MAC Meeting MIGET

Leaps of Faith

Jan F. A. Hendrickx, M.D., Ph.D., Philip J. Peyton, M.D., Ph.D., M.B.B.S., F.A.N.Z.C.A., Andre M. De Wolf, M.D.

WE don't know whether Ted Eger, Larry Saidman, Bob Stoelting, Peter Wagner, and Göran Hedenstierna joined for dinner recently, but the article by Kretzschmar *et al.*[1] in this issue of ANESTHESIOLOGY might very well have been the result of misters MAC (minimal alveolar concentration)[2–4] and misters MIGET (multiple inert gas elimination technique)[5,6] getting together. The former three developed the MAC and MAC-awake concepts, reflecting the probability of immobility in the presence of a nociceptive stimulus and response to verbal command, respectively, when using inhaled anesthetics to provide general anesthesia, whereas the latter two used inhaled agents as some of the components of MIGET to determine the distribution of ventilation/perfusion ratios ($\dot{V}_A/Q$) in the lungs. MAC is based on end-expired agent partial pressures measurements at steady state. However, in discussions of uptake and distribution, Alveolar–arterial (A-a) partial pressure gradients are often glibly passed over and considered to be insignificant. On the other hand, MIGET determines $\dot{V}_A/Q$ scatter based on simultaneous end-expired and arterial blood agent partial pressure measurements of six inert gases after intravenous infusion.[5] The underlying basis is that the wide differences in solubility of these six gases cause them to be washed out differently by areas with differing $\dot{V}_A/Q$ ratios, resulting in widely divergent A-a differences. Some of these gases are inhaled anesthetics (usually cyclopropane, halothane, and ether). So, on the one hand we like to assume that A-a gradients of inhaled anesthetics are small or nonexistent, but on the other hand, we use these same inhaled agents to study $\dot{V}_A/Q$ scatter based on A-a gradients! The work by Kretzschmar *et al.*[1] is the first in which MIGET is used to help elucidate the finer aspects of anesthetic agent uptake. The authors determined in an animal model how methacholine-induced $\dot{V}_A/Q$ mismatching (assessed by MIGET) affects agent uptake of two clinically used agents with different blood–gas partition coefficients, isoflurane and desflurane. They are to be commended for this approach, but some aspects relating to methodology have to be scrutinized.

"Approximations and assumptions…facilitate the use of drugs or devices in our day-to-day clinical practice.…But in clinical research, reliance on outputs from models, systems, or devices with limited external validation has serious risks…yet is becoming increasingly common in anesthesiology."

To calculate agent uptake using Fick's method, one needs to measure arterial and mixed-venous blood content (*i.e.*, the product of partial pressure and blood solubility) and cardiac output. However, the investigators did not directly measure blood solubility, and, even more importantly, to determine agent partial pressure in blood using micropore membrane inlet mass spectrometry, they calibrated the device assuming that, before methacholine administration, there would be no A-a difference for either of the agents. This is a somewhat surprising assumption, because an increase in $\dot{V}_A/Q$ scatter is almost universal in humans under general anesthesia, resulting in A-a partial pressure differences of 15 to 35% for the modern volatile agents during maintenance.[7–9] In addition, measuring

Image: J. P. Rathmell.

Corresponding article on page 800.

Accepted for publication July 21, 2017. From the Department of Anesthesiology, Intensive Care and Pain Therapy, OLV Hospital, Aalst, Belgium (J.F.A.H.); Perioperative and Pain Medicine Unit, Melbourne Medical School, University of Melbourne, Melbourne, Victoria, Australia (P.J.P.); Department of Anesthesiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois (A.M.D.W.).

Copyright © 2017, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2017; 127:741-3

Copyright © 2017, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

<zdoi;10.1097/ALN.0000000000001848>

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/127/5/741/379015/20171100_0-00010.pdf by guest on 18 April 2024

these parameters would have helped clarify the mathematic predictions of anesthetic gas behavior *in vivo* on which we have previously relied to grasp how these agents behave. Fortunately, however, at least for the purpose of this study, these limitations are probably not critical ones. Their data show that the mean A-a difference for carbon dioxide before methacholine was not significant, implying that overall $\dot{V}_A/Q$ scatter in their pigs at baseline was minimal. This was further supported by the narrow $\dot{V}_A/Q$ distributions that they measured at baseline using MIGET. Finally, A-a differences are unlikely to heavily affect the comparison of the uptake of the two agents, which is the primary objective of the study.

Approximations and assumptions like considering A-a partial pressure gradients to be insignificant in discussions of uptake and distribution facilitate the use of drugs or devices in our day-to-day clinical practice. As another example, target-controlled infusion (TCI) helps in the rational administration of propofol as long as TCI targets are modified by the anesthesiologist in response to clinical observation of both depth of anesthesia in the patient and the intensity of the nociceptive stimulus of the procedure. The clinician should understand both the limited accuracy of predicted plasma and effect site concentrations in a given patient, as well as the variable relationship of these predicted values to pharmacodynamic endpoints like anesthetic depth or bispectral index. Indeed, in clinical practice it is recommended that these systems never be used uncritically. But in clinical research, reliance on outputs from models, systems, or devices with limited external validation has serious risks (creation of false knowledge), yet is becoming increasingly common in anesthesiology. An example is the use of TCI model predictions instead of measurements of plasma concentrations of drugs such as propofol, which can lead to similar concerns about the reliability of conclusions drawn from studies on intravenous anesthesia.[10] An additional example is the use of cardiac output monitors such as pulse contour devices for hemodynamic studies. These devices frequently use opaque, proprietary algorithms to estimate stroke volume from peripheral pulse pressure without individual calibration in a given patient. Although they are designed for convenient and minimally invasive clinical use, conclusions reached about hemodynamic relationships and physiology using uncalibrated devices will remain unclear. Concerns about the assumptions we make when using such black box technologies have been raised before, such as the use of processed electroencephalogram devices like bispectral index to monitor depth of anesthesia.[11] At best we risk merely validating only surrogate variables instead of the pharmacologic and physiologic variables. At worst, we risk introducing circularity and error into the results of such a study.

In summary, administering inhaled anesthetics is at the heart of what we do every day in our clinical practice. We owe it to our patients and profession to thoroughly understand all aspects of it. Failing to address the complexities of lung gas exchange has already led to an underestimation of the second gas effect of nitrous oxide.[9] The MIGET–MAC encounter has the potential to address at least the following intriguing questions. To what degree will $\dot{V}_A/Q$ scatter cause A-a gradients for modern inhaled agents with different blood–gas partition coefficients? Also, are there any clinical circumstances in which this A-a gradient might be of such magnitude that it could affect the use of end-expired gas analysis as a measure of anesthetic depth? How would $\dot{V}_A/Q$ scatter quantitatively affect anesthetic agent uptake (milliliters of vapor *per* minute), and would that influence the speed of induction and emergence? Despite its limitations, the complex study from Kretzschmar *et al.*[1] is an important step toward a better and more refined understanding of the kinetics of inhaled anesthetics.

Competing Interests

Dr. Hendrickx has received several forms of support from companies involved with inhaled agent delivery (lecture support, travel reimbursements, equipment loans, consulting fees, and meeting organizational support) including the following: AbbVie (North Chicago, Illinois), Acertys (Aartselaar, Belgium), Air Liquide (Paris, France), Allied Healthcare (Staffordshire, United Kingdom), Armstrong Medical (Lincolnshire, Illinois), Baxter International (Deerfield, Illinois), Draeger (Lübeck, Germany), General Electric (Boston, Massachusetts), Hospithera (Bruxelles, Belgium), Heinen und Lowenstein (Hamburg, Germany), Innomediq (Aarschot, Belgium), Intersurgical (Berkshire, United Kingdom), Maquet (Rastatt, Germany), MDMS (New York, New York), MEDEC (Aalst, Belgium), Micropore (Newark, Delaware), Mindray (Shenzhen, China), Molecular Devices (Sunnyvale, California), Philips (Amsterdam, the Netherlands), Piramal (Mumbai, India), and Quantium Medical (Barcelona, Spain). Dr. Peyton holds two patents related to cardiac output monitoring. The other author declares no competing interests.

Correspondence

Address correspondence to Dr. Hendrickx: jcnwahendrickx@yahoo.com

References

1. Kretzschmar M, Kozian A, Baumgardner JE, Borges JB, Hedenstierna G, Larsson A, Hachenberg T, Schilling T: Effect of bronchoconstriction-induced ventilation–perfusion mismatch on uptake and elimination of isoflurane and desflurane. Anesthesiology 2017; 127:800–12
2. Saidman LJ, Eger EI 2nd: Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 1964; 25:302–6
3. Stoelting RK, Longnecker DE, Eger EI 2nd: Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluroxene anesthesia: MAC awake. Anesthesiology 1970; 33:5–9
4. Eger EI 2nd: A brief history of the origin of minimum alveolar concentration (MAC). Anesthesiology 2002; 96:238–9
5. Wagner PD: The multiple inert gas elimination technique (MIGET). Intensive Care Med 2008; 34:994–1001

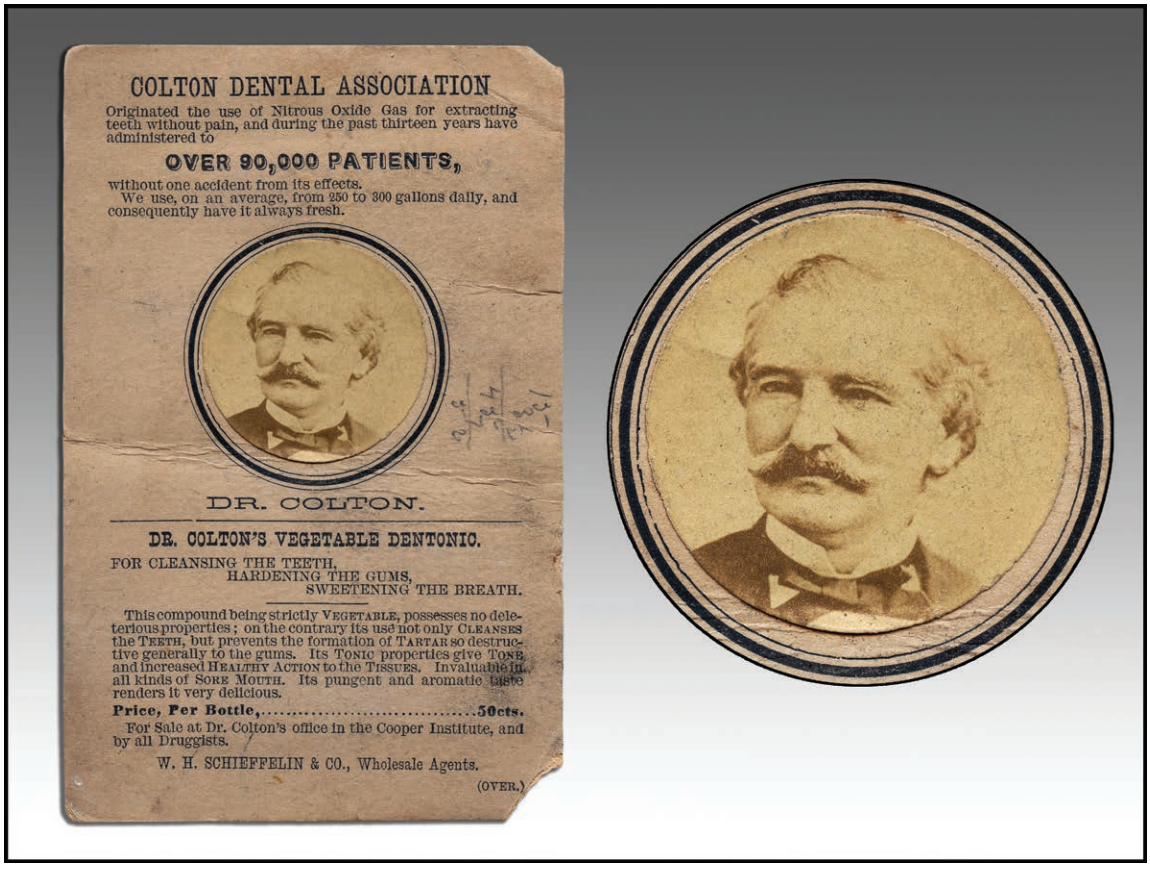
Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/127/5/741/379015/20171100_0-00010.pdf by guest on 18 April 2024

Copyright © 2017, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

6. Wagner PD, Hedenstierna G, Bylin G, Lagerstrand L: Reproducibility of the multiple inert gas elimination technique. J Appl Physiol (1985) 1987; 62:1740–6
7. Dwyer RC, Fee JP, Howard PJ, Clarke RS: Arterial washin of halothane and isoflurane in young and elderly adult patients. Br J Anaesth 1991; 66:572–9
8. Landon MJ, Matson AM, Royston BD, Hewlett AM, White DC, Nunn JF: Components of the inspiratory-arterial isoflurane partial pressure difference. Br J Anaesth 1993; 70:605–11
9. Peyton PJ, Horriat M, Robinson GJ, Pierce R, Thompson BR: Magnitude of the second gas effect on arterial sevoflurane partial pressure. Anesthesiology 2008; 108:381–7
10. Avram MJ: Presenting data *versus* predictions as basic scientific information: Target-controlled infusions *versus* microgram per kilogram per minutes. Anesthesiology 2011; 114:723
11. Ruskin KJ, Shelley KH: Patent medicine and the "black box." Anesth Analg 2005; 100:1361–2

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Picturing "Dr. Colton" at the Cooper Institute: His Honorific Doctorate



The reverse of this trade card (*left*) features a circular photo-portrait of Gardner Q. Colton (1814 to 1898, *right*). A medical school dropout who popularized nitrous-oxide anesthesia for dental extraction, Colton was photographed no longer sporting the Lincolnesque beard from 1863, when his namesake Colton Dental Association was founded in Manhattan. Rather, Colton now has the beardless but moustached look popularized in the mid-1870s by writer Mark Twain and his contemporaries. Having styled himself with an honorific doctorate, "Dr. Colton" boasts that he "originated the use of Nitrous Oxide Gas for extracting teeth without pain, and during the past 13 years have administered [it] to **OVER 90,000 PATIENTS,** without one accident from its effects." Because his namesake association was founded in 1863, this trade card (from the Wood Library-Museum's Ben Z. Swanson Collection) can be dated reliably to the year 1876 or soon after. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Copyright © 2017, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/127/5/741/379015/20171100_0-00010.pdf by guest on 18 April 2024