Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

Lung-protective Ventilation in the Operating Room

Time to Implement?

Neil M. Goldenberg, M.D., Ph.D., Benjamin E. Steinberg, M.D., Ph.D.,
Warren L. Lee, M.D., Ph.D., F.R.C.P.C., Duminda N. Wijeysundera, M.D., Ph.D., F.R.C.P.C.,
Brian P. Kavanagh, M.B., F.R.C.P.C.

A RECENT multicenter, randomized, controlled trial has concluded that the use of low tidal volumes (V_T) for ventilation during surgery improves postoperative outcomes.[1] The report is based on the context of a general acceptance that survival is increased when lower tidal volumes are used in patients with acutely diseased lungs, such as acute respiratory distress syndrome (ARDS) or asthma, who require mechanical ventilation in intensive care units (ICUs).[2] Although extensive laboratory and clinical data confirm that higher V_T worsens lung inflammation[3] and lowers survival[4] when lung injury is established, recent data suggest an analogous phenomenon during general anesthesia; in this study, using higher V_T to ventilate patients whose lungs are normal seems to cause lung injury. Because choosing lower V_T incurs no financial cost and is within the skill set of all anesthesia providers, many think that low V_T should be the standard for ventilating all patients during surgery.[5] As approximately 250 million people undergo general anesthesia each year throughout the world,[6] broad acceptance of this approach would cause a massive change in worldwide practice. In addition, because the frequency of morbidity or mortality after general anesthesia is generally low, risk–benefit analysis is complex. This perspective examines the evidence to support a widespread shift in standard care and proposes approaches for going forward.

Lung Protection—Knowledge Transfer from Intensive Care

The idea of lung-protective ventilation originated in critical care medicine with the recognition that high inflation pressure or V_T caused lung damage (and possibly decreased survival) in mechanically ventilated patients with neonatal lung disease,[7] chronic obstructive pulmonary disease, asthma, or ARDS.[4,8] Among these conditions, ARDS became a particular focus because it is associated with substantial mortality, healthcare costs, and long-term disability in survivors; and patients with ARDS commonly require mechanical ventilation.[9]

Although classic barotrauma from excessive ventilator pressures can cause air leaks (*e.g.*, pneumothorax) that are usually obvious at the bedside, the consequences of ventilator-associated lung injury are insidious. This type of injury has several elements (*e.g.*, barotrauma, volutrauma, and biotrauma),[10] and laboratory studies over 4 decades clearly demonstrate that higher V_T causes greater lung injury.[11] In addition, the histologic appearances of such injury are indistinguishable from the changes observed in ARDS. Categorical confirmation of much of this research came in 2000 with a landmark randomized trial demonstrating that lower V_T improves survival in ventilated patients with ARDS.[2] This knowledge has resulted in adoption of lower V_T as a standard of care in patients with ARDS.

This article is featured in "This Month in Anesthesiology," page 3A. The figures were created by Annemarie B. Johnson, C.M.I., Medical Illustrator, Vivo Visuals, Winston-Salem, North Carolina.

Submitted for publication October 9, 2013. Accepted for publication December 26, 2013. From the Department of Anesthesia, University of Toronto, and The Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Ontario, Canada (N.M.G.); Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada, and The Laboratory of Biomedical Science, The Feinstein Institute for Medical Research, Manhasset, New York (B.E.S.); Interdepartmental Division of Critical Care Medicine, University of Toronto, and The Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Ontario, Canada (W.L.L.); Department of Anesthesia, Toronto General Hospital and University of Toronto, Toronto, Ontario, Canada, and the Li Ka Shing Knowledge Institute, St. Michael's Hospital, and the Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada (D.N.W.); and Departments of Anesthesia and Critical Care Medicine, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada (B.P.K.).

 Anesthesiology 2014; 121:184–8

Although lower V_T is widely recognized as a key element in protective ventilation, laboratory studies have identified a second component: maintenance of lung volume. This is usually accomplished by a "recruitment maneuver" and maintained with ventilator pressure applied throughout expiration (termed positive end-expiratory pressure [PEEP]). Maintenance of lung volume lessens the amount of atelectatic lung, thereby lessening intrapulmonary shunt and more evenly distributing inhaled V_T.[12] Despite compelling rationale and consistent laboratory data, the role of recruitment maneuvers or PEEP remains uncertain in patients with ARDS.

Background—Protective Ventilation in Healthy Lungs

Patients undergoing general anesthesia—up to 250 million per annum by recent estimates[6]—constitute a far larger population of mechanically ventilated patients than those with ARDS, but protective ventilation is not universally practiced during anesthesia. If the gains associated with protective ventilation in the ICU could be translated to the operating room, then substantial numbers of patients might benefit. Indeed, a recent prominent randomized trial of 400 patients reported that the use of lower V_T during anesthesia resulted in a better postoperative outcome[1]; this study followed several uncontrolled studies as well as two smaller clinical trials that yielded mixed results.[13,14] However, in weighing translation from critical care to the operating room, it is important to understand that the populations are very different: patients in the operating room usually have normal lungs whereas patients with ARDS—by definition—do not.

A randomized study of 56 patients undergoing open abdominal surgery compared "standard" ventilator management (V_T 9 ml/kg ideal body weight; PEEP, 0 cm H_2O) *versus* protective management (V_T 7 ml/kg ideal body weight, together with recruitment maneuvers and PEEP).[13] Thus, "lung protection" consisted of only a slight reduction in V_T but considerable attention to lung recruitment, and this resulted in superior intermediate outcomes (*e.g.*, atelectasis, oxygenation, and lung infection) with some effects lasting up to 5 days.

A larger (101 patients) double-blind study focused primarily on the impact of V_T.[14]; the difference in V_T between the groups was large, with the control patients receiving 12 ml/kg predicted body weight compared with 6 ml/kg predicted body weight in the "protective" group. In addition, maintenance of lung volume was minimal—and equal—in each group (only PEEP, 5 cm H_2O, no recruitment maneuvers). This protective strategy did not provide benefit; moreover, lower V_T was associated with lower arterial oxygen tension (Pa_{O_2}) immediately after surgery, and more atelectasis by day 5.

The composite message from these two randomized, controlled trials[13,14] might be that during anesthesia, protective ventilation is beneficial when both lower V_T and a recruitment strategy are included, but not when lower V_T is used alone. This conclusion would be consistent with findings initially reported 50 yr ago,[15] where low V_T during general anesthesia without a volume recruitment strategy resulted in progressive atelectasis that impaired lung compliance and oxygenation.

Protective Ventilation for Abdominal Surgery—Recent Results

The most recent study examined 400 patients undergoing abdominal surgery who were considered to be at higher risk for postoperative pulmonary complications and incorporated both elements (lower V_T and volume recruitment) into the study design.[1] These patients were randomized to a control ventilation strategy (*i.e.*, standard V_T without PEEP) or a protective strategy (*i.e.*, low V_T, recruitment maneuvers every 30 min, and PEEP), and the composite primary outcome (major pulmonary or extrapulmonary events) was measured on day 7 after surgery. The results were striking; the primary outcome was reduced by over 60% (control 55 of 200, protective 21 of 200), and the control group had higher rates of noninvasive ventilation and sepsis and had a longer length of hospital stay.

There are reasons for caution in implementing the conclusions of this article. *First*, the title and conclusions of the article suggest that low V_T is beneficial.[1] However, the protective intervention applied low V_T, PEEP, and recruitment maneuvers, and assuming the results are valid, it is not possible to be certain which elements (or combinations thereof) are responsible for the outcome differences. *Second*, the effect size seems unrealistically high. In any outcome with a multifactorial etiology (especially when measuring a composite outcome), the effect size from a single intervention will necessarily be modest,[16] suggesting that imbalances in the group characteristics (notwithstanding randomization) may magnify (or account for) the observed effect. Such imbalance is not surprising in a moderate-sized study,[17] and additional indicators suggest that the two groups were not balanced at baseline. For example, the rate of anastomotic leak is significantly different between groups (44 of 200 control, 24 of 200 protective; $P = 0.009$); but, anastomotic leak is not pathogenically linked with ventilator strategy, and it can therefore be considered a "tracer" to detect between-group imbalances.[18] Because the causes of the imbalance are unknown, the imbalance cannot be corrected by multivariate adjustment.

Differences between ICU and Operating Room

Important differences between the ICU and the operating room may impact ventilator management. In the operating room, the patients' lungs are usually normal, compliant, and readily oxygenated. In addition, important surgical events are often predictable (or controllable), and a single specialist physician (or other anesthesia provider) is present to manage all aspects of care. In many anesthesia practices, intraoperative PEEP is seldom used. Finally, optional therapies can be discussed with the patient beforehand. In the ICU, most of these circumstances differ considerably; thus "cultural" and context differences may need to be considered when translating practices from the ICU to the operating room.

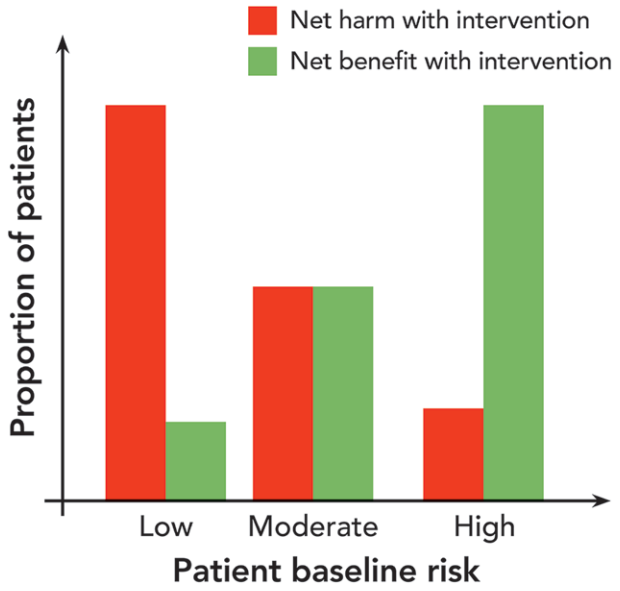

Fig. 1. Knowledge translation decision making is influenced by baseline patient risk. The benefit of an intervention can be described by a relation between the risk of no treatment (*i.e.*, the patient's baseline risk), the benefit of the intervention (*green bars*), and the risk of harm posed by the intervention (*red bars*). As the patient's baseline risk decreases, the harm of the intervention will eventually predominate over the intervention's therapeutic benefit. As such, implementation of an intervention aimed at a huge population of low baseline risk is unwise; instead, further study is advised. In contrast, an extremely high-risk population, such as those with acute respiratory distress syndrome, is more likely to benefit from the implementation of a new intervention.

Lessons from Previous Perioperative Interventions

The large treatment effect observed by Futier *et al.* has already led several outlets to champion an immediate adoption of this ventilation strategy for most surgical patients.* Such enthusiasm is not surprising, for at least two reasons.

First, protective ventilation with low V_T and lung recruitment is a simple inexpensive intervention that seems to cause major reductions in postoperative morbidity without important adverse effects. The desire to immediately change clinical practice based on such findings is understandable, especially when perioperative medicine lacks much in the way of interventions proven to prevent important morbidity and mortality. Nonetheless, several examples in the literature should warn us against rapidly changing clinical practice based on a single, although promising, study. For example, proponents of evidence-based practice and patient safety initially embraced β-blockade as a simple intervention to prevent perioperative cardiac complications,[19] largely based on two small randomized trials.[20,21] Nonetheless, subsequent larger trials found instead that this seemingly safe intervention could also increase patients' risks of postoperative stroke and mortality.[22] Similarly, two initial randomized trials identified supplemental perioperative oxygen as a simple and physiologically sensible intervention for preventing surgical-site infections,[23,24] yet these benefits were not replicated by a subsequent large randomized trial.[25] These two examples demonstrate the importance of replicating the results of a single promising study in different populations.

Second, the previously observed benefits of protective ventilation in critically ill patients with ARDS may have led to insufficient skepticism of studies showing such benefits in surgical patients with healthy lungs. Indeed, it is highly unlikely that the overall risk–benefit profile of protective ventilation is similar in the two populations. Patients with ARDS by definition already have lung injury, yet the overall risk of postoperative pulmonary complications after elective surgery may be as low as 1.5%.[26] Thus, the *relative* magnitude of any adverse effects from protective ventilation will be much larger in surgical patients *versus* critically ill patients (fig. 1). When the overall level of patient risk is low, the harmful effects of a therapy tend to dominate[27] (fig. 2).

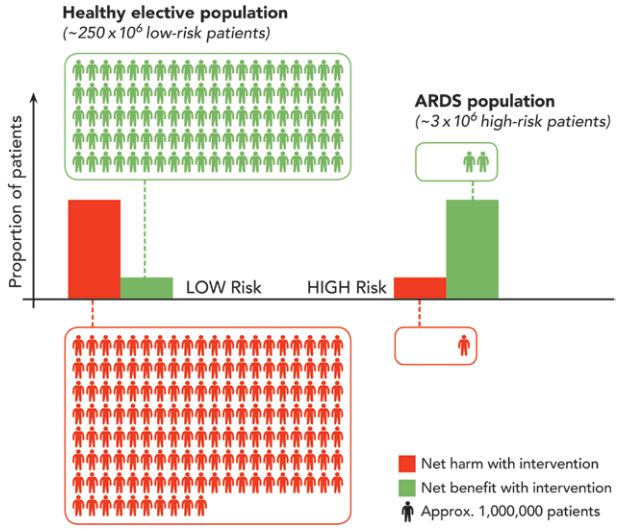

Fig. 2. The effects of population size and baseline risk on clinical decision making. The *schematic* above outlines the potential effects of a new ventilation strategy as implemented in a large, low-risk population (*left*) or in a smaller, high-risk population (*right*). *Green shading* represents benefit, whereas *red* represents harm. In the large, low-risk population, the proportion of harm of the intervention will predominate, because baseline risk is exceedingly low (as indicated in fig. 1). In addition, the large population size (thought to be 250 million people per year) results in a large absolute number of patients being harmed, in spite of a low *risk* of harm. In the high-risk population of smaller size (*right*), there is more opportunity for the benefit of the treatment to be actualized. As such, a greater percentage of patients will benefit, and due to the small population size (an estimate of 3.2 million cases of acute respiratory distress syndrome [ARDS] worldwide per year), a smaller absolute number will be harmed. This effect forms the basis for the suggestion that an intervention that will be applied to a large, low-risk population requires extensive study before implementation, because the potential for harm, in terms of absolute patient number, is high.

* Lung Protective Ventilation | Now@NEJMat. Available at: http://blogs.nejm.org/now/index.php/lung-protective-ventilation/2013/07/31. Accessed October 5, 2013; anesthesiologynews.com available at: http://www.anesthesiologynews.com. Accessed October 5, 2013.

Going Forward

In summary, we believe that the balance of rationale, evidence, and experience suggests that the ideal approach to intraoperative ventilation is certainly an important question, but that the answer remains unknown. The experience from the ICU, coupled with extensive laboratory data and provocative clinical studies, has set the scene for large-scale trials in the field. In addition, the design—*and reporting*—of such studies should carefully detail the interventions used in terms of V_T and lung recruitment. Fortunately, large-scale perioperative clinical consortia exist that have the capacity to execute such studies. Finally, for anesthesia providers who decide that the current level of evidence is sufficient to change practice, we suggest that they consider carefully the interventions detailed by Futier *et al.* (*i.e.*, management of both V_T by predicted body weight and lung recruitment) and perhaps restrict the specific intervention to comparable patient populations.[1]

Acknowledgments

Dr. Goldenberg receives funding from The Alan K. Laws Clinician-Scientist Award, Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada, and from the Physicians' Services Incorporated Foundation, Toronto, Ontario, Canada. Dr. Steinberg is supported by a Clinician Investigator Program fellowship from the Ministry of Health (Canada) as well as the Joseph M. West Memorial Fund and the Javenthey Soobbiah Scholarship. Dr. Wijeysundera is supported by a Clinician-Scientist Salary Award from the Canadian Institutes of Health Research, Ottawa, Ontario, Canada, and a Merit Award from the Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada. Dr. Kavanagh is supported by the Dr. Geoffrey Barker Chair in Critical Care Research, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. Drs. Lee and Kavanagh received operating grant support from the Canadian Institutes of Health Research, Ottawa, Ontario, Canada.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Kavanagh: Department of Anesthesia, University of Toronto, Fitzgerald Building, Room 121, 150 College Street, Toronto, Ontario, M5S 3E2, Canada. brian.kavanagh@utoronto.ca.

References

1. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med 2013; 369:428–37
2. Acute Respiratory Distress Syndrome Clinical Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8
3. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, Bruno F, Slutsky AS: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. JAMA 1999; 282:54–61
4. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P: Meta-analysis: Ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. Ann Intern Med 2009; 151:566–76
5. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O: What tidal volumes should be used in patients without acute lung injury? Anesthesiology 2007; 106:1226–31
6. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: An estimation of the global volume of surgery: A modelling strategy based on available data. Lancet 2008; 372:139–44
7. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT; Neonatal Ventilation Study Group: High-frequency oscillatory ventilation *versus* conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002; 347:643–52
8. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin Definition. JAMA 2012; 307:2526–33
9. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, Stewart TE, Barr A, Cook D, Slutsky AS; Canadian Critical Care Trials Group: One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003; 348:683–93
10. Tremblay LN, Slutsky AS: Ventilator-induced injury: From barotrauma to biotrauma. Proc Assoc Am Physicians 1998; 110:482–8
11. Dreyfuss D, Soler P, Basset G, Saumon G: High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 1988; 137:1159–64
12. Muscedere JG, Mullen JB, Gan K, Slutsky AS: Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 1994; 149:1327–34
13. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, Dionigi G, Novario R, Gregoretti C, de Abreu MG, Schultz MJ, Jaber S, Futier E, Chiaranda M, Pelosi P: Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology 2013; 118:1307–21
14. Treschan TA, Kaisers W, Schaefer MS, Bastin B, Schmalz U, Wania V, Eisenberger CF, Saleh A, Weiss M, Schmitz A, Kienbaum P, Sessler DI, Pannen B, Beiderlinden M: Ventilation with low tidal volumes during upper abdominal surgery does not improve postoperative lung function. Br J Anaesth 2012; 109:263–71
15. Bendixen HH, Hedley-Whyte J, Laver MB: Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation. A concept of atelectasis. N Engl J Med 1963; 269:991–6
16. Yusuf S, Collins R, Peto R: Why do we need some large, simple randomized trials? Stat Med 1984; 3:409–22
17. Chu R, Walter SD, Guyatt G, Devereaux PJ, Walsh M, Thorlund K, Thabane L: Assessment and implication of prognostic imbalance in randomized controlled trials with a binary outcome—A simulation study. PLoS One 2012; 7:e36677
18. Hackam DG, Mamdani M, Li P, Redelmeier DA: Statins and sepsis in patients with cardiovascular disease: A population-based cohort analysis. Lancet 2006; 367:413–8
19. Leape LL, Berwick DM, Bates DW: What practices will most improve safety? Evidence-based medicine meets patient safety. JAMA 2002; 288:501–7
20. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac

surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996; 335:1713–20

21. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H: The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341:1789–94
22. Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH: Perioperative β-blockers in patients having noncardiac surgery: A meta-analysis. Lancet 2008; 372:1962–76
23. Belda FJ, Aguilera L, García de la Asunción J, Alberti J, Vicente R, Ferrándiz L, Rodríguez R, Company R, Sessler DI, Aguilar G, Botello SG, Ortí R; Spanish Reduccion de la Tasa de Infeccion Quirurgica Group: Supplemental perioperative oxygen and the risk of surgical wound infection: A randomized controlled trial. JAMA 2005; 294:2035–42
24. Greif R, Akça O, Horn EP, Kurz A, Sessler DI; Outcomes Research Group: Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000; 342:161–7
25. Meyhoff CS, Wetterslev J, Jorgensen LN, Henneberg SW, Høgdall C, Lundvall L, Svendsen PE, Mollerup H, Lunn TH, Simonsen I, Martinsen KR, Pulawska T, Bundgaard L, Bugge L, Hansen EG, Riber C, Gocht-Jensen P, Walker LR, Bendtsen A, Johansson G, Skovgaard N, Heltø K, Poukinski A, Korshin A, Walli A, Bulut M, Carlsson PS, Rodt SA, Lundbech LB, Rask H, Buch N, Perdawid SK, Reza J, Jensen KV, Carlsen CG, Jensen FS, Rasmussen LS; PROXI Trial Group: Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery: The PROXI randomized clinical trial. JAMA 2009; 302:1543–50
26. Arozullah AM, Khuri SF, Henderson WG, Daley J; Participants in the National Veterans Affairs Surgical Quality Improvement Program: Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med 2001; 135:847–57
27. Quanstrum KH, Hayward RA: Lessons from the mammography wars. N Engl J Med 2010; 363:1076–9

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Wrenching Experiences from the Heidbrink Company

Jay Albion Heidbrink, D.D.S. (1875–1957) founded one of America's most successful manufacturing companies for anesthesia machinery for physicians and for dentists. Never shy about advertising his wares, Dr. Heidbrink devised this open-ended advertising wrench (or spanner) for use on his anesthesia machines and other appliances. The left side of "THE HEIDBRINK CO" wrench services a ½-inch span; the right side spans successively ¾, 1, and 1-⅛ inches. The use of inches was not accidental. Dr. Heidbrink resisted adopting the metric system and was one of the last to stop manufacturing anesthesia machines "metered" (hah!) to deliver gases in "gallons per hour." (Copyright © the American Society of Anesthesiologists, Inc.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.