An Early Example of Evidence-based Medicine

Hypoxemia due to Nitrous Oxide

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In 1955, Dr. Bernard Raymond Fink published his findings that described the mechanism by which hypoxemia occurred when nitrous oxide–oxygen anesthesia was discontinued and room air breathing commenced. Using an ear oximeter and brachial artery blood gases, he measured oxygen saturation in eight healthy patients who had received 75% nitrous oxide–25% oxygen for gynecologic surgery. He showed that oxygen saturation decreased from 5% to 10% and often reached a value below 90% when the patient began room air breathing after the nitrous oxide–oxygen was discontinued. The effect was seen over a 10-min period. He concluded that “anoxia arises because the outward diffusion of nitrous oxide lowers the alveolar partial pressure of oxygen.” This phenomenon can become a causative factor of cardiac arrest in patients with impaired pulmonary or cardiac reserves.

IN 1955, Dr. B. Raymond (Ray) Fink (1914–2000) was faculty in the Department of Anesthesiology, Columbia University College of Physicians and Surgeons (New York, New York) when he published one of the first articles describing a mechanism by which anesthesia could cause hypoxemia.1 At the time, cyanosis was a recognized phenomenon during recovery from general anesthesia despite apparently good ventilation. It was also recognized that this was more frequent in patients anesthetized with a nitrous oxide–oxygen mixture. There were previous reports of a decrease in arterial oxygen saturation as measured by an ear oximeter when patients began to breathe room air, especially after a nitrous oxide–oxygen anesthetic.2,3 Dr. Fink postulated that this hypoxemia was due to the high tension at which nitrous oxide was administered for anesthesia and its high solubility in the blood relative to the nitrogen in room air. In an in vitro experiment, he saturated water in a half-filled flask with nitrous oxide. He stoppered the flask and showed an increased pressure in the flask due to nitrous oxide diffusing out of the water. As the gas equilibrated in the flask, the oxygen concentration of the gas in the flask decreased to approximately 17%. He hypothesized that this simulated the condition in the lungs at the end of a nitrous oxide–oxygen anesthetic.

Ray followed this simple experiment with clinical observations in eight otherwise healthy patients undergoing gynecologic surgery who were anesthetized with 75% nitrous oxide–25% oxygen supplemented with sodium thiopental. Blood oxygen saturations were measured by either a Wood ear oximeter or brachial arterial blood analysis. Removal of the facemask at the end of the nitrous oxide–oxygen anesthetic resulted in a decrease in arterial oxygen saturation from 4.5% to 10.3% with an average of 7.9%, an effect that lasted approximately 10 min. Figure 2 of his article1 (fig. 1) showed the effect of air breathing after 3.5 l/1 l nitrous oxide–oxygen anesthesia in one patient. The “diffusion anoxia” peaked at 3 min and was readily reversed by inhalation of 100% oxygen.

The variability of change in oxygen saturation among the patients studied was attributed to differing levels of ventilation and lung volume. Fink observed that if patients were hyperventilating, the effect would be less, and the effect would be greater in patients with low lung volumes in which to dilute the nitrous oxide. The diffu-
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Tom F. Hornbein, M.D., an Associate Professor (and later Chair) of Anesthesiology at the University of Washington (Seattle, Washington), where Ray Fink had migrated in 1964 as Director of Anesthesia Research, questioned the validity of Frumin and Edelist’s findings in a letter to the editor of Anesthesiology. These investigators had measured arterial oxygen tension (PaO₂) and converted it to SaO₂. Hornbein pointed out that changes in SaO₂ are less dramatic than PaO₂ because of the slope of the dissociation curve at the PaO₂ levels studied. He opined that the patients might tolerate a “touch of” diffusion hypoxia, but when added to other possible factors threatening oxygenation during emergence from anesthesia, it does place the “diffusion” effect in the realm of clinical significance.

EARLY EXAMPLE OF EVIDENCE-BASED MEDICINE

In 1969, Frumin and Edelist (Department of Anesthesiology, Albert Einstein College of Medicine, Yeshiva University, Bronx, New York) published an article titled “Diffusion Anoxia: A Critical Reappraisal.” They studied 18 healthy, spontaneously breathing patients during change from breathing 79% nitrous oxide–21% oxygen to air breathing and observed SaO₂ values above 90 and usually above 93%. However, they did observe SaO₂ values below 90% in 4 patients who had respiratory irregularities or airway obstruction. These low saturations lasted only as long as the period of obstruction. The authors concluded that the entity of diffusion anoxia was not a clinically significant phenomenon in healthy patients who maintained normal ventilation.

Fig. 1. Arterial oxygen saturation during recovery from nitrous oxide–oxygen anesthesia. Patient M.R. From Fink1; reproduced with permission.
Belgica. After his classic article on diffusion anoxia in *Anesthesiology*, while still at Columbia, Ray turned his fertile mind to the study of laryngeal and diaphragmatic mechanics and regulation of respiration.

Ray and I joined the Department of Anesthesiology at University of Washington at about the same time in 1964. I was an Instructor and he was Professor and Research Director. Over the next 20 yr, he contributed original knowledge to the specialty in the areas of anesthesia toxicity, cell metabolism, local anesthetics, and nerve conduction. His inventive mind, sense of humor, and grasp of science were an inspiration to junior faculty such as myself.

After his retirement to Emeritus status in 1984, he remained active as a researcher and scholar until his death in October 2000. One of the unusual features of Ray’s career is that of 129 publications, he was first author of 104. This is evidence that Ray was the main source of his published creative ideas. His contributions to new knowledge in the specialty were recognized by the American Society of Anesthesiologists in 1987 when he received the Excellence in Research Award and again in 1993 when he received the Distinguished Service Award.

Therefore, this classic article on diffusion anoxia was not only an early example of evidence-based medicine, but also heralded the beginning of a long and productive research career that produced many more important scientific contributions to the scientific basis of the specialty.

References

1. Fink BR: Diffusion anoxia *Anesthesiology* 1955; 16:511–4