Letter to the Editor
Oxygen Gradient Hypothetical Means to Detect Malignant Hyperthermia
To the Editor:

Dr. Rosenberg and Mr. Rothstein should be commended for their sensitive and in-depth report on the unfortunate circumstances surrounding the death of a healthy, young man from malignant hyperthermia (MH).1 The authors summarize 3 main factors as being responsible for the decline in mortality from MH over the past several years: education of the anesthesia community, the routine measurement of exhaled carbon dioxide and body temperature, and the US FDA approval of dantrolene sodium IV for the treatment of MH in 1979. Despite these advances, MH remains a potentially lethal, ever-present danger during general anesthesia as shown by this case report.

We would like to draw attention to another potentially sensitive monitoring parameter that could aid in the earlier detection of an impending MH crisis.

Inspired oxygen concentration (FiO2) is routinely monitored during general anesthesia. In addition, during the last decade, end-tidal oxygen concentration (FeO2 monitoring) has also become available. With the fast response paramagnetic oxygen sensors that are now integrated into most anesthesia gas monitoring systems (such as the Phillips M1026B AGM), we can analyze breath-by-breath end-tidal oxygen concentrations. The "oxygen difference" calculated as the F (inspired - end-tidal) O2 is a very sensitive measure of metabolism and ventilation.2,3 This oxygen difference reflects the overall balance between alveolar oxygen consumption and oxygen delivery. Metabolism influences oxygen removal from the alveoli and ventilation influences oxygen entry into the alveoli. The measurement of adequate ventilation in relation to oxygen consumption or the VO2/VA ratio shows good correlation with the oxygen difference.4

Pathophysiologically, MH is a skeletal muscle hypermetabolic syndrome that is associated with increasing O2 consumption and CO2 production. Clinically, a rise in exhaled CO2 is typically seen in the early stages of MH. However, we know that tissue stores of CO2

far exceed those of O2.5 In addition, the body has tremendous ability to buffer CO2 but lacks O2 buffering systems. Therefore, the rise in the alveolar CO2 concentration with MH will be slower than the fall in alveolar O2 concentration.3 So, when CO2 production and O2 consumption abruptly increase in MH, the increase in the removal of oxygen from the alveoli should effectively widen the F (inspired - end-tidal) O2 difference quickly. We believe that such an increasing oxygen difference under general anesthesia could be an earlier marker for MH. Further, we believe that this oxygen difference will change faster and more (as a percentage change from its initial value) than the changes in end-tidal CO2. Finally, as the alveolar CO2 levels start to rise while maintaining the same minute ventilation (i.e., a state of relative hypoventilation), the oxygen difference should increase even more. The following equation will help explain our assertions: VO2 = VA * F {inspired - end-tidal} O2.2

In MH, the increase in VO2 and relative decrease in VA will result in an increasing oxygen difference. While the FiO2 will influence FeO2 measurements, the oxygen difference should be usable at any given FiO2. At the FiO2 settings used during most general anesthetics (i.e., 30-60%), this oxygen difference parameter will be within the sensitive range of the paramagnetic oxygen sensors. In addition, the oxygen difference may be influenced by changes in cardiac output, hemoglobin concentration, arterial oxygen saturation, and changes in anesthetic state. These parameters will need to be considered while interpreting changes in the oxygen difference.

In conclusion, we suggest that our hypothesis be tested in an experiment. This experiment could be designed to evaluate whether changes in oxygen difference occur earlier than changes in end-tidal CO2 during an MH episode. Use of an animal model for MH such as the pig model would be ideal. Simultaneous measurements of FiO2, FeO2, FeCO2, invasive monitoring of arterial pressures and blood gases, and cardiac output should be carried out and the effects of MH on these measures can then be studied. We appeal to the larger university hospitals/MH research laboratories to consider such as study. If we find that empirical observations confirm our hypothesis, we will be able to use a currently available monitoring parameter to detect or suspect MH at an earlier stage. This will move us closer to the goal of safer anesthesia for all patients.

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References

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In Reply:

I appreciate the comments concerning measurement of oxygen consumption during anesthesia as a marker for the hypermetabolic response that is the hallmark of malignant hyperthermia (MH).

The suggestion that the difference between inspired and end-tidal oxygen would indicate an increase in oxygen consumption provided that minute ventilation is kept constant is quite reasonable in the same way that measurement of end-tidal carbon dioxide is used as an indicator of metabolic rate.

For more accurate measurement of oxygen consumption, mixed expired oxygen tension measurement would be needed. I do not believe that current anesthesia monitors have a built-in mixing chamber in order to obtain mixed expired values.

For that reason the proposed experiment is reasonable and should include mixed expired oxygen measurement as well.

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