Published in final edited form as:

Int Anesthesiol Clin. 2020 ; 58(4): 41–45. doi:10.1097/AIA.0000000000000291.

The future of research in anesthesiology | International Anesthesiology Clinics

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Introduction

Research in anesthesiology spans the translational spectrum and reflects the breadth of clinical settings in which anesthesia providers now practice. The goal of this paper is to summarize the diversity of scholarship in anesthesiology, discuss challenges to anesthesiology research, and to highlight the bright potential of anesthesiology research. Given that most research in anesthesiology is conducted by scientists with MD/DO or PhD degrees (or both), our commentary is focused on these investigators.

Anesthesia research across the translational spectrum

The United States National Institutes of Health (NIH) characterizes biomedical research according to a “translational spectrum.” According to this scheme, all research relating to human health and disease is located on that spectrum, not just those inquiries that explicitly bridge the “bench to bedside” divide.[1] Using this conceptual context, we highlight the types of scientific inquiry that relate to anesthesiology and perioperative care. Specifically, we break down the spectrum into three distinct categories, early, middle and late stage, and illustrate the types of research being conducted within those stages.

Basic science and “early stage” translational research

Research in this realm is sometimes called “pure,” as it focuses on elucidating fundamental biological and pathobiological mechanisms while minimizing confounding influences such as biological and environmental diversity. Although not always addressing clinical issues, basic science is often inspired by observations made within a clinical setting. This process is thought of as “bedside to bench” or “reverse translation.”[2] Examples of anesthesia research in basic science include determining the molecular targets for different anesthetic drugs, identifying novel compounds with favorable properties for research and/or clinical practice, ascertaining how drugs interact in the brain to create the anesthetized state, and

identifying genes responsible for atypical anesthetic responses, either directly or through the creation of transgenic animals. Most research involving animals, from fruit flies to large mammals, would be considered early stage or pre-clinical research.

Clinical and “middle stage” translational research

Clinical research in anesthesia involves testing potentially therapeutic drugs, procedures, or care pathways. Both observational (retrospective or prospective) and prospective interventional approaches are used in clinical research. This research can address efficacy, such as testing if a drug or procedure achieves its expected or desired effect in tightly controlled settings (e.g., randomized controlled trials). Clinical research can also focus on effectiveness, asking whether the drug or procedure works in the “real world,” under less well controlled settings. Examples of clinical anesthesia research include testing antifibrinolytic agents to promote hemostasis, comparing regional versus general anesthesia for appropriate surgical cases, and the use of extracorporeal membrane oxygenation (ECMO) to improve outcomes in cardiopulmonary failure. Additionally, clinical researchers have started focusing on long-term outcomes of the perioperative period, such as pain, function, cognition and cancer recurrence, as the anesthesiology community begins to query the lasting impact of their seemingly transient interventions.

Population and “late stage” translational research

A natural progression from middle stage research, late stage research focuses on the health outcomes of communities or entire populations. Late stage translational approaches include dissemination and implementation research focused on bridging the evidence-to-practice gap,[3] community-based participatory research, global health research, and correlational research using large secondary databases. Examples of late stage translation relevant to anesthesiology include describing the influence of post-operative opioid prescribing strategies on long-term opioid use and addiction, determining the association between health care policy changes and health care resource utilization like elective surgery, or interventions to educate anesthesia providers in low and middle-income countries to improve surgical safety.

Anesthesia research across the perioperative care spectrum

Classically, anesthesiology researchers and practitioners focused their attention on what happens during an episode of surgical care, particularly during the time within the operating theater. More recently, however, anesthesiology has taken a broader focus on perioperative medicine, beginning when a surgical procedure is being contemplated and following through to the completion of a care episode ending in recovery or in end-of-life care that is consistent with patients’ and families’ goals and preferences. For each phase of care, there are examples of all types of translational research being conducted.

Pre-operative planning

Anesthesiology researchers are increasingly interested in patient care that precedes a surgical episode. Within the basic science realm, research is ongoing to understand brain aging and the mechanisms through which the brain may be vulnerable to dysfunction after

surgical stress and anesthesia. From a clinical standpoint, pre-operative risk stratification research is helping with both the decision to proceed with surgery and with the selection of a facility (e.g., outpatient surgicenter versus hospital). For deconditioned patients, studies on “prehabilitation” interventions are continuing to improve exercise tolerance before surgery and may decrease the risk of perioperative complications. Social scientists study shared decision-making and the approaches used to discuss operative alternatives to patients.

Intraoperative management

The earliest anesthesiology research focused on approaches to safely anesthetize patients and optimize the surgical field. In the modern era, this work continues, albeit with an expanded focus on anesthetic and adjunct drugs, monitoring technologies, and management of fluids and hemodynamic parameters. Basic science relevant to intraoperative management may focus, for example, on understanding how anesthetics affect the developing brain, or understanding how electroencephalography can be used to assess brain functioning and anesthetic depth. Clinical studies may retrospectively or prospectively characterize the relationship between intraoperative parameters such as bispectral index or blood pressure and outcomes such as post-operative cognitive dysfunction or myocardial infarction. Population-level studies may unmask associations between intraoperative exposures and outcomes, informing additional basic or clinical mechanistic studies. Implementation research can test strategies to facilitate the uptake of evidence-based intraoperative care practices, such as quantitative neuromuscular blockade monitoring.

Post-operative management

As the comorbidity burden of surgical patients continues to rise and the consequences of fluid and hemodynamic management become clearer, more research has focused on optimal management of patients after surgery. This work ranges from a focus on where patients should recover (e.g., post-anesthesia care unit versus intensive care unit) to enhanced recovery after surgery programs [4] that guide the management of fluids, vasopressors, and analgesics after surgery. In the era of the opioid epidemic, newer research investigates the viability of avoiding opioids altogether in the postoperative period.

Recovery and return to function

Anesthesiology researchers are increasingly interested in understanding the downstream effects of perioperative and periprocedural management. Basic scientists continue to delve into the side effects of anesthetic medications including the long-term cognitive effects of these drugs and of surgical inflammation on the developing and elderly brains. Clinical trialists and outcomes researchers are interested in demonstrating the conditions under which patients develop post-operative delirium and understanding the interaction between delirium and sustained post-operative cognitive decline. Anesthetic techniques have also been implicated in cancer recurrence and the development of chronic pain; basic, clinical, and health services research approaches have all been used to shed light on these questions.

Outpatient management

Pain research in anesthesia is not limited to the inpatient setting. Chronic pain, neuropathic pain, opioid-induced hyperalgesia, and opioid use disorder are areas of active research in anesthesiology. Basic researchers seek to characterize neural pathways that govern the perception and experience of pain and to identify novel compounds that can provide analgesia without respiratory depression or addiction. Clinical research in this area includes trials of different pain regimens, while population-level research includes testing policy changes that impact opioid and opioid reversal agent prescriptions.

End-of-life care

Anesthesiologists are often involved in the care of patients at the end of life, whether for palliative surgical procedures (e.g., venting gastrostomy in obstructive oncologic disease) or for palliative care and hospice focused on more holistic psychosocial needs. Research in this area tends to be at the later translational stages and may include testing interventions to increase the availability of palliative care consultation or testing policies that incentivize goals-of-care discussions with patients and their families.

The funding landscape for anesthesia research

Institutions

Most academic departments and institutions have funding mechanisms for faculty who are forming a new laboratory or pilot projects for more established investigators. Typically, the number of applications is not large, but neither are the award amounts. The pilot awards are generally designed to provide preliminary data to bolster a larger extramural grant application that comes with indirect (Facility and Administration (F&A)) funds. Some departments will have established endowment accounts, either for a specific area of research or for an individual. Depending on institutional rules, the proceeds from these accounts may be used to fund research. Some departments and institutions have gap-funding programs, whereby previously funded labs can survive a transient loss of extramural funding. Hospital administrative budgets represent another source of research support, especially for clinical or late stage translational research. Hospitals and health systems may fund such research projects if they are aligned with health system priorities. This “learning health system” approach [5] is designed to create synergy between research, quality improvement, and operational efforts.

Foundations and Societies

Multiple foundations and societies offer grant funding to support anesthesia-related research. An advantage of foundation grants is that there is typically a smaller pool of applicants, which increases the chances of successful funding. Further, foundation grant reviewers are likely to have a more robust understanding of important research topics in the field. This, in turn, requires less background to justify a topic of interest, for example, the importance of neuromuscular blockade monitoring or elucidation of anesthetic mechanisms of action. Foundations also may be willing to fund grants in educational research, an area with limited extramural funding options. On the other hand, foundation grants tend to be smaller and of

shorter duration than governmental grants. There may be fewer grants available in any given cycle, and foundations usually restrict the amount that can be earmarked for F&A to the grantee institution. In fact, F&A support may be disallowed entirely by some foundations. Given this limited F&A recovery, foundation grants are seen as financially risky, and institutions often have rules regarding who can apply for them, and when. In some cases, the institution will require “subvention,” whereby the department pays the F&A costs associated with the research.

An exhaustive list of potential foundation funders is outside the scope of this article, but most institutions maintain lists of potential funding sources. Interested readers are encouraged to seek out foundations that support early stage investigators, such as the Foundation for Anesthesia Education and Research (FAER) and the International Anesthesia Research Society (IARS). Certain foundations have declared areas of interest within anesthesiology research, such as the Anesthesia Patient Safety Foundation (APSF; with a focus on perioperative safety) and the American Society of Regional Anesthesia and Pain Medicine (ASRA; with a focus on regional anesthesia/analgesia and pain). The FAER and American Board of Anesthesiology have coordinated to offer grants focused on education research in anesthesiology. Importantly, the FAER and IARS grants commit the department to providing significant non-clinical time to the awardee to develop their science, which is difficult when a significant clinical workload is expected.

State and Federal

In the United States, many states offer funding opportunities for research, but these opportunities are typically limited and highly focused. For example, funds flowing from the tobacco settlements, or special taxes (marijuana) are sometimes used to fund priority areas of research. In the state of Pennsylvania, for example, the state funded research on traumatic brain injury and health care innovation in 2015–2016, and funded grants related to the opioid epidemic in 2018–2019.¹

The majority of funds for biomedical research of all types in the United States flow from the federal government, primarily the National Institutes of Health (NIH). The NIH is comprised of 27 individual institutes and centers (ICs), each with a large extramural funding mission, and many of which fund anesthesiology research. There are many grant “mechanisms”, designed for all forms of research, and at different stages of ones’ career. For example, T- and F- series grants are designed for either pre- or post-doctoral fellows, and the K-series are generally start-up grants for junior faculty still in need of significant mentorship. Like the FAER and IARS awards, these K awards also come with a requirement for significant non-clinical time, but over a longer time period (4 to 5 years) than the foundation and society awards. Those applying for mentored scientist applications should devote as much attention to the training plan and environment as they do to the science. The next step is generally the R-series awards, which are evaluated on significance to health and biology, quality of the applicant, how innovative the project is and finally how the applicant plans to actually accomplish the project. Review and scoring of these applications are generally carried out by

¹https://www.health.pa.gov/topics/Documents/Research/2001%20to%20date%20Priorities%20for%20Web_Rev%209-9-19.pdf. Accessed 2/29/2020.

an independent body, the Center for Scientific Review (CSR) via a host of initial review groups (IRGs) or study sections, comprised of other investigators in relevant disciplines. Typically, only applications scoring in the top 10–20% (institute dependent) of those reviewed will be considered for funding.

Finally, there are larger consortia grant mechanisms, such as the U- and P- series. These are multi-investigator and generally focused in a given area, but perhaps from different technologies and perspectives. Permission is usually required for submission of such an application, as they are often large (>\$1M/year) and require specialized review. Many anesthesiology researchers have held these large multidisciplinary grants. Not all institutes use all the above mechanisms, and many use them in different ways. A thorough discussion is found at each ICs website, which can be found on the NIH.gov website.

Outside the United States, governmental funders include the Canadian Institutes for Health Research, the European Commission, and the Australian Research Council. In limited circumstances, the NIH will fund investigators based outside the United States.

Industry

Many companies have products that are used in procedural, surgical and critical care settings. Not only does this include a myriad of drugs, but also supplies, devices and sophisticated monitoring and anesthetic delivery systems. In many cases, these companies seek anesthesiology practice settings to test their products for safety and efficacy and provide funding to support this investigative work. However, these funds are often made available as contracts rather than grants. Companies also tend to look for healthcare settings that include an existing clinical research infrastructure, as they typically provide funds on a per patient basis, and rarely provide sufficient up-front costs to establish the necessary infrastructure. Nevertheless, this has been an important source of support for anesthesiology researchers.

Challenges for the future of anesthesia research

Despite the depth and breadth of scholarship in anesthesia and perioperative care, there are several challenges that warrant consideration: maintaining and growing the anesthesia research workforce, threats to rigor and reproducibility, the need for multicenter research, and the introduction of emerging research methods.

Workforce growth and development

Over the past 20 years, numerous articles have discussed a “crisis in academic anesthesiology.”[6–9] In 2019, just 52 of the more than 130 academic anesthesiology departments in the United States had any federal funding from the NIH, according to the Blue Ridge Institute for Medical Research.² A 2014 study showed that just 37% of anesthesia faculty members published at least one manuscript in a two-year period.[10] As a well-compensated clinical specialty, prospective clinician-scientists may be compelled to choose between maximizing clinical income by forgoing research or taking a relative

²http://www.brimr.org/NIH_Awards/2019/NIH_Awards_2019.htm. Accessed February 22, 2020.

reduction in pay, at least initially, to pursue their research agenda.[11] In the United States, numerous efforts are underway to grow the pipeline of anesthesia researchers. For example, the FAER Medical Student Anesthesia Research Fellowship (MSARF) matches undergraduate medical studies with anesthesiology labs across the country, providing an 8-week combined research and clinical experience.[12] Multiple residency programs have created academic anesthesiology pathways to provide mentorship, dedicated research time, and a presumably smoother transition to a faculty research position.

For instructors and junior faculty, protected time to learn research skills and to conduct and publish research is instrumental to their ability to gain a foothold in the research world. This protected time can be provided by departmental funds or through training grants, as with the NIH T-32 grant mechanism. However, the resources to provide protected time depend on the financial viability of supporting departments and the availability of training grant funds. As of February 2020, there were just 20 NIH T-32 training grants focused on anesthesia; these were granted to 16 universities.³

Potentially promising strategies to grow the anesthesia research workforce include mentorship, provision of protected time to develop one's research agenda, and strategies to encourage research by historically underrepresented groups. Mentorship has been shown to facilitate the successful launch of a research career, both within and outside of anesthesia. Multiple mentors may be useful for the aspiring anesthesia researcher[13] given the expanding scope of anesthesia and related research described earlier. Mentors fulfill multiple roles, including imparting research skills; providing and advocating for space, equipment and supplies for research; providing critical feedback on research ideas and products; and guidance in applying for fellowships and grants.[11]

Rigor and reproducibility

Researcher John Ioannidis and others have noted the crisis of reproducibility facing science in general and medical research in particular.[14] There are multiple causes of unreproducible research; for clinical research in anesthesia, small sample sizes, single center studies, and heterogeneous outcome measures are especially problematic. There is a growing movement in anesthesia and perioperative research to bolster rigor and reproducibility in two ways.

First, creating a standard set of outcomes measures as proposed by Paul Myles and colleagues[15] promotes research that can be directly compared and combined in subsequent meta-analyses. Myles' Standardised Endpoints in Perioperative medicine (StEP) and Core Outcomes Measures in Perioperative and Anaesthetic Care (COMPAC) initiatives use systematic reviews and expert consensus to develop and promulgate sets of outcome measures that will streamline and standardize the measurement of outcomes ranging from clinical indicators[16] to patient-centered outcomes.[17]

Second, multicenter research is needed to achieve large sample sizes, optimize the generalizability of research findings, and guard against single-center statistical anomalies

³Data from NIH REPORTer: <https://projectreporter.nih.gov/reporter.cfm>

that suggest large effects. The Outcomes Research Consortium based at the Cleveland Clinic,[18] the Multicenter Perioperative Outcomes Group based at the University of Michigan,[19] the Anesthesia Quality Institute National Anesthesia Clinical Outcomes Registry,[20] and the Australian and New Zealand College of Anaesthetists Trials Network[21] all represent efforts to facilitate multicenter retrospective and prospective research in anesthesia and perioperative care. These consortia provide the substantial infrastructure that is needed to coordinate multicenter research, facilitating ethics review, grant subcontracts, and authorship with potentially large author groups.

Emerging methods

With an estimated medical knowledge doubling time of just 79 days,[22] maintaining fluency with research methodological approaches is a formidable task. As anesthesia research has expanded to fit the full translational spectrum and as it has turned its attention to the full continuum of perioperative care, new methods have been introduced to the field. These new methods are exciting and potentially transformative but present a challenge to funding agencies and grant reviewers, journal editors and reviewers, and readers of the scientific literature. For example, qualitative and mixed methods approaches are commonly used in social science research, but they have achieved only modest penetration in anesthesia research. Machine learning and “big data” approaches bear promise in phenotyping patients and uncovering associations between perioperative exposures and outcomes, but require sophisticated and computationally expensive software packages. Educational research in anesthesia is also growing, driven in part by interest in point of care ultrasound [23], changes in work hours restrictions, and a growing appreciation for resident burnout and wellness. This type of research typically involves mixed methods and quasi-experimental study design and is limited by the difficulty in linking educational outcomes to patient and provider outcomes.

Conclusion

The future of anesthesia research is scholarship that reflects the full scope of translational research and the perioperative continuum of care. This research is likely to be funded by a diverse range of sources and it will be conducted by a workforce using both established and emerging tools and methodologic approaches to inquiry.

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