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Review Article

REVIEW ARTICLE

Refocusing on work-based hazards for the anaesthesiologist in a post-pandemic era

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Abstract

The coronavirus pandemic has raised public awareness of one of the many hazards that healthcare workers face daily: exposure to harmful pathogens. The anaesthesia workplace encompasses the operating room, interventional radiology suite, and other sites that contain many other potential occupational and environmental hazards. This review article highlights the work-based hazards that anaesthesiologists and other clinicians may encounter in the anaesthesia workplace: ergonomic design, physical, chemical, fire, biological, or psychological hazards. As the anaesthesia work environment enters a post-COVID-19 pandemic phase, anaesthesiologists will do well to review and consider these hazards. The current review includes proposed solutions to some hazards and identifies opportunities for future research.

Keywords: anaesthesia; biomedical hazards; environment; fire; personal protection equipment; safety; work-based hazards

The coronavirus pandemic has raised public awareness of one of the many hazards that healthcare workers face daily: exposure to harmful pathogens. The focus of occupational hazards in anaesthesiology throughout the pandemic has been on personal protective equipment (PPE) and anaesthesiologists' safety during aerosol-generating procedures.[1] It is important to recall that the practice of anaesthesia includes many other occupational and environmental hazards in the operating room, interventional radiology suite, and other sites. A recent review provided a brief overview on occupational risks in anaesthesia.[2] The current review delves more in depth into the literature on each of the hazard domains that anaesthesiologists and other clinicians encounter in the anaesthesia workplace: ergonomic, biological, physical, chemical, and fire and psychological.

Methodology

A literature search was performed to find articles of interest. PubMed was searched for articles published using the keywords 'work hazards' AND 'Anesthesia'; 'personal protection equipment' AND 'anesthesia'; 'Noise' AND 'Anesthesia'; 'operating room hazards' AND 'anesthesia'; 'fire AND anesthesia'; 'radiation' AND 'anesthesia'; 'Ergonomics' AND 'anesthesia'; 'Smoke' AND 'anesthesia'; 'Substance abuse' AND 'anesthesia'; 'infection risk' AND 'anesthesia'. Articles

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were reviewed to identify those relevant to work hazards and anaesthesia. The original search was performed in June 2020 and then updated in November 2022 and July 2023.

Ergonomics

Ergonomics is the study of the interactions between humans and their environment.[1] Significant focus has been given to how anaesthesiologists work with their equipment.[3,4] The overwhelming majority of this has been from a patient safety perspective. Machine design, alarms, etc., have all been extensively studied. Human factors are continuously reviewed in medicine to reduce patient harm. However, few studies focus on potential injuries to anaesthesiologists and other operating room personnel that relate to how they move within their environment and interact with their equipment.

The study of the entire operating room environment as a dynamic and evolving workspace is frequently overlooked. The operating room environment is intended as state of the art at the time of design. Some operating rooms are designed by architects in consultation with hospital administration, with users involved in initial designs. The initial design is built around specific equipment with its dimensions considered. Human factors experts may or may not be involved in the initial design phase. However, the design phase may be hampered by key members coming from significantly different backgrounds. There may be insufficient time dedicated between the users, designers, and ergonomics consultations to fully comprehend the use of the space including how this may evolve. This can result in inadequate design and insufficient allowances and considerations given for future uses.[5] The design is frequently out of date at the time the room is opened.[6] During the lifespan of an operating room, equipment is updated as technology changes, and new technology adopted.[6] However, rarely is the entire room design re-evaluated. Implementation of new technology may further constrain the use of the space and introduce new ergonomic barriers.[7]

Palmer and colleagues[8] utilised human factors to study flow disruptions during cardiac surgery, and reported that the most prevalent source of disruption was physical layout. The most prevalent disruptions overall were attributed to inadequate use of space, wrongful position of furniture and equipment. Specific to the anaesthesia team several issues were identified. Poor layout, inappropriate equipment positioning, inadequate use of space, and furniture location interrupting flow were most prevalent. With regards to usability, issues identified include equipment, design of surfaces, and computer-related problems.

The operating room environment presents risks for trips, falls, and impacts with equipment on a daily basis. The floor may be wet because of fluids and present a slip hazard.[9] Wires connecting the anaesthesia workstation and other electrical equipment to a power supply are rarely of ideal length. Excess length results in a higher likelihood of entanglement injuries.[6,9] Too short a length increases the risk of trip hazards.[10,11] Ceiling-mounted equipment such as laparoscopic displays present risks for head injuries. Use of equipment can present risks of repetitive motion and position-related injuries. Anaesthesia workstations have a limited ability to adjust for users' differing heights. This can lead to low back strain for tall users and neck strain for shorter users. Most anaesthesia workstations have the gas outlets designed for a right-sided setup. This becomes the default setup in most operating rooms. This permits the user to hold a mask with the left hand and operate the gas machine with their right hand. This may work well for right-handed individuals; however, it gives little consideration to left-handed users who may prefer the opposite setup. Protective equipment, such as lead aprons, create muscle strain predisposing wearers to ergonomic injuries.[12]

Poor ergonomic design in the operating room can at best lead to inefficient use of time, resources, and personnel. However, poor design has potential to lead to occupational injuries. This area requires further attention from a research perspective and during operating room design and renovation stages.

While providing direct patient care, healthcare providers, including anaesthesiologists, are at increased risks of musculoskeletal occupational injuries. The ongoing obesity epidemic continues to place increased physical demands on healthcare providers with risk of musculoskeletal injuries such as low back strain or rotator cuff injuries when transferring patients.[13] Anaesthesiologists, as with other healthcare providers, are at risk of repetitive motion injuries related to poor ergonomics.[14] In the name of efficiency, ideal positioning of the table for intubation can easily be overlooked.[15] Failure to adjust the table to an optimal height can result in poor body positioning placing the operator at risk of repetitive motion injuries. Newer technologies in anaesthesia practice introduce risks that are not completely understood. For example, up to 90% of ultrasonographers report work-related musculoskeletal disorders.[16] Transducer grip and grip pressure are frequently associated with these injuries.[17] Whereas there has been significant study of ultrasound ergonomics in ultrasonographers, there has been little study of these implications in the operating room.

Biological hazards

Exposure and transmission of pathogens from patient to healthcare provider has been a long-standing concern for anaesthesiologists. The recent COVID-19 pandemic has increased visibility of these concerns; however, this is not new. It has long been recognised that there are risks of transmission of infection from patient to healthcare provider.[18] Despite this, effective means to reduce transmission risk, and compliance with recommendations continue to be less than optimal. For example, transmission of herpes simplex virus 1 (HSV-1) causing herpetic whitlow from patient to anaesthesiologist was recognised in 1970, and despite this, infections continue to occur because of variable compliance with wearing gloves, which is lowest among paediatric anaesthesia providers.[19,20]

The nature of anaesthesia care leads to close contact with both blood and hollow bore needles. Transmission of blood-borne pathogens has been understood since the 1940s when hepatitis B was determined to be transmitted via reused syringes.[21] During the 1980s, concerns with hepatitis C and human immunodeficiency virus (HIV) arose introducing heightened awareness, new protective equipment, and significant anxieties. Universal precautions were introduced in response to this crisis.[22] The application of universal precautions decreases exposure to blood and glove wearing decreases the incidence of needlestick injury.[20,23] Decades of work developing safety intravenous cannulae and safety needles continues to decrease the risk of needlestick injuries.[24,25] However, barriers continue to exist that limit the adoption of these technologies.[26,27] In other situations, effective safety devices do not exist for needles such as spinal needles or suture needles.[28,29] While blood-borne pathogens continue to be a risk, immediate institution of

antiviral therapy for post-exposure prophylaxis reduces the risk for seroconversion.[30–32] Today, with antiviral post-exposure prophylaxis started immediately after exposure, the risk of seroconversion for HIV is approaching zero.[31] Hepatitis C seroconversion rates with post-exposure prophylaxis continue to be higher than that for HIV and range from 0.1% to 2.2%.[33]

Because they are routinely instrumenting the airway and being exposed to the mucus membranes, anaesthesiologists are frequently exposed to respiratory pathogens. Respiratory pandemics such as SARS-COV2, SARS-COV1, and H1N1 continue to disproportionately affect anaesthesiologists.[31,32] Anaesthesiologists continue to be at increased risks for other longstanding pathogens such as tuberculosis, which has been decreasing in incidence, however risks for exposure to this difficult to treat respiratory pathogen continue to occur.[34,35]

Studies of indoor air quality in the operating room have focused mostly on anaesthesia gases, smoke, and the potential spread of pathogens increasing the risk of surgical site infections.[36,37] Anaesthesia gases and smoke are discussed elsewhere in this review. Clinicians should be aware that poor air quality can place them at risk of exposure to pathogens and contaminants.[38] Heater-cooler units have been identified as a potential source of airborne infection in the operating theatre.[39] Air quality in operating rooms should be monitored not only to reduce surgical infections, but also to minimise exposure of operating room personnel to contaminants and pathogens.[37,40–42] Airborne microbial contamination can be reduced by minimising airborne particles and contaminants, and maintaining technical systems and equipment according to manufacturers' recommendations.[43–45] The exposure risk associated with working in the operating room environment requires appropriate precautions to be taken. This generally translates to additional PPE worn by the healthcare provider.[46,47] These barriers such as respirators, gloves, face shields, and additional layers of clothing reduce risks of pathogenic transmission to the healthcare providers, but they introduce new physical constraints.[48–54] Providers may experience reduced dexterity, communication barriers, heat stress, and dehydration.[55,56] Disposable respirators such as N95 masks have been associated with rebreathing and increased skin breakdown on the nasal bridge.[55,57]

The impacts on mental health related to the ongoing exposure to any pathogen and the PPE required is significant. Increased stress and anxiety are reported in healthcare providers frequently caring for patients with infectious diseases.[58,59] This may be related to concerns related to increased risk of infection, potential spread to the healthcare providers own family or to other patients.[58,60] Fatigue and burnout is higher as a result of both protective equipment and repeated exposures to infectious patients.[60] In addition, the physical and economic effects of a healthcare provider becoming ill from a hospital acquired infection cannot be overlooked. Occupational exposures have the potential to shorten careers, affect families and relationships, and can have devastating economic impacts on the provider.[61]

Physical hazards

Anaesthesia care providers can be exposed to a variety of physical hazards with the potential for acute and long-term deleterious effects. Excessive noise can cause hearing loss, cognitive dysfunction, anxiety, and an increased risk of cardiovascular disease.[62] Occupational exposure to noise pollution in anaesthesiology arises from both staff and equipment, and noise levels can frequently exceed recommended safe limits established by regulatory agencies.[63–65] Noise pollution during general anaesthesia not only affects care providers' health, but also can affect their concentration and communication and place patients at risk of harm.[65–67] In a prospective study of 23 surgical cases, Ginsberg and colleagues[62] found noise in the operating room was consistently louder during the critical anaesthesia stages of induction and emergence. Excessive noise causes stress and negatively impacts both surgeons' and anaesthesiologists' attention and performance.[68,69]

The easiest and most effective solution for noise pollution is to minimise noise production during anaesthesia care. Quality improvement initiatives can reduce the risks of unacceptable noise levels and distractions. Crockett and colleagues[70] reported an initiative termed the 'distraction-free induction zone', in which distraction during induction of anaesthesia in paediatric operating rooms decreased from 61% to 15% over a 3-month period.

Exposure to ionising radiation has been recognised for decades as a hazard in the anaesthesia workplace, particularly in areas where fluoroscopy is used.[71] Medical radiation exposure may occur from three sources: 1) direct exposure from the primary X-ray beam, 2) scattered radiation from patient body surface, and 3) radiation emitted from the X-ray tube in areas other than the primary beam, defined as leakage X-rays.[72,73] During some procedures, the anaesthesiologist can receive a radiation dose greater than that by the interventional radiologist.[73] The eye is the most sensitive organ to radiation injury, and operators should use eye protection at all times. The primary source of radiation exposure is through scattered radiation from the patient; thus, maximising the distance between the provider and the patient is crucial to minimise occupational exposure.[73] Studies have shown that at a distance of 1.5 m or greater from the radiation source, anaesthesia personnel receive miniscule amounts.[74]

A study by Whitney and colleagues[75] found that surveyed paediatric anaesthesiologists do not adhere routinely to measures designed to reduce radiation exposure, and many work in institutions that lack a culture of radiation safety. This study and others have highlighted the need to improve radiation safety education and safety culture and more fully investigate the utility of dosimeters, lead shielding, and eye safety measures in anaesthesia practice.[74,73] Routine radiation monitoring and safety equipment should be available to anaesthesia providers who frequently work in areas where ionising radiation is used, and appropriate education and training on radiation protection should be provided.[72,73]

MRI machines expose clinicians and staff to electromagnetic fields. Infants and children often require anaesthesia for their MRIs; thus, paediatric anaesthesiologists are the anaesthesia clinicians who should be most cognisant of the potential risks of working in or near static magnetic fields. Transient vertigo, nausea, and dizziness are associated with exposure to MRI-related static magnetic fields, motion-induced time-varying magnetic fields, or both.[76,77] An association between MRI-related occupational static magnetic field exposure and an increased risk of accidents during the commute from work to home has been reported.[78] Although anaesthesia staff reassuringly have the lowest exposure among workers in the MRI unit, additional research is needed to understand the occupational hazard inherent with exposure to strong magnetic fields in MRI.[79,80]

A debate rages daily regarding the optimal ambient operating room temperature, as surgeons often request that the

temperature be lowered, while anaesthesiologists and other personnel routinely prefer that the temperature remain higher to limit hypothermia and associated morbidities.[81–83] Studies of the hazards of extremes of operating room temperature on performance have focused primarily on the impact of hot conditions on surgery staff rather than anaesthesia personnel.[84] One study reporting slight impairment in manual dexterity in a simulated burn surgery in an operating theatre at 34°C.[85] Most studies in a meta-analysis of active warming during Caesarean delivery reported ambient operating room temperatures between 21 and 24°C.[86] A meta-analysis of hot and cold temperature exposure on performance found that hot temperatures of 32.2°C or above and cold temperatures of 10°C or less resulted in the greatest decrement in performance on task performance than neutral temperatures.[87] The paucity of temperature-related anaesthesia work hazard studies may be because typical operating room temperatures do not pose a significant risk to anaesthesia personnel who can don extra layers or use blankets for warmth in cold operating rooms and do not typically have to wear sterile gowns and gloves in hot operating rooms.

Although lasers used for surgical procedures primarily pose a risk to patients from burns or fires, there are also risks of operator and bystander eye damage or burns from lasers.[88,89] A culture of safety should be emphasised during laser use, with appropriate education.[90,91] Anaesthesia personnel should understand and observe the basics of laser safety while also recognising the risk for medication errors and other potential issues with vision impairment when wearing laser goggles.[92,93]

Chemical hazards

Anaesthetic gas exposure

Concern over occupational exposure to anaesthetic gases in the operating room dates back to a questionnaire from the 1960s showing higher than expected spontaneous abortions in Russian anaesthetists.[94] The National Institute of Occupational Safety and Health (NIOSH) published its first guidelines for exposure limits a decade later.[95] Subsequent animal models and studies utilising measurement of anaesthetic gas concentrations in the operating room examine various potential adverse health effects of occupational anaesthetic exposure. Areas of investigation include teratogenicity, carcinogenicity, genetic damage, and increased inflammation. Older studies focused on exposure to halothane and nitrous oxide, but newer volatile agents are more widely used.[96–98]

Increased awareness of the possible long-term health effects of inhaled anaesthetics spurred development of systems to decrease exposure to operating room personnel. The most commonly used systems include waste anaesthetic gas scavenging systems (WAGs) and operating room ventilation systems with laminar flow and turnover of operating room air at least 15 times per hour.[99] Nonetheless, in low-resource settings, such safeguards may not exist. A Brazilian study found that anaesthetic exposure was significantly decreased in the 50% of the operating rooms equipped with scavenging systems.[100] In the high resourced setting of the United States, a NIOSH survey of anaesthesia clinicians found that scavenging systems were used by 97% of respondents, but the use of other practices to decrease exposure was far from universal.[101]

Position within the operating room may change exposure. An examination of sitting *vs* standing anaesthesia providers failed to find a significant difference; however, proximity to the patient's head was associated with higher levels of sevoflurane exposure.[102] A small study of cardiac patients maintained with volatile anaesthetic and nitrous oxide before cardiopulmonary bypass found that surgeons and perfusionists were exposed to higher than recommended levels of desflurane during cardiopulmonary bypass because of their proximity to the oxygenator.[103] Inhalation induction, most commonly performed during paediatric anaesthesia, is associated with 50-fold higher levels of anaesthetic gas exposure.[99]

Several studies have found DNA damage or changes in operating room workers chronically exposed to anaesthetic gases.[101,99] However, not all studied environments had scavenger systems and recommended operating room ventilation. Acute neurologic impairment, such as decreased mental acuity or manual dexterity, headache, and drowsiness related to anaesthetic exposure has also been reported.[102,99] Slower reaction times were found at the end of a work week with exposure to enflurane and nitrous oxide.[100] A study found that female dental assistants exposed to nitrous oxide in dental offices showed higher rates of spontaneous abortion than unexposed dental assistants.[95] Later studies in the setting of scavenger system utilisation found mixed results on rates of spontaneous abortion rates or congenital anomalies.[99] Paediatric anaesthesiologists may have higher rates of spontaneous abortion, presumably because of higher anaesthetic exposure during inhalation inductions.[104]

Hepatic and renal effects of long-term, low-level anaesthetic exposure have not been studied as extensively as other health effects.[95] There have been some reports of development of halothane hepatitis after low-level halothane exposure and one study found elevated liver enzymes in healthcare workers exposed to anaesthetic gases.[100]

Exposure to anaesthetic gases in the workplace would seem to carry special significance and risk for clinicians who are susceptible to malignant hyperthermia.[105] Fortunately, triggering of malignant hyperthermia is a dose-dependent phenomenon and is related to both the dose of the anaesthetic inhaled and the duration of exposure.[106] Typical concentrations of inhalation anaesthetics in the operating theatre are much lower than the minimum dose believed to trigger malignant hyperthermia; thus, there is no contraindication to individuals susceptible to malignant hyperthermia working in the perioperative setting.[105]

Strategies to reduce exposure to volatile anaesthetics include: 1) verifying that gas scavenging systems are turned on and functioning optimally before every use of a volatile anaesthetic agent; 2) confirming that operating laminar flow systems are operating and all vents are unobstructed; 3) maintaining a tight mask seal during inhalation inductions of anaesthesia and being mindful of high fresh gas flow during moments when the mask is removed from the patient's face; and 4) positioning oneself as far from sources of exposure (e.g. bypass oxygenator, patient's face) as possible while maintaining safety and vigilance.

Intravenous anaesthetic medication and opioid exposure

Medications intravenously administered to the patient can be detected in the expiratory limb of the anaesthesia machine. A study found that propofol and fentanyl administered intraoperatively could be detected in patients' exhaled breath and fentanyl could be detected above the sharps container in the

operating room and near the cardiopulmonary bypass circuit.[107] Effects of chronic exposure to intravenously administered medications on operating room staff merits further study. Whereas not commonly used in clinical medicine, carfentanil is a potent opioid, the presence of which has grown in the illicit drug market. Individuals exposed to carfentanil show opioid overdose symptoms, but may need high naloxone doses for treatment. Anaesthesiologists and other healthcare workers should observe general occupational hygiene measures, including regular decontamination with soap and water and should wear PPE (nitrile gloves, N95 mask, and eye goggles) including having naloxone on hand, although rare accidental poisonings are usually unconfirmed.[108]

Surgical smoke and volatile organic compound exposure

Exposure of operating room staff and patients to surgical smoke from lasers, electrocautery, or ultrasonic scalpels is associated with inhalation of particulate matter and chemical and infectious risks.[109] The burden of smoke inhalation depends on the extent of smoke generated by the procedure, the number of operating room air exchanges per hour, and most importantly, use of devices specifically designed to scavenge smoke.[110] Smoke evacuation systems are the most effective method of decreasing the amount of smoke; however, they tend to be used more frequently during procedures involving lasers.[110] Exposure to volatile organic compounds occurs commonly indoors in healthcare settings, and these compounds have been suggested as potential carcinogens when individuals are exposed for long durations.[111,112]

Operating room fires

The operating room is deemed a very safe place but can be turned immediately into a dangerous working zone by a fire. The presence of fire ignitors and fuel such as 100% oxygen make the operating room a place of potential fire hazard. A fire can immediately harm patients, anaesthesiologists, and other healthcare workers. Fire prevention in the operating room starts from the standards used in construction and the implementation of procedures to avoid fires. Training all medical personnel on fire prevention and suppression measures in the operating room is mandatory in most hospitals, in addition to teaching these principles in the healthcare workers' respective professional training programmes. A fire can still occur in the operating room despite all preventative plans and strategies. Overbey and colleagues[113] reported an increase in voluntarily reported surgical instrument-related fires from 10 in 2006 to 45 in 2015. The injury to the patient can be significant and catastrophic leading to significant legal ramifications for the operating room team.[114] Teams should develop a culture of safety regarding fire safety and not only be knowledgeable on mandatory fire safety features and algorithms for managing a patient fire, but also receive practical fire and evacuation training including simulation.[113,115]

A few key elements may assist in the mitigation of harm to the patient, anaesthesiologist, and other occupants of the operating room. The existence of evacuation plans, and routes should be well known to all healthcare workers in the operating room. Escape routes should be clearly marked and well known to anaesthesiologists. The duty to care for the patient is associated with a huge burden of responsibility. In the event of an operating room fire that is catastrophic and likely to result in the ability to move patients out of harm's way, there should be a clear ethical consideration of prioritising evacuation of patients and staff and when to consider attempts to evacuate patients to be impossible. A review of 13 significant hospital fires occurring between 1913 and 2014 reported at least 590 deaths.[116] It is important that hospital administrators have a competent person designated with the authority for ordering evacuation and 'abandon ship' calls to assist with the ethical responsibility of staff saving themselves in the face of a likely death. While fire can be a sudden and dramatic event, natural disasters such as cyclones, flooding, and earthquakes can also occur necessitating evacuation procedures. The practice and simulation of evacuation drills should occur frequently in the operating room to assist with effective safety management and the implementation of meticulously planned logistics and readiness in case of an emergency.[117,118]

Psychological hazards

Healthcare providers, especially anaesthesiologists, often grapple with unique challenges that can significantly impact their mental and emotional well-being. Operating in highly stressful environments, anaesthesiologists are frequently confronted with adverse events that can be both mentally taxing and emotionally draining.[119,120] Compounding these challenges, many anaesthesiologists experience a sense of disconnection from their peers. Unlike most team-based specialties where frequent interactions with colleagues are the norm, anaesthesiologists often find themselves isolated, without the camaraderie or support of fellow anaesthesiologists. Furthermore, the nature of their role can lead to a dearth of positive feedback from patients. As anaesthesiologists typically have limited follow-up beyond the perioperative period, they may not receive the gratification and assurance that comes from witnessing patient recovery and gratitude.[120] This triad—intense stress, lack of peer support, and absence of positive patient feedback—can severely affect their mental well-being.[121,122] Studies have shown that anaesthesiologists are at a higher risk for burnout, depression, and even suicide compared with many other specialties.[121,123–125] Additionally, considering the recent challenges associated with the global health crisis, burnout has been further exacerbated by the constant risk of infection and the physical and psychological toll of continuous PPE use and shortages.[126–130] Addressing these issues is paramount to ensuring the well-being of these vital healthcare professionals and optimising patient care outcomes and several strategies including peer support, multisource feedback, control over work hours, self-care, equal pay, and career advancement.[125,131] Shinde and colleagues[131] have recently outlined guidelines to assist with reducing suicide among anaesthesiologists. They recommend that anaesthesiologists should promote mental well-being in the workplace; each anaesthetic department should designate a representative, possibly outside their specialty, to monitor and support the mental health of staff; provide ongoing mental health and suicide prevention education, tackling stigmas; provide immediate medical consultations, while maintaining confidentiality, and suggest a 'safety plan' for those at risk. They also recommend departments needing a crisis management strategy, including handling suicides.

Whereas an in-depth discussion of drug abuse and the anaesthesiologist is out of scope of this article, emotional stress and access to controlled substances are known to play a role in addiction development among anaesthesiologists and

should be considered with the appropriate supports including comprehensive standard operating procedures for handling and safe disposal of controlled substances, treatment for anaesthesiologists, involving care team family members, and considering a change in career for the anaesthesiologist.[132–135]

Conclusion

The anaesthesiologist continues to face difference hazards in the workplace. Design standards, personal protection equipment, policies, and procedures have kept anaesthesiologists safe for the most part. However, anaesthesiologists will need to advocate for themselves and engage in processes that set a safety culture and standards within their workspaces.

Authors' contributions

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Drafting of the manuscript: all authors
Critical revision of the manuscript for important intellectual content: all authors
Final manuscript approval: all authors

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