Anesthetics, the Ryanodine Receptors, and the Heart

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CARDIOVASCULAR complications are still a major cause of perioperative mortality and morbidity.[1] Myocardial ischemia, arrhythmias, and cardiac pump failure usually harm patients with preexisting cardiac disease and/or during extreme hemodynamic challenges. To prevent these complications, a substantial body of research aims to understand the effects exerted by anesthetic agents on the heart. We have learned that volatile anesthetics usually depress cardiac contractility,[2] especially at large doses, and in patients with preexisting cardiomyopathy. We know that volatile anesthetics are also protective during ischemia/reperfusion injury, a phenomenon known as *anesthetic-induced preconditioning*.[3] General anesthesia prolongs the electrocardiogram QT interval[4] and is potentially arrhythmogenic. But are these effects similar for equianesthesthetic doses of various agents? In other words, are some anesthetics better than others at protecting the heart?

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The study by Laver *et al.*[5] in the current issue addresses this question directly. The authors focus on the myocardial ryanodine receptors (RyR), an important calcium (Ca^{2+})–handling protein. Cardiac RyR are responsible for Ca^{2+} release from the intracellular stores (the sarcoplasmic reticulum [SR]), when activated by Ca^{2+} influx into the cell through the L-type Ca^{2+} channels during the action potential. This mechanism, called Ca^{2+}-induced Ca^{2+} release, is the pinnacle of excitation–contraction coupling in the heart.[6] Ca^{2+} released from the SR activates the myofilaments and initiates cardiac contraction and is the primary determinant of cardiac contractile force.

In the skeletal muscle, anesthetic gases are known to activate RyR, a phenomenon that triggers malignant hyperthermia crises.[7] How anesthetics affect the RyR in the heart is less well characterized, and this is where the study by Laver *et al.*[5] brings much needed new insights.

The approach is biophysical and reductionist. The scientists isolate RyR proteins from (healthy) sheep hearts, imbed them in artificial membranes and measure their opening times by electrophysiologic methods. They attempt to replicate the intracellular milieu (and add ATP, and calmodulin, accordingly), but we all agree that important regulators are probably missing in this isolated system.

In these conditions, anesthetics also activate cardiac RyR opening. The effect is much less than in the skeletal muscle (so there is no immediate fear for a malignant hyperthermia syndrome of the heart), but significant at clinically used concentrations. Halothane was the most potent RyR activator (which is fortunate, since we are not using it much anymore), followed by sevoflurane and desflurane. Isoflurane had almost no effect. To apply this new information clinically, we still need to establish what are the functional consequences of RyR opening, as we discuss below. However, pending this information, the current study suggests that, in patients in which augmenting RyR opening would be detrimental, we should use an isoflurane-based anesthetic. On the other hand, we should use sevoflurane or desflurane in cases in which RyR activation may be beneficial, by facilitating preconditioning, for example, as the authors propose.

The authors further detail the mechanism of action, and show that the effect of halothane is independent of ATP, contradicting a previously held idea,[8] but leaving the mechanism still unclear. Halothane activated RyR at both systolic and diastolic levels of Ca^{2+}, so it may temporary potentiate Ca^{2+}-induced Ca^{2+} release,[9] but it will also cause diastolic Ca^{2+} leak and decrease the SR Ca^{2+} content.[10] Dantrolene blocked the RyR and antagonized halothane non-competitively. The use of halothane for these mechanistic studies

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Corresponding article on page 495.

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 Anesthesiology 2017; 126:373-5

<zdoi;10.1097/ALN.0000000000001520>

makes experimental sense, because halothane had the greatest effect, but is a little disappointing for those of us more clinically minded.

What are the physiologic consequences of activating RyR opening? This is where the reductionist approach of the current study becomes insufficient, since this question requires whole cell and/or whole-organ experiments. These experiments must be left for the future, but we can hypothesize.

First, activating the RyR will likely lead to an increase in diastolic *leak* of Ca^{2+} from the SR into the cytosol. This will decrease the SR Ca^{2+} content and decrease the amplitude of Ca^{2+} release from the SR.[10] Thus, it will have a negative inotropic effect, which (except in the ischemic heart) is usually detrimental. Second, a slow Ca^{2+} release in diastole will impede relaxation and may induce diastolic dysfunction. Third, persistent RyR opening may be arrhythmogenic[11,12] and predispose to ventricular fibrillation. Balancing these negative effects, a smaller SR Ca^{2+} content may protect the ischemic heart and represent one of the mechanisms underlying anesthetic preconditioning, as the authors propose.

All these putative effects will have to be confirmed experimentally in the future. We will also need to see whether these effects are also present in the diseased heart. In this study, the authors used hearts from healthy sheep, but it is well known that cardiomyopathy and cardiac hypertrophy are associated with distinct cardiac phenotypical changes. Failing hearts have already dysfunctional RyR, with increased diastolic leak, a decreased SR load and propensity for ventricular arrhythmias.[13] Are the effects of anesthetics the same for the hyperphosphorylated,[14,15] oxidized,[16] and denitrosylated[17] RyR of the failing heart?[13] Moreover, are the functional consequences of RyR activation comparable in the normal and diseased hearts?

We also need to expand these studies to other anesthetic agents. The authors compare here different volatile anesthetics, but modern anesthetics also employ intravenous agents, such as propofol, dexmedetomidine, and opioids. Could a total intravenous anesthesia combination (*e.g.*, propofol and remifentanil) exert less effect on the RyR than equianesthetic halogenated agents? Could this be preferable in certain patients?

This is where the value of the current study really lies. The authors offer solid biophysical evidence, and a platform on which further research can be built. A lot of work remains, no doubt, and the ultimate success is not guaranteed. But the potential is there, and the reward is enthralling. If we could understand the distinct effects of anesthetics on key cardiac regulatory mechanisms, we may be able to avoid potential detrimental effects that exacerbate a diseased myocardium and/or potentiate the beneficial preconditioning effects in ischemic hearts. We could tailor the anesthetics we use for individual patients, distinct cardiac conditions, and surgical interventions and someday, perhaps, deliver *Precision Anesthesia*.[18]

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

"Laughing Gas Given" by Brooklyn's Celebrated and Celebrating Dr. G. E. Travis

For over 30 yr, from 1878 to 1908, Dr. George E. Travis (ca. 1854 to 1931) managed his celebrated dental parlors on Grand Street in Brooklyn, Eastern District, New York. A man who partied heartily, Travis was sued by a neighboring firm whose plate glass window was shattered by one of Travis's firework celebrations. After office hours, along with many German-American businessmen in the Amphion Society and the Home and Hanover Clubs, Travis celebrated from a tallyho (horse-drawn coach) on his way to drink and/or dine in clubs, restaurants, and theaters. Because of the "German dentist in attendance" whom he advertised on his trade card (*top*), Travis hired only bilingual office staff. Rotating and enlarging his card's right border reveals a botanically overgrown notice, "Laughing gas given" (*bottom*). The clipped upper-right corner of the card reinforced the trompe-l'oeil ("trick-the-eye") effort at convincing viewers that the corner was rolled and pinned down by a sprig. The laughing gas doctor's last laugh? (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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