occurs frequently after the acute phase of trauma-induced coagulopathy.[14,15]

Dr. Flores suggests the use of multilevel continuous intercostal nerve block catheter in a patient with flail chest. Although the risk of epidural hematoma may be lower with intercostal nerve blocks compared with epidural analgesia, other risks such as pneumothorax/hematothorax and inadequate efficacy may limit its use under the condition described in our case scenario.

We need to develop specific outcome-oriented clinical pathways in critical care medicine that do not exclusively take into account the data taken from elective surgical procedures in the operating room. In patients with flail chest presenting with traditional contraindications for neuraxial analgesia, careful risk–benefit analysis may indicate that epidural analgesia improves important outcome measures. We believe that thromboelastography or thromboelastometry and aggregometry (if available) are helpful instruments for decision support in such a case scenario.

Young Ahn, M.D., Klaus Görlinger, M.D., Matthias Eikermann, M.D., Ph.D.* *Massachusetts General Hospital, Boston, Massachusetts. meikermann@partners.org

References

1. Ahn Y, Görlinger K, Alam HB, Eikermann M: Pain-associated respiratory failure in chest trauma. Anesthesiology 2013; 118:701–8
2. Sibbing D, Braun S, Morath T, Mehilli J, Vogt W, Schömig A, Kastrati A, von Beckerath N: Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. J Am Coll Cardiol 2009; 53:849–56
3. Price MJ, Teirstein PS: Dynamics of platelet functional recovery following a clopidogrel loading dose in healthy volunteers. Am J Cardiol 2008; 102:790–5
4. Perakis PG, Yunus T, Long G, Cheema ZF, Hammond R, Shanley CJ: Platelet function after cessation of chronic clopidogrel therapy. Am Surg 2012; 78:51–6
5. Bergmann L, Kienbaum P, Görlinger K, Peters J: Uneventful removal of an epidural catheter guided by impedance aggregometry in a patient with recent coronary stenting and treated with clopidogrel and acetylsalicylic acid. Reg Anesth Pain Med 2007; 32:354–7
6. Benzon HT, McCarthy RJ, Benzon HA, Kendall MC, Robak S, Lindholm PF, Kallas PG, Katz JA: Determination of residual antiplatelet activity of clopidogrel before neuraxial injections. Br J Anaesth 2011; 107:966–71
7. Limper U, Lynch J: [Removal of epidural catheter under dual antiplatelet therapy following acute coronary syndrome: Scenario without special consideration to the current guidelines on epidural regional anesthesia]. Anaesthesist 2012; 61:686–90
8. Velik-Salchner C, Maier S, Innerhofer P, Streif W, Klingler A, Kolbitsch C, Fries D: Point-of-care whole blood impedance aggregometry *versus* classical light transmission aggregometry for detecting aspirin and clopidogrel: The results of a pilot study. Anesth Analg 2008; 107:1798–806
9. Sibbing D, Braun S, Jawansky S, Vogt W, Mehilli J, Schömig A, Kastrati A, von Beckerath N: Assessment of ADP-induced platelet aggregation with light transmission aggregometry and multiple electrode platelet aggregometry before and after clopidogrel treatment. Thromb Haemost 2008; 99:121–6
10. Sibbing D, Schulz S, Braun S, Morath T, Stegherr J, Mehilli J, Schömig A, von Beckerath N, Kastrati A: Antiplatelet effects of clopidogrel and bleeding in patients undergoing coronary stent placement. J Thromb Haemost 2010; 8:250–6
11. Görlinger K, Dirkmann D, Hanke AA, Kamler M, Kottenberg E, Thielmann M, Jakob H, Peters J: First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: A retrospective, single-center cohort study. Anesthesiology 2011; 115:1179–91
12. Weber CF, Görlinger K, Meininger D, Herrmann E, Bingold T, Moritz A, Cohn LH, Zacharowski K: Point-of-care testing: A prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. Anesthesiology 2012; 117:531–47
13. Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, Hart D, Pearse R, Pasi KJ, MacCallum P, Stanworth S, Brohi K: Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med 2011; 39:2652–8
14. Ang L, Palakodeti V, Khalid A, Tsimikas S, Idrees Z, Tran P, Clopton P, Zafar N, Bromberg-Marin G, Keramati S, Mahmud E: Elevated plasma fibrinogen and diabetes mellitus are associated with lower inhibition of platelet reactivity with clopidogrel. J Am Coll Cardiol 2008; 52:1052–9
15. Mahmud E, Cavendish JJ, Tsimikas S, Ang L, Nguyen C, Bromberg-Marin G, Schnyder G, Keramati S, Palakodeti V, Penny WF, DeMaria AN: Elevated plasma fibrinogen level predicts suboptimal response to therapy with both single- and double-bolus eptifibatide during percutaneous coronary intervention. J Am Coll Cardiol 2007; 49:2163–71

(Accepted for publication July 1, 2013.)

The Power of Unbiased Genetic Screens to Discover Novel Anesthetic Targets

To the Editor:

We are writing in response to Dr. Forman's[1] editorial "The Expanding Genetic Toolkit for Exploring Mechanisms of General Anesthesia" in the April issue of Anesthesiology. Dr. Forman covers many excellent points about the use of genetics in understanding anesthetic mechanisms. However, we think that he has overlooked, and perhaps unintentionally discounted, the key ability of an unbiased forward genetic screen to study anesthetic action. A forward screen generates mutations randomly and then looks for those mutations that affect a particular trait. Its unique beauty or power is that it can discover novel mechanisms that would not be found if one presupposed to know an anesthetic target. Forward genetic screens *have* identified plausible possible targets of volatile anesthetics. They have included leak channels,[2] neurotransmitter release machinery,[3] and mitochondria.[4] All three possibilities have been

shown to be directly affected by volatile anesthetics and have been shown to affect anesthetic sensitivity in multiple organisms.[5–7] By dismissing mitochondrial complex I as a possible anesthetic target, it seems that Dr. Forman does not appreciate the full power of a genetic approach to solve difficult problems.

Because to date no single target has been identified as both necessary and sufficient to produce the anesthetic state for most drugs and because more than one pathway contributes to the anesthesia state even for the same drug, other relevant targets clearly exist. The search for the mechanism of action of volatile anesthetics started many decades ago, and yet new targets are occasionally discovered and validated—why should we believe that we have discovered them all? Unbiased approaches such as forward genetics seem well suited to help discover these elusive remaining targets.

Phil G. Morgan, M.D., Margaret M. Sedensky, M.D.*
*Seattle Children's Research Institute, University of Washington, Seattle, Washington.
margaret.sedensky@seattlechildrens.org, sedenm@uw.edu

References

1. Forman SA: The expanding genetic toolkit for exploring mechanisms of general anesthesia. Anesthesiology 2013; 118:769–71
2. Humphrey JA, Hamming KS, Thacker CM, Scott RL, Sedensky MM, Snutch TP, Morgan PG, Nash HA: A putative cation channel and its novel regulator: Cross-species conservation of effects on general anesthesia. Curr Biol 2007; 17:624–9
3. Hawasli AH, Saifee O, Liu C, Nonet ML, Crowder CM: Resistance to volatile anesthetics by mutations enhancing excitatory neurotransmitter release in *Caenorhabditis elegans*. Genetics 2004; 168:831–43
4. Kayser EB, Morgan PG, Sedensky MM: GAS-1: A mitochondrial protein controls sensitivity to volatile anesthetics in the nematode *Caenorhabditis elegans*. Anesthesiology 1999; 90:545–54
5. Bayliss DA, Barrett PQ: Emerging roles for two-pore-domain potassium channels and their potential therapeutic impact. Trends Pharmacol Sci 2008; 29:566–75
6. Herring BE, Xie Z, Marks J, Fox AP: Isoflurane inhibits the neurotransmitter release machinery. J Neurophysiol 2009; 102:1265–73
7. Quintana A, Morgan PG, Kruse SE, Palmiter RD, Sedensky MM: Altered anesthetic sensitivity of mice lacking Ndufs4, a subunit of mitochondrial complex I. PLoS One 2012; 7:e42904

(Accepted for publication July 5, 2013.)

In Reply:

I thank Drs. Sedensky and Morgan for highlighting an area of genetic research on general anesthetics that, because of space limitations, was not included in my editorial.[1] Their research dating back to 1987[2] has used unbiased forward genetic screens in a nematode, *Caenorhabditis elegans*, identifying genes that influence sensitivity to volatile anesthetics in tests of motor function. Others have similarly exploited the fruit fly, *Drosophila melongaster*. This research has contributed to our understanding of anesthetic mechanisms and bolsters my view that volatile drugs probably act *via* a wide variety of targets, which may include ion channels, neurotransmitter release mechanisms, mitochondria, and others not yet discovered.

One area where my thinking diverges from that of Sedensky and Morgan relates to the role of mitochondrial complex I as a putative anesthetic target. Logically, unless confounding effects perturb the pertinent phenotype, knockout of an important primary anesthetic target gene should *reduce anesthetic sensitivity* in the transgenic organism. However, knockout of Ndufs4 in mitochondrial complex I in mice results in a dramatic *gain of sensitivity* to volatile anesthetics,[3] undermining the idea that volatile anesthesia depends on the presence of this protein in normal animals. Clearly, other targets are mediating general anesthesia in the knockout animals. As noted by the authors,[3] there are myriad mechanistic explanations for this phenotype, including that inhibition of complex I contributes to anesthesia. Thus, inferences regarding a role of mitochondrial complex I in general anesthesia are quite weak and require more rigorous experimental assessment. Nonetheless, the Ndufs4 knockout animal is a useful model for patients with mitochondrial diseases, who are also remarkably sensitive to volatile anesthetics.[4]

Volatile anesthetics are a mainstay of clinical practice, and understanding the mechanisms of their therapeutic actions and toxicities is a worthy scientific goal with potential implications for future drug development. As noted by Sedensky and Morgan, volatile anesthesia is a "difficult problem." Its solution will require sophisticated research models and approaches, as well as thoughtful data analysis.

Stuart A. Forman, M.D., Ph.D., Massachusetts General Hospital, Boston, Massachusetts. saforman@partners.org

References

1. Forman SA: The expanding genetic toolkit for exploring mechanisms of general anesthesia. Anesthesiology 2013; 118:769–71
2. Sedensky MM, Meneely PM: Genetic analysis of halothane sensitivity in *Caenorhabditis elegans*. Science 1987; 236:952–4
3. Quintana A, Morgan PG, Kruse SE, Palmiter RD, Sedensky MM: Altered anesthetic sensitivity of mice lacking Ndufs4, a subunit of mitochondrial complex I. PLoS One 2012; 7:e42904
4. Morgan PG, Hoppel CL, Sedensky MM: Mitochondrial defects and anesthetic sensitivity. Anesthesiology 2002; 96:1268–70

(Accepted for publication July 5, 2013.)

Supported in part by National Institutes of Health (Bethesda, Maryland) grants GM089745 and GM58448.