A Second Look at the Second Gas Effect

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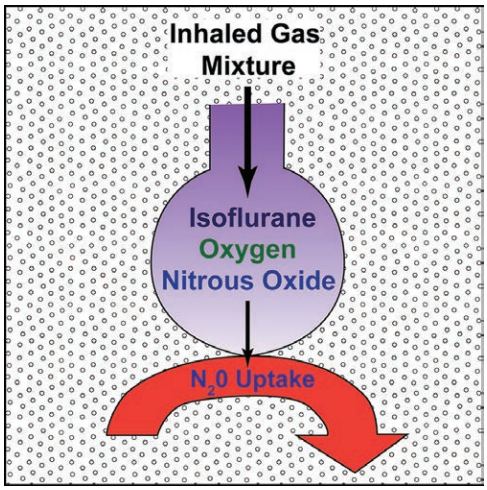
THE Newtonian laws of physics explain the behavior of objects in the everyday physical world, such as an apple falling from a tree. For hundreds of years Newton provided a complete answer until the work of Einstein introduced the concept of relativity. The discovery of relativity did not suddenly prove Newton wrong, relativistic corrections are only required at speeds above about 67 million mph. Instead, improving technology allowed both more detailed observations and techniques for analysis that then required explanation. While most of the consequences of a Newtonian model are intuitive, much of relativity is not and is only approachable though complex equations, modeling, and highly simplified examples.



"…[T]he second gas effect is real, and not just a theoretical construct..."

In this issue, Korman *et al.*[1] provide data from a model of the second gas effect on arterial partial pressures of volatile anesthetic agents. Most readers might wonder what this information adds, some will struggle to remember what the second gas effect is, and others will query the value of modeling rather than "real data." This editorial attempts to address these questions.

The second gas effect[2] is a consequence of the concentration effect[3] where a "first gas" that is soluble in plasma, such as nitrous oxide, moves rapidly from the lungs to plasma. This increases the alveolar concentration and hence rate of uptake into plasma of the "second gas." The second gas is typically a volatile anesthetic, but oxygen also behaves as a second gas.[4] Although we frequently talk of inhalational kinetics as a single process, there are multiple steps between dialing up a concentration and the consequent change in effect. The key steps are transfer from the breathing circuit to alveolar gas, from the alveoli to plasma, and then from plasma to the "effect-site." Separating the two steps between breathing circuit and plasma helps us understand both the second gas effect and the message underlying the paper by Korman *et al.*[1]

While the classical model of the concentration effect and second gas effect persists in most textbooks and teaching, aspects of this description have been challenged for more than 20 yr. In 1997, Korman and Mapleson[5] identified shortcomings in the "standard model" of the concentration and second gas effects, which assume constant lung volume. Korman and Mapleson[5] acknowledged that the "standard diagram has probably helped…students gain some insight," but made a plea for understanding of the limitations. In 2006, Hendrickx *et al.*[6] confirmed a significant effect of nitrous oxide on the rate of uptake of sevoflurane and found the pattern of results that matched the approach of Korman and Mapleson.[5] Hendrickx *et al.* also found the second gas effect persisted longer than predicted by the classical model.[6] Based on the work of Peyton *et al.* modeling respiratory gas exchange,[7] they proposed that the persistence of the second gas effect over time could be explained by the effect of ventilation/perfusion ratio ($\dot{V}/\dot{Q}$) mismatch. That same year, Peyton *et al.* presented data confirming that the second gas effect also persisted with oxygen[4] and then in 2008 reported that the arterial partial pressure of oxygen showed a larger second gas effect than the alveolar partial pressures.[8]

The paper by Korman *et al.*[1] neatly brings these threads together. They present a model that separates the effects of solubility of the second gas and of $\dot{V}/\dot{Q}$ mismatch. Their model suggests that as $\dot{V}/\dot{Q}$ mismatch increases, the second gas effect is more pronounced in the blood but reduced in the gas phase. Furthermore, this effect increases as the solubility of the second gas decreases. Persistence of a measurable second gas effect, as seen by Hendrickx *et al.*[6] and Peyton *et al.*,[8] also is predicted by this model.

Why should we be interested? Or is this the anesthetic equivalent of traveling at more than 67 million mph? The first lesson is that the second gas effect is real, and not just a theoretical construct developed to torment trainees in anesthesia. The second is the magnitude of the effect. According to figure 2 from the paper by Korman *et al.*,[1] using a midpoint on the $\dot{V}/\dot{Q}$ distributions and with nitrous oxide uptake 95% complete, the second gas effect on alveolar gas, which is seen by our gas analyzers, the partial pressure of desflurane or sevoflurane

Image: J. P. Rathmell.

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will be approximately 3% greater than when nitrous oxide is not present. However, the partial pressure in blood will be 6% greater with nitrous oxide, and the effect on blood will not be detected by gas analyzers. The third message is that the increases in volatile concentrations caused by the second gas effect persist for a significant time period. The net effect is, as Korman *et al.* point out, that the partial pressure of inhaled anesthetic in the blood, and hence at the site of action, will be higher than the monitor displays for the first 15 to 20 min of an anesthetic.[1]

The paper by Korman *et al.* is entirely based on modeling.[1] Some will question the value of information derived from a model. After all, it is not real data from real patients and includes many approximations and assumptions,[9] so how can it be relevant to the next patient you anesthetize, who is a unique individual? There are many advantages of models, including the ability to investigate conditions that are difficult to reproduce in a clinical setting and to tightly control some conditions while varying others. A key component of the paper by Korman *et al.* is the investigation of the effect of varying $\dot{V}/\dot{Q}$ ratios across the lung.[1] These are very difficult to measure, let alone control, in a real world experiment.

Dr. Edmond Eger II's autobiography, currently being edited by Dr. Steven Shafer, describes afternoons in 1958 spent at Fort Leavenworth, using a mechanical calculator to calculate the changes in nitrous oxide concentration (to 16 decimal places) over the course of a 50 min anesthetic. These calculations gave unexpected, but repeatable, results. Although it was several years before he fully understood the significance of his results, by using a model based on a series of iterative equations, Dr. Eger had discovered what we now know as the concentration effect.[3] It is appropriate that modeling, based on a series of equations, should enhance our understanding of a phenomenon first elucidated by modeling 60 yr ago.

In an essay entitled "On the Nature of Science,"[10] Isaac Asimov discusses the iterative nature of scientific endeavor. This process is nicely illustrated by the way our understanding of the second gas effect has changed over the past 20 yr. Asimov reminds us that each layer of knowledge requires a robust foundation. For anyone interested in the kinetics of modern volatile anesthetic agents, reading the series of papers from Eger and others in the early 1960s describes a fascinating journey of discovery. The reader can sense the group developing the tools and language to describe their observations. Many of the constructs they developed,[11] such as minimum alveolar concentration and F_A/F_I curves, are used in almost their original form to teach and illustrate the kinetics of volatile anesthetics nearly 60 yr after they were first described.

If the foundations of knowledge are robust, new observations that change our view of a topic do not invalidate previous work. Instead they enhance the earlier work. As Newton said, "If I have seen further it is by standing on the shoulders of giants." Asimov[10] argues that it is essential to recognize the value and quality of earlier work, but that we also need to continually question existing constructs and explore new ideas. The way the kinetics of inhaled anesthetic agents is taught has remained relatively constant for more than 50 yr.[11] For me the underlying message of the work of Korman *et al.* is that if anesthesia is to be considered a scientific endeavor, we need to keep reevaluating our understanding of the characteristics and behaviors of all the medications we use, no matter how familiar and well established they may be.

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Competing Interests

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References

1. Korman B, Dash RK, Peyton PJ: Can mathematical modeling explain the measured magnitude of the second gas effect? Anesthesiology 2018; 128:1075–83
2. Epstein RM, Rackow H, Salanitre E, Wolf GL: Influence of the concentration effect on the uptake of anesthetic mixtures: The second gas effect. Anesthesiology 1964; 25:364–71
3. Eger EI II: Effect of inspired anesthetic concentration on the rate of rise of alveolar concentration. Anesthesiology 1963; 24:153–7
4. Peyton PJ, Stuart-Andrews C, Deo K, Strahan F, Robinson GJ, Thompson BR, Pierce R: Persisting concentrating and second gas effects on oxygenation during N2O anaesthesia. Anaesthesia 2006; 61:322–9
5. Korman B, Mapleson WW: Concentration and second gas effects: Can the accepted explanation be improved? Br J Anaesth 1997; 78:618–25
6. Hendrickx JF, Carette R, Lemmens HJ, De Wolf AM: Large volume N2O uptake alone does not explain the second gas effect of N2O on sevoflurane during constant inspired ventilation. Br J Anaesth 2006; 96:391–5
7. Peyton PJ, Robinson GJ, Thompson B: Ventilation-perfusion inhomogeneity increases gas uptake in anesthesia: Computer modeling of gas exchange. J Appl Physiol (1985) 2001; 91:10–6
8. Peyton PJ, Fortuin M, Robinson GJ, Stuart-Andrews C, Pierce R, Thompson BR: The rate of alveolar-capillary uptake of sevoflurane and nitrous oxide following anaesthetic induction. Anaesthesia 2008; 63:358–63
9. Shafer SL: All models are wrong. Anesthesiology 2012; 116:240–1
10. Asimov I. On the nature of science, The World Treasury of Mathematics and Physics. Edited by Ferris T. Boston, Little Brown, 1991, pp 781–3
11. Eger EI II. Anesthetic Uptake and Action. Baltimore/London, Williams & Wilkins, 1974