen Mary University of London, London, United Kingdom (R.A.D.). ross.davenport@qmul.ac.uk

References

1. Davenport RA, Guerreiro M, Frith D, Rourke C, Platton S, Cohen M, Pearse R, Thiemermann C, Brohi K: Activated protein C drives the hyperfibrinolysis of acute traumatic coagulopathy. Anesthesiology 2017; 126:115–27

(Accepted for publication June 1, 2017.)

Dealing with Ophthalmic Chemosurgery Complications

To the Editor:

We read with great interest the review by Scharoun *et al.*[1] in which the authors discuss anesthesia management for ophthalmic artery chemosurgery focusing on unexpected respiratory and cardiovascular complications. We address some issues.

The authors advocate systematic and early intravenous administration of epinephrine to treat any decrease in lung compliance, which is the main complication of this procedure. This therapeutic option is questionable. Admittedly, epinephrine dilates bronchial airways.[2] However, the main action of this mixed α- and β-adrenergic receptor agonist is on the cardiovascular system, with vasoconstricting, chronotropic, and inotropic effects, also causing several side effects including arrhythmia and systemic hypertension. A decrease in lung compliance can often occur on its own, with neither bradycardia nor hypotension, so cardiovascular therapy is not required and should be used with caution.

Propofol is a therapeutic alternative for the following reasons. First, it provides bronchodilatory effects, acting directly on the smooth muscle of the airway, as well as centrally on γ-aminobutyric acid receptors located in the airway-related vagal neurons in the nucleus of the solitary tract.[3,4] Second, because the decrease in lung compliance is caused here by an autonomic reflex, propofol administration, by inducing deeper anesthesia, should inhibit vagal response and thus prevent a steep rise in intrathoracic pressure. This is supported by a systematic review suggesting a relationship between trigeminal reflex and depth of anesthesia during skull base surgery.[5] Moreover, a previous study reports that an adequate Bispectral Index target inhibits the oculocardiac reflex during sevoflurane anesthesia for pediatric strabismus surgery.[6] Lastly, these respiratory complications do not affect adults but only toddlers and children, whose sympathetic immaturity and increase in vagal tone are more susceptible to autonomic reactions.[7,8] This supports the use of hypnotic agents, such as propofol, to prevent and treat the respiratory events. We acknowledge, however, that to date no prospective study has assessed the

effect of anesthetic depth on complications during ophthalmic artery chemosurgery.

We agree with the theory that catheter manipulation of the ophthalmic artery may stimulate trigeminal afferents and cause a trigeminal reflex, resulting in respiratory and cardiovascular complications. However, a few questions remain. Although all intracranial arteries are innervated by trigeminal afferents, there are few reports of trigeminal reflex during endovascular procedures involving other intracranial arteries.[9] Why does the trigeminal reflex occur particularly in the internal carotid artery and ophthalmic artery? What kind of trigger (*e.g.*, pain stimulus or stretching stimulus) causes these complications and at what threshold? Research focusing on the mechanism of these specific complications could help to prevent or reduce them.

Competing Interests

The authors declare no competing interests.

Marie-Claire Nghe, M.D., Anne Godier, M.D. Fondation Adolphe de Rothschild, Paris, France (M.-C.N.). mnghe@for.paris

References

1. Scharoun JH, Han JH, Gobin YP: Anesthesia for ophthalmic artery chemosurgery. Anesthesiology 2017; 126:165–72
2. Tanaka Y, Yamashita Y, Horinouchi T, Koike K: Adrenaline produces the relaxation of guinea-pig airway smooth muscle primarily through the mediation of beta(2)-adrenoceptors. J Smooth Muscle Res 2005; 41:153–61
3. Gallos G, Gleason NR, Virag L, Zhang Y, Mizuta K, Whittington RA, Emala CW: Endogenous gamma-aminobutyric acid modulates tonic guinea pig airway tone and propofol-induced airway smooth muscle relaxation. Anesthesiology 2009; 110:748–58
4. Jin Z, Choi MJ, Park CS, Park YS, Jin YH: Propofol facilitated excitatory postsynaptic currents frequency on nucleus tractus solitarii (NTS) neurons. Brain Res 2012; 1432:1–6
5. Meuwly C, Chowdhury T, Sandu N, Reck M, Erne P, Schaller B: Anesthetic influence on occurrence and treatment of the trigemino-cardiac reflex: A systematic literature review. Medicine (Baltimore) 2015; 94:e807
6. Yi C, Jee D: Influence of the anaesthetic depth on the inhibition of the oculocardiac reflex during sevoflurane anaesthesia for paediatric strabismus surgery. Br J Anaesth 2008; 101:234–8
7. Paques M, Vallée JN, Herbreteau D, Aymart A, Santiago PY, Campinchi-Tardy F, Payen D, Merlan JJ, Gaudric A, Massin P: Superselective ophthalmic artery fibrinolytic therapy for the treatment of central retinal vein occlusion. Br J Ophthalmol 2000; 84:1387–91
8. Goto M, Nagashima M, Baba R, Nagano Y, Yokota M, Nishibata K, Tsuji A: Analysis of heart rate variability demonstrates effects of development on vagal modulation of heart rate in healthy children. J Pediatr 1997; 130:725–9
9. Meuwly C, Golanov E, Chowdhury T, Erne P, Schaller B. Trigeminal cardiac reflex: New thinking model about the definition based on a literature review. Medicine (Baltimore) 2015; 94:484.

(Accepted for publication June 1, 2017.)

In Reply:

We thank Drs. Nghe and Godier for their constructive comments on our recent article[1] as they point toward a useful alternative approach to the anesthetic problems seen during ophthalmic artery chemosurgery. However, we disagree with their conclusions.

We advocate using low-dose (0.5 to 1.0 μg/kg) intravenous epinephrine at the first sign of respiratory compromise during cannulation of the internal carotid or ophthalmic artery.[1] The anesthetic is maintained using 1.0 to 1.2 minimum alveolar concentration (MAC) of sevoflurane during the cannulation process, which probably attenuates the hemodynamic changes one would otherwise expect from epinephrine. Typically, we see a 20 to 25% increase in heart rate and blood pressure lasting approximately 2 min, along with nearly instantaneous and complete correction of respiratory parameters. Most of these cases are performed in children aged 3 months to 6 yr. In the absence of underlying cardiac disease, we expect, and have found, this brief cardiovascular effect to be well tolerated. The duration of action of the single bolus of intravenous epinephrine neatly matches the expected duration of the respiratory compliance changes; both disappear simultaneously. We have found that since introducing early low-dose epinephrine to our protocol, the hypotension and bradycardia often seen during the ophthalmic artery cannulation process are rarely seen. It is possible that the epinephrine is treating both the respiratory and hemodynamic responses.

We agree that the literature supports the view that insufficient anesthesia can increase the likelihood of a trigeminocardiac reflex (TCR) occurring.[2,3] Meuwly *et al.*[2] defined deep anesthesia as an inhaled sevoflurane concentration that corresponded to 1 MAC for their population. Yi and Jee[3] likewise defined deep anesthesia as an inhaled anesthetic mixture corresponding with 1.2 MAC. We do in fact keep our patients deeply anesthetized with sevoflurane at 1.0 to 1.2 MAC. This has the advantage of maintaining immobility without having to administer neuromuscular blockers repeatedly during the case.

Given that our patients are already deeply anesthetized with sevoflurane, a potent bronchodilator, we feel that any additional benefit from adding propofol at this point is outweighed by the harm that it may cause. Giving an effective dose of propofol while under 1.0 to 1.2 MAC of anesthesia can reliably be expected to cause significant hypotension.[4]

In vitro, trigeminal afferent nerve stimulation eventually results in firing of the cardiac vagal neurons of the nucleus ambiguous.[5] This effect is blocked by isoflurane and ketamine, unaffected by propofol, and enhanced by fentanyl.[5]

Based on these findings there is a theoretical superiority of sevoflurane over propofol in preventing the TCR, and these findings are corroborated *in vivo*. Maintenance of anesthesia