

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/hemothorax 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.

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(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's¹ 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.

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(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 1987² 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.

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(Accepted for publication July 5, 2013.)

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