The Importance of Definitive Trials: The VIXIE Trial

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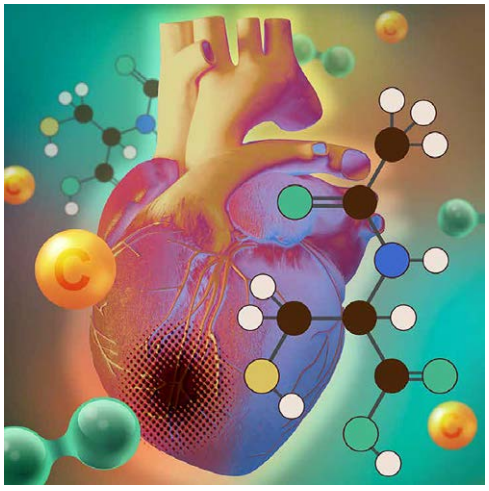
The VIXIE trial (Vitamin and Oxygen Interventions and Cardiovascular Events), whose results are reported in this issue of Anesthesiology,[1] aimed to answer two important questions: First, does a high inspiratory oxygen concentration increase the risk of perioperative myocardial injury attributable to oxidative stress; and second, does the coadministration of antioxidants mitigate such risk? Accordingly, the investigators compared 80% with 30% inspiratory oxygen concentration as first intervention and intravenous vitamin C and N-acetylcysteine *versus* placebo as second intervention in their trial. The VIXIE trial was conducted in four centers in Denmark and enrolled 600 patients with elevated cardiac risk (*e.g.*, previous stroke, coronary artery disease, and heart failure) who underwent major noncardiac surgery under general anesthesia. The trial included elective and emergent surgery, which is important for generalizability of the trial findings, because the risk of myocardial injury increases several-fold in emergent surgery. The primary study outcome was a cumulative measure of acute myocardial injury or cardiac troponin elevation over the first 3 postoperative days.



"If inspiratory oxygen concentration does not influence the risk of perioperative myocardial injury, it may be reasonable to conclude that the etiology of perioperative myocardial injury is not ischemic in most instances."

Acute myocardial injury is an umbrella term for new-onset cardiac troponin elevation where at least one value exceeds the 99th percentile of the upper reference limit of the troponin assay but where there is no evidence for acute myocardial infarction. In the perioperative setting, cardiac troponin elevation after noncardiac surgery is common in high-risk patients. The dominant etiology of perioperative myocardial injury is thought to be mismatch of myocardial oxygen supply and demand, although alternative hypotheses such as oxidative stress, as tested in the VIXIE trial, have been proposed.[2–4] The results of the VIXIE trial demonstrated convincingly that neither assignment to 80% *versus* 30% inspiratory oxygen concentration nor administration of vitamin C and N-acetylcysteine influenced postoperative myocardial injury. If inspiratory oxygen concentration does not influence the risk of perioperative myocardial injury, it may be reasonable to conclude that the etiology of perioperative myocardial injury is not ischemic in most instances.

The VIXIE trial was a 2 × 2 factorial trial, which is an elegant and efficient way to investigate two interventions in one clinical trial instead of two. The VIXIE investigators wanted to study the effects of inspiratory oxygen concentration and the effects of antioxidants on perioperative myocardial injury. In a standard experiment, they would study each intervention in a separate trial. But what if there is a mutual benefit of both interventions? In statistical terms, this is referred to as an interaction. Clinical trials with a single intervention cannot measure interactions with another intervention. The beauty of 2 × 2 factorial trials is that they can. A 2 × 2 factorial trial can determine not only whether each of the two interventions has an independent effect on outcomes but also whether an interaction between the two interventions exists, causing a stronger or—alternatively—weaker overall effect.

There is another aspect of the VIXIE trial that deserves to be mentioned: the fact that the interventions did not show an effect (previously referred to as "negative" trials). What readers may often find challenging when seeing a study in which the trial interventions had no effects on study outcomes is to determine whether it was conclusive or inconclusive. Evidence-based medicine depends on conclusive studies. Conclusive studies require adequate statistical power (sufficient sample size) to determine with

Image: A. Johnson, Vivo Visuals Studio.

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a high degree of certainty that the findings are "true negative" and not "false negative" in a statistical sense. An example of a true negative study result would be if we compared a novel intervention to placebo in 20,000 patients and did not find a significant difference between the groups. It is extremely likely that there is no effect of the novel intervention, and thus, this is a true negative. If we compared only five patients each, we could not be certain—it is possible that we simply did not have enough observations and thus missed an effect. This is called a type II error leading to inconclusive false negative results and is often seen in underpowered studies.

Thankfully, the VIXIE trial had adequate power and thus was a conclusive study with true negative results. For the practicing clinician, it is thus reasonable to conclude that even for high-risk patients, the selection of intraoperative inspiratory oxygen concentration will not have a meaningful influence on postoperative myocardial injury and that one should not administer antioxidants for the same reasons.

Acknowledgments

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Competing Interests

Dr. Nagele has received research funding and speaker fees from Roche Diagnostics (Indianapolis, Indiana) and Abbott Diagnostics (Lake Forest, Illinois) and serves on an advisory board at Becton-Dickinson (Franklin Lakes, New Jersey).

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