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Autonomous Systems in Anesthesia: Where Do We Stand in 2020? A Narrative Review

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As most of us are aware, almost every facet of our society is becoming, for better or worse, progressively more technology-dependent. Technological advancement has made autonomous systems, also known as robots, an integral part of our life in several fields, including medicine. The application of robots in anesthesia could be classified into 3 types of robots. The first ones are pharmacological robots. These robots are based on closed-loop systems that allow better-individualized anesthetic drug titration for optimal homeostasis during general anesthesia and sedation. Recent evidence also demonstrates that autonomous systems could control hemodynamic parameters proficiently outperforming manual control in the operating room. The second type of robot is mechanical. They enable automated motorized reproduction of tasks requiring high manual dexterity level. Such robots have been advocated to be more accurate than humans and, thus, could be safer for the patient. The third type is a cognitive robot also known as decision support system. This type of robot is able to recognize crucial clinical situation that requires human intervention. When these events occur, the system notifies the attending clinician, describes relevant related clinical observations, proposes pertinent therapeutic options and, when allowed by the attending clinician, may even administer treatment. It seems that cognitive robots could increase patients' safety. Robots in anesthesia offer not only the possibility to free the attending clinicians from repetitive tasks but can also reduce mental workload allowing them to focus on tasks that require human intelligence such as analytical and clinical approach, lifesaving decision-making capacity, and interpersonal interaction. Nevertheless, further studies have yet to be done to test the combination of these 3 types of robots to maintain simultaneously the homeostasis of multiple biological variables and to test the safety of such combination on a large-scale population. (Anesth Analg 2020;130:1120–32)

GLOSSARY

BIS = bispectral index; **CDS** = clinical decision support system; **EEG** = electroencephalogram; **HSS** = hybrid sedation system; **MIMO** = multiple input multiple output; **SISO** = single input single output; **TCI** = target-controlled infusion

BACKGROUND: THE RATIONALE FOR ROBOTS IN ANESTHESIA

Robots now surround our daily activities, doing everything from cleaning our homes to flying airplanes, and they exist in fields ranging from industry to medicine. In science fiction, we tend to conceptualize "robots" as human-shaped automata, but in general, a "robot" generally refers to any mechanical system capable of interacting with the environment with directed interventions.

In medicine, automation offers precision therapy in combination with a high level of reproducibility. These features make robots appealing in the medical fields, and they have been used in the field of anesthesia for several decades assisting clinicians.[1,2] However, many well-tested autonomous systems and known to be safe have not been adopted yet into clinical practice on a daily basis. When we consider that repetitive execution of trivial technical tasks is subject to vigilance decrement in humans, as well as the fact that human providers may suffer from fatigue, boredom, and bias, there is a strong rationale for the role such systems may play in clinical care.[3,4] Using robots to assist in the acquisition of patient data, simple decision-making, and manual tasks may leave physicians freer to focus efficiently on tasks requiring human intelligence and judgment.[5]

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At present, in the field of anesthesiology, we find primarily 3 different kinds of robots.[6] The first 2 types, pharmacological and mechanical (or manual) robots, are designed to eliminate the repetitive part of the workload by automating simple tasks and giving support to the clinician, respectively. The third category of robots, broadly referred to herein as "artificial intelligence" systems, offer updated and pertinent recommendations related to specific clinical scenarios detected automatically. They could either help physicians identifying promptly critical actions in emergency scenarios or even respond autonomously if allowed. The integration of these robots into clinical practice aims to assist the attending clinician increasing accuracy and safety of the care delivered.

This article first provides an overview of the most recent advancements of each type of robot in anesthesiology and then hypothesize as to their future application.

PHARMACOLOGICAL ROBOTS

Pharmacological Robots: How Do They Work?

Pharmacological robots in anesthesia are designed around the concept of maintaining patient homeostasis by keeping specific parameters of interest (eg, blood pressure or hypnosis) as close as possible to a defined target value. In some ways, target-controlled infusion (TCI) systems were the first pharmacological robots. These robots use software that, rather than delivering a steady rate infusion, deliver loading boluses designed to more rapidly obtain a specific plasmatic drug concentration. These boluses are then followed by automatic changes of the infusion rate to maintain the drug concentration chosen by the practitioner. These robots calculate both the boluses and the infusion rates based on a pharmacokinetic model of the drug used.[7] Of note, a clinically appealing option of TCI devices is that they can theoretically be programmed to take into account the time lag between the plasma infusion and the site of action in the brain. However, TCI systems have major limits because they use pharmacokinetic models derived from studies that were not intended for specific clinical procedures and for patients with extreme anthropomorphic characteristics.[8] The newest types of pharmacological robots achieve patient homeostasis through titration of anesthetic drugs via the robot's rapid calculation of current need and adjustment of drug delivery.[9] These versions of pharmacological robots use closed-loop systems that allow marginal reaction delay and minimal amplitude excursion from the desired target resulting in better performance compared to both manually administered intravenous anesthesia and TCI delivery.[10,11]

Pharmacologic robots use algorithms that may range in complexity from simple linear transformation to complex machine-learning algorithms. The aim of these control systems is to reach a set "goal" for the controlled variable of relevance (arterial pressure, heart rate, electroencephalogram monitor, etc). Therefore, these control systems compare a measured value of the controlled variable (the target) against that "goal" and adjust the actuator (the drug delivery mechanism) to reduce the gap between "goal" and actual value (Figure 1). For clarity, it has to be underlined that some research groups have developed closed-loop systems that include TCI technology in their algorithms.[12]

Pharmacological Robots in Anesthesia

In anesthesiology, pharmacological robots have been designed mainly to induce and maintain the 3 components of general anesthesia: hypnosis, analgesia, and neuromuscular block.[13] However, there are both historical and more recent investigations showing that pharmacological robots could effectively maintain other parameters of anesthetic interest such as blood pressure.[2,14–16] Indeed, the first closed-loop system described, that was also commercially available, has been designed for autonomous control of blood pressure (Figure 2).

Pharmacological Robots for General Anesthesia

The first investigations using pharmacological robots in anesthesia were performed more than 65 years ago.[17] At that time, few trials testing pharmacological robots were performed because of the technical limitations of monitoring and custom pump control at that time. In the mid-90s, the progress in computing and the introduction of processed electroencephalogram indices such as the bispectral index (BIS; Aspect Medical System, Inc, Newton, MA) monitor to measure more objectively the depth of anesthesia opened the door more widely to this field of investigation. At an early stage, pharmacological robots were designed for a single drug using a single-loop system also known as single input single output (SISO) systems. More recently, pharmacological robots are able to analyze multiple inputs adjusting automatically to multiple outputs. The latter multiple-loop systems are also known as multiple input multiple output (MIMO) systems.[13]

Single Closed-Loop System for General Anesthesia: SISO. Initially, closed-loop systems that were most commonly studied were conceived mainly for the control of hypnosis and muscle relaxation because no monitor was able to reliably assess pain during general anesthesia.[18] At the beginning of the present century, Gentilini et al[19] showed that maintenance of hypnosis using single closed-loop system for isoflurane was feasible. Soon after, Locher et al[20] demonstrated that maintenance of hypnosis using closed-loop system for isoflurane could perform better

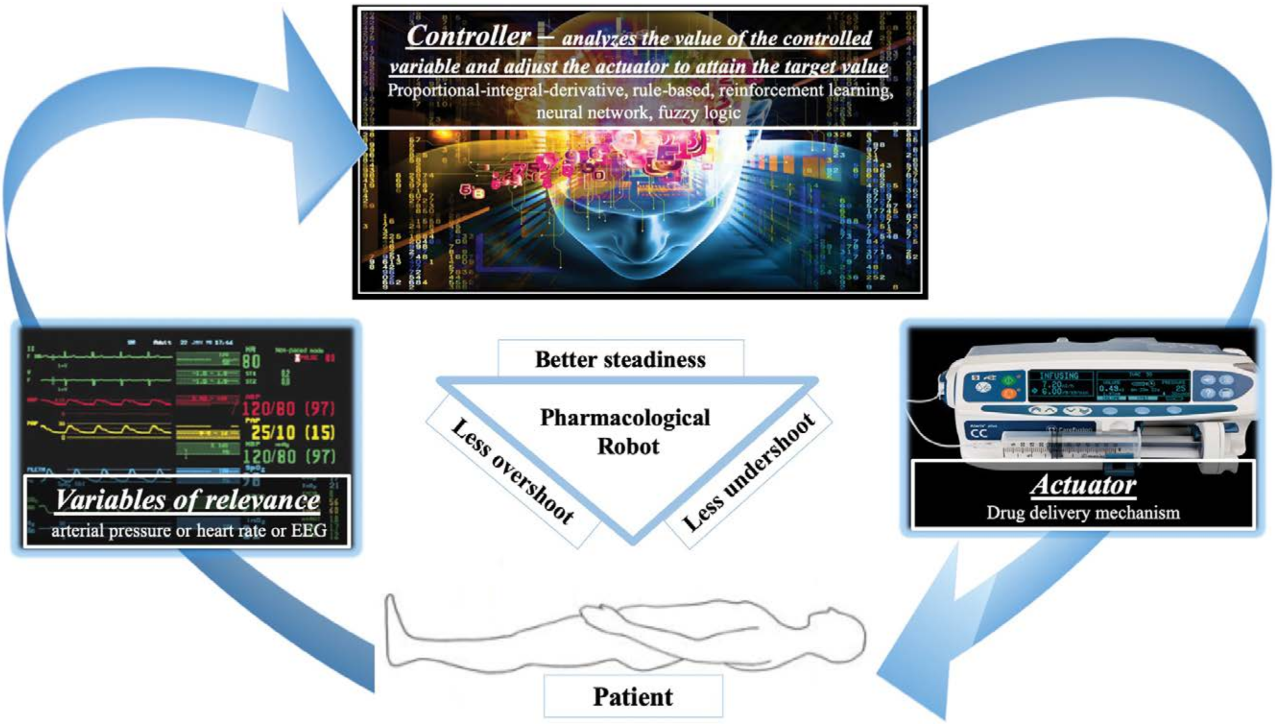

Figure 1. Description of a closed-loop system. EEG indicates electroencephalogram.

Figure 2. Picture of the IVAC titrator (Becton, Dickinson, and Company, San Diego, CA), the first electronically controlled infusion pumps with fluid flow technology. The photograph is courtesy of Bob Butterfield, used with permission from Becton, Dickinson, and Company (San Diego, CA).

than manual control. Concurrently, other research groups developed closed-loop systems for propofol using a variety of mathematical algorithms for robotic drug delivery.[21] In 2001, Struys et al[22] demonstrated that induction and maintenance of hypnosis using a patient individualized model-based adaptive closed-loop control system for propofol is feasible. In their randomized trial, 10 patients received automated administration of propofol setting the target BIS value at 50. Patients in the automated delivery group had less overshoot of the BIS target, less drop of blood pressure, and faster extubation time compared to the other 10 patients who had the propofol administration controlled manually. They enhanced their initial algorithm by incorporating Bayesian optimization technology[23] and illustrated feasibility and usability in various experimental[24] and clinical situations.[25–27] In 2006, Liu et al[28] developed a pharmacological robot using a closed-loop titration of propofol TCI based on a proportional-integral-differential algorithm. In their trial, they compared their system to a TCI system for propofol administration. They have shown that automated delivery of propofol could reduce BIS overshoot and propofol consumption compared to TCI. In 2007, Puri et al[29] developed a closed-loop anesthesia delivery system integrating a model-based adaptive algorithm and showed their system to be efficient in difficult environments[30] and for complex surgery in both adult[31] and pediatric subjects.[32] In 2010, Hemmerling et al[33] described a novel single closed-loop system for propofol administration, which has been demonstrated to outperform manual administration. This system has an adaptive, rule-based algorithm, which takes into account a set of rules aiming to reach and maintain the target. These rules aim to increase the hysteresis control, including different factors of clinical importance such as the surgery period, previous adjustments, BIS trend, BIS artifacts, and maximum and minimum dosing allowance. In 2011, Moore et al[34] also presented an innovative system for propofol-induced hypnosis control using reinforcement learning which is an artificial intelligence aiming to control biological systems more steadily. The incorporation of artificial intelligence in their algorithm showed promising results with significantly shorter periods of overshoot and more rapid achievement of steady state compared to a conventional proportional-integral-derivative controller.[35] Lately, a multicenter randomized controlled trial confirmed that single closed-loop control for propofol outclasses manual infusion rate control.[36] In addition, 2 recent meta-analyses listed available BIS-guided autonomous systems and concluded that they provided both better clinical performance and better safety compared to manual control.[10,11]

Multiple Closed-Loop System for General Anesthesia: MIMO. Although Liu et al[12] were the first to demonstrate that a closed-loop system could control the delivery of both propofol and remifentanil with good results, from an engineering perspective, such a system is not a MIMO system because both propofol and remifentanil target concentration infusions change according to a single input variable, the BIS. Liu et al[12] made the assumption that painful surgical stimuli induce small BIS variation, whereas reduction of the hypnosis depth causes wider BIS oscillations. Thereby, in the former situation, only remifentanil infusion rate change while in the latter case, both remifentanil and propofol infusion rate change. In their trial, robotic control of hypnosis and analgesia was deemed acceptable allowing a faster extubation time. Hemmerling et al[13] have developed an innovative pharmacological robot using independent controlled variables for each component of anesthesia. Thus, this system is a proper MIMO. This autonomous system, also known as McSleepy, is able to administer simultaneously hypnosis, analgesia, and neuromuscular block from induction to emergence of anesthesia.[18] A randomized controlled trial on 186 patients indicates that McSleepy could deliver better control of both hypnosis and analgesia.[13] Also, McSleepy has been shown to be robust for both complex cardiac procedures[37] and telemedicine applications.[38]

Pharmacological Robots for Conscious Sedation

Single Closed-Loop System for Conscious Sedation. In 1998, Mortier et al[39] were the first to describe a closed-loop system for propofol composed of a TCI system controlled by an adaptive model-based artificial intelligence. The system was tested on 10 patients who received a spinal block to undergo elective lower limb surgery. Patients, 48 years old on average, had an individualized BIS target value equivalent to a score of 1 on the Observer Assessment Alertness and Sedation scale,[40] which corresponded on average to a BIS value of 64. All patients underwent the surgical procedure breathing spontaneously via a tight-fitting facemask. None became apneic during the automated administration of propofol and none had an oxygen saturation <90%. None of the patients reported either implicit or explicit awareness. In 2002, Leslie et al[41] conducted a similar investigation in 16 patients undergoing a colonoscopy. In their trial, they tested a pharmacological robot that uses a TCI system controlled by a proportional-integral-differential algorithm. Patients, 60 years old on average, had an individualized BIS target value equivalent to a score of 3 on the observer assessment alertness and sedation scale which corresponded on average to a BIS value of 80. During the automated sedation no patient became apneic. The minimum oxygen saturation was 93%. This system proved to be efficient in maintaining the sedation target 75% of the closed-loop control time. However, the sedation target for maintenance was not reached using the closed-loop system but was obtained with manual increment.

Multiple Closed-Loop System for Conscious Sedation. In 2016, Zaouter et al[42] published a landmark trial describing a closed-loop delivery system for propofol sedation integrating a decision support system specifically conceived to assist the anesthesia team. Using BIS, respiratory rate, and peripheral oxygen saturation as control variables and an infusion pump served as the actuator, this hybrid robot called hybrid sedation system (HSS) showed better maintenance of the target BIS value[42] and fewer episodes of hypoxemia[43] compared to manual administration. The HSS evaluated the hypnosis depth with BIS values every 5 seconds to determine the sedation depth. In contrast to Mortier et al[39] and Leslie et al's[41] automated sedation system, the HSS does not encompass a TCI technology but uses other algorithms to guide the infusion rate by the BIS index. Another important feature of the HSS shown to be efficient is its decision support system conceived to help the anesthesiologist to detect and treat critical cardiorespiratory impairments.[1] Future autonomous system for sedation will combine a closed-loop system with cognitive aids such as decision support system.

Pharmacological Robots for Hemodynamic Management

Optimal hemodynamic management aims to supply oxygenated blood with enough pressure to reach each part of every organ present in the human body. To do so, anesthesiologists' armamentarium is grounded on 4 types of pharmacologic agents: fluids, vasopressors, catecholamines, and vasodilator drugs.

Closed-Loop System for Goal-Directed Fluid Therapy. Computer assistance of intravenous resuscitation was one of the first clinical interventions attempted. In the 1970s, a group in Texas developed a closed-loop system for fluid administration based on urine output.[44,45] In the past 20 years, many measures have been used to direct fluid resuscitation, including mean arterial pressure,[46,47] spectroscopy,[48] pulse pressure variation and stroke volume variation,[49] or a combination thereof.[50]

One of the challenges of fluid therapy is that, unlike other measures like heart rate or blood pressure, "optimal" fluid status is neither clearly defined nor easily assessed.[51,52] Despite these challenges, algorithms can nevertheless be designed to mimic with high fidelity the way that clinicians administer fluid, particularly when guided by established algorithms like goal-directed fluid therapy.[52] While the question of "optimal" fluid strategy remains open, closed-loop systems may in the meantime ensure that protocols that have been shown effective may be implemented with higher consistency than when implemented manually.[53–56] Some authors of this narrative review have published numerous human trials using this type of closed-loop goal-directed fluid therapy algorithm and have shown increased protocol adherence,[57–59] decreased length of hospital stay,[58] and decreased postoperative complications[60] in patients undergoing major surgery.

Several teams around the world are currently working on closed-loop fluid resuscitation algorithms.[61–64] Moreover, there have been early attempts to look at combining fluid resuscitation with other common resuscitation drugs like vasopressors.[65,66] For the most part, many of these efforts are using independent, noncooperative controllers, but showing this is safe is a necessary step in the progression of these technologies.[65,66] Finally, closed-loop fluid delivery systems have also been used as an "unbiased interventionalist" in studies examining the effects of different resuscitation fluids.[67,68]

Closed-Loop System for Vasopressor Titration. Several retrospective studies highlighted the key role of blood pressure control in the operating room, and there is published evidence that the titration of vasopressors by hand is inefficient and inaccurate.[69] Thus the development of a more effective titration system may be particularly clinically impactful and be the future for blood pressure management in both surgical and intensive care unit patients.[70,71] Vasopressor administration, having a single "controlled" physiologic variable readily measured (arterial blood pressure), provides a more direct target than fluid therapy; it is another intervention that earlier researchers attempted to automate.[72–74] However, there was little commercial development—likely due to a variety of factors, not the least of which is regulatory concerns and safety. More recently, some authors believe that such systems have a huge potential for the future.[70,71] Available prototypes were developed for operating room and intensive care unit use,[75–77] obstetrics and spinal-induced hypotension,[15,78,79] and septic shock.[80] Moreover, Libert et al[81] in Paris developed and tested a closed-loop system that can administer vasopressors and fluids with good performance metrics.

Closed-Loop System for Catecholamines to Improve Cardiac Function. Cardiac function has not been studied much for pharmacological closed-loop systems. This may be a natural consequence of the properties of inotropic cardiac medications as well as difficulty in assessing ventricular contractility in an objective and continuous manner. In addition, many cardiac drugs have nonlinear effects, and ceiling effects are common and often occur at low infusion rates. The obvious exception is the implantable cardiac pacemaker. The most modern pacemakers are quite advanced containing many layers of autonomous systems that combine several algorithms governing their function, but this is an electrical system and not a pharmacologic one.[82]

Nevertheless, pharmacologic rate control of heart rate by automated systems has been done in cardiac stress tests.[83] Inotropes have also been studied in at least 2 published manuscripts.[84,85]

Closed-Loop System for Vasodilators. Vasodilators, like vasopressors, have a directly measurable controlled variable and were thus also early autonomous system prototypes.[86] Because of the relative infrequent need for vasodilation drips in clinical care, however, and the risks of overtreatment, there has not been much progression of this research. Two studies did explore titration of vasodilators via closed-loop for neurosurgery[87] and cardiac surgery.[88]

MECHANICAL ROBOTS

Mechanical robots are designed to give support to the anesthesiologist. The 2 main areas of application to date are endotracheal intubation and regional.

In regard to intubation, a first trial involved the use of the DaVinci Surgical System in the performance of 2 simulated fiberoptic intubations, which were both successful even if technically difficult due to the robot design with multiple robotic arms.[89] The Kepler Intubation System[90] is composed of 1 robotic arm linked to a standard videolaryngoscope in one end and remotely controlled by a joystick controlled, in turn, by a specific software and interface (Figure 3).

Figure 3. Picture of the Kepler Intubation System.

Intubations can be performed automatically or semiautomatically, under direct vision or remotely: procedural time ranged overall from 40 to 60 seconds in 90 simulated intubations, all of which were successful on the first attempt.[90] In a trial in 12 clinical patients, the Kepler Intubation System showed a success rate of 91% with a mean procedural time of 93 seconds, without complications.[91] More recently, a research group from China developed a mechanical robot designed specifically for intubation.[92] This research group conducted an experimental animal study demonstrating that a mechanical robot remotely controlled could allow individual with no experience with endotracheal intubation to achieve a higher first-pass rate and overall success rate by the robot system than with the standard direct laryngoscopy.[92] However, the total intubation time using the mechanical robot was longer compared with the other group using a direct laryngoscopy (75 vs 53 seconds; $P < .01$).[92]

Robotic assistance with regional anesthesia has been tried via ultrasound-guided nerve block and placement of perineural catheter performed on a phantom using the DaVinci System, with the same constraints mentioned above for intubations.[93] The Magellan system was developed to perform robot-assisted ultrasound-guided nerve blocks by the use of a robotic arm with a nerve block needle at the end, guided by a joystick and controlled by custom software and interface (Figure 4).[94] A success rate of 100% was achieved on a standard ultrasound phantom[94] and subsequently in 13 patients undergoing popliteal block with a maximum procedural time of 4 minutes.[95] This system could be integrated with software that allows for the automatic recognition of the nerve on the ultrasound image without human search.[96] While the system is still under development, the first results are promising.[96] In addition, it has been recently shown that the use of robots for ultrasound-guided nerve blocks is associated with faster learning and a lower intersubject variability than manual performance in a simulated setting.[97]

COGNITIVE ROBOTS

Cognitive Robots: How Do They Work?

Cognitive robots in anesthesia are designed to provide support to an anesthesiologist in clinical decision-making. They analyze various patient data elements to offer immediate pertinent clinical suggestions/reminders and specific up-to-date treatment options, typically enhancing compliance with guidelines. Cognitive robots, also known as clinical decision support systems (CDS), could be differentiated in 2 types, either expert-based build-in algorithms or nonknowledge based. Expert-based build-in algorithms systems use expert clinical knowledge to detect clinical events. In contrast, non–knowledge-based systems use artificial intelligence to develop algorithms from real clinical scenarios. For a more exhaustive description regarding clinical consideration of the CDS, we invite the readers to consult Nair et al's review.[98] The first cognitive robot tested clinically was in the early 50s. However, a more diffuse adoption of this type of cognitive aid has been possible via the introduction of anesthesia information management systems in the operating room.[98] For clarity, CDS could be divided into preoperative, intraoperative, and postoperative system. For an extensive list of articles on CDS constantly updated the readers could access the following link: http://www.franklindexter.net/bibliography_AIMS.htm.

Clinical decision support should be differentiated from closed-loop systems; they are in many ways at opposite ends of the automation implementation curve. CDS are cognitive aids for the clinician who then must implement suggestions provided by the system to perform an action. Conversely, a closed-loop system works autonomously, and human intervention is not necessary, except for the clinician directing the therapy by choosing targets and/or treatment goals. To date, no clinical automation in anesthesiology has been responsible for both implementation of therapy and choosing the target or goal of that therapy.

Preoperative Cognitive Robots

Smart Alarms for Early Detection of Abnormal Laboratory Values. Automated smart alarms for abnormal laboratory values in general medicine have been shown to improve patient outcome.[99] In anesthesia, only 1 trial has demonstrated that CDS could be a helpful tool to prevent adverse events informing attending clinicians of abnormal preoperative laboratory values.[100]

Figure 4. Picture of the Magellan System (popliteal sciatic nerve block performed via a posterior approach).

However, evidence showing that improved patient outcome is possible using this type of CDS is missing.

Preoperative Reminder to Ensure Drug Administration Compliance. Before arrival for surgery patients who are receiving beta-blockers should continue to take their prescription to reduce perioperative cardiovascular morbidity and mortality after both cardiac and noncardiac surgery.[101] Nair et al[101] have conducted an investigation suggesting that CDS could be an excellent tool to ensure the observance of the administration of beta-blockers. Indeed, many modern electronic medical record systems include such reminders.

Dynamic Electronic Cognitive Checklist Aid. Implementation of a static surgical checklist has been shown to be associated with both a decrease in the incidence of perioperative complications and mortality.[102] Recently, a trial conducted in anesthesia comparing a dynamic electronic cognitive checklist assistance using a CDS versus a standard checklist demonstrated that the group using a CDS performed more checklist items correctly.[103] It could be inferred that such CDS could reduce perioperative complications. However, no study has investigated whether an anesthesia checklist using a CDS could improve patient outcome.

Intraoperative Cognitive Robots

Smart Alarms for Appropriate Perioperative Antibiotic Administration. Antibiotic injection before the surgical incision and intraoperative readministration, when appropriate, has been associated with improved patient outcome. Nair et al[104] have developed a CDS that offers a more accurate identification of the most appropriate prophylactic antibiotics with the latest recommendations of dosing intervals.

Smart Alarms to Help Clinicians in Decision-Making. Cognitive robots have been successfully integrated into intraoperative alarms, creating "smart" alarm systems that can analyze several parameters simultaneously by artificial intelligence using rule-based expert knowledge. The main advantage of these smart alarms is that they could lower the rate of false alarm.[105]

Better Compliance With Antiemetic Prophylaxis. Kappen et al[106] have conducted a study showing that a CDS could help attending anesthesiologists to follow more strictly the recommendations related to optimal prophylaxis for nausea and vomiting. Using a CDS increased the number of antiemetic drugs prescribed when patients were at high risk compared to the group that did not benefit from the help of a cognitive robot.[106] However, the rates of nausea and vomiting between the 2 groups were similar.

More Efficient Anesthetic Gas Delivery. Anesthetic gas wastage through inappropriate use of fresh gas flows may lead to a substantial increase in the cost of this drug. A simple CDS using smart alarms has been shown to significantly reduce anesthetic gas wastage saving more than $100,000 per year.[107]

More Efficient Billing Implementation. In addition to direct patient care, several studies have shown that CDS with the help of smart reminders could improve professional billing observance and reimbursement.[98]

FUTURE DIRECTIONS

Given the current applications of autonomous systems and robotics in anesthesiology, we can make some educated hypotheses about future applications of these technologies.

For the past 20 years, several research groups (including our own) have created and developed different automated closed-loop systems to control the administered amount of hypnotic, analgesic, fluid and vasoactive drugs, among others. An unexplored area until recently was the use of simultaneous closed-loop systems during major surgeries. In 2016, Joosten et al[66] described the first application of automated anesthesia and fluid management based on a combination of several physiological variables (BIS, stroke volume, and stroke volume variation) using 2 independent closed-loop systems in a patient undergoing high-risk surgery. Two years later, they tested the same strategy in a small cohort of 13 high-risk patients undergoing major vascular surgeries and showed the feasibility of 2 independent controllers to maintain their targets for the majority of the surgical case time without harmful cross-interference.[108]

If published articles on closed-loop systems have demonstrated that such automated systems can better maintain the target variable in the desired range, there is still no data on whether it can improve patient outcomes. Joosten et al[109] have very recently demonstrated that among older patients scheduled for noncardiac surgery, automated management of anesthetic depth, cardiac blood flow, and protective lung ventilation using 3 independent controllers outperformed manual control of these variables. In addition, as a result of the improved management, the automated strategy may have had an impact on delayed neurocognitive recovery. Importantly, in the above articles, each closed-loop still operated independently, guided only by its own respective inputs (BIS for the propofol and remifentanil; stroke volume and stroke volume variation for the fluid boluses). In an ideal situation, there would be cross-communication such that a fall in blood pressure may cause a reduction in the anesthetic administration, for example, if there was wiggle room in the BIS value.

One area that is obviously ripe for exploration with automated systems is research specifically designed around the unbiased and consistent implementation of interventions by these systems. An existing example is the use of a closed-loop fluid administration system as an unbiased interventionalist to answer the question of whether crystalloids or colloids were superior for intraoperative goal-directed fluid therapy.[67,68] Before the automation of such tasks, complete removal of bias from implementation of such protocols was not possible. There are many avenues of exploration, for example, in which determination of optimal vasopressor therapy has been historically hampered by challenges with study group overlap and low time-in-target.[110] With closed-loop vasopressor systems, clearer benefits and limitations may be explored.

Another possibly farther future possibility is systems, which choose both appropriate, targets, and manage the interventions to reach the target. As noted above, to date, there are no clinical automation systems that both choose the clinical targets for therapy and implement that therapy. It is unlikely that we will see such systems in the near term, as in many cases, the appropriate clinical targets are still not well understood. Nevertheless, eventually, we will start to see the emergence of not just systems that provide advice on the appropriate actions but are capable of independently implementing that action.

Another likely future direction would be the movement from automation based on current conditions to "predictive therapy." Even simple closed-loop controllers will make "predictions" about the immediate future states of the patient; "predictive therapy," however, refers to longer-term predictions than this. The basic concept behind predictive therapy is that if one could accurately predict whom, when, and why patients develop a problem during the perioperative period, then effective preemptive treatments could be started in advance to improve postoperative outcome and more effectively use health care resources. One team from Pittsburgh in the United States has already developed, validated, and tested real-time intraoperative risk prediction tools based on electronic health record data and high-fidelity physiological waveforms to predict cardiopulmonary instability in the intensive care unit.[111] More recently, another team from London developed the "Artificial Intelligence Clinician" to learn optimal treatment strategies for sepsis in intensive care.[112] The authors demonstrated that using their "Artificial Intelligence Clinician" allowed better treatment selection which could lead to lower mortality rates in patients.[112] When it comes to the operating theatre, collection of real-time high-fidelity physiological waveform data streams and their integration with patient demographics from the electronic health record to build large data sets now allows the derivation of actionable information based on machine-learning analytics. This, in turn, allows the system to display this information in real time at the bedside to drive clinical decision support in this specific setting. At present in the operating arena, anesthesiologists are surrounded by a multitude of hemodynamic monitoring devices and electronic medical records; machine-learning–derived, actionable alerts based on this wide array of information could be very useful to offer a truly personalized medical care. Recently, Hatib et al[113] demonstrated that high-resolution analysis of arterial pressure waveforms could be analyzed to produce a new parameter ("hypotension predictive index"), which has been shown to predict hypotension 10–15 minutes before any hypotension occurring in >80% of hypotensive episodes. This has recently been confirmed by Davis et al[114] who have analyzed retrospective data from patients scheduled for major surgeries. Another team from New York successfully demonstrated the feasibility of machine-learning models to predict postinduction hypotension with similar efficacy.[115] Machine learning seems an appealing strategy to revolutionize the effect that computational systems have on process measure and outcomes. We may expect that one day, individualized administration of drugs will be performed by intelligent technologies, which would compare the patients they are currently taking care of to data from prior patients with similar demographics and previous drug responses. Thus, the responses of individual patients to a given pharmacologic agent may be more accurately predictable than presently. Finally, more sophisticated analytics involving machine learning could be used to better explore the interactions between disparate closed-loop systems working concurrently. It has to be stated that the technologies described in this article are still considered experimental medical devices and can only become clinically acceptable if considerable thought and effort are put into safety. This particular topic was recently covered in a special article by members of the Center for Devices and Radiological Health at the US Food and Drug Administration.[116] Based on this and ongoing development, we expect that as early as 2020, the regulatory acceptance of these technologies may begin to occur. The regulatory approval process for such devices will take time and significant effort from thought leaders and industry and clinical safety and efficacy will need to be shown, all of which will require significant investment of resources for the development of automated systems. To reach this goal, clinicians should understand basic principles, potential advantages, and limitations of closed-loop system.[2,117] To the extent possible, these systems should not be a "blackbox"; clinicians should have full transparency into how adjustments are made, full understanding of the algorithm and its controlled variables, and have an adequate understanding of potential failures and risk to use it appropriately and safely. While every anesthesiologist to use the device may not need this level of detail, the technophiles among us should have access so better vet the performance of these systems and refine them over time. Moreover, clinician input will be essential for commercial entities developing these systems because it is essential for establishing control system performance metrics and their clinical relevance. Consensus standards developed by national and international anesthesia societies may be an appealing strategy to warrant a wide clinical acceptance and standardized comparison between alternative algorithms.

Finally, as previously noted, attention will eventually need to be focused on the codevelopment and coordination of multiple closed-loop systems into a single robust fully autonomous closed-loop system. If appropriately developed and validated, such a system may even be incorporated into an optimized user interface of the anesthesia workstation machine.

LIMIT TO EMBRACE ROBOTIC ANESTHESIA IN CLINICIANS' EVERYDAY PRACTICE

Anesthesiologists have always been early adopters of novel technologies, and open and comfortable incorporating new technological innovations to improve patient safety. However, when it comes to perioperative automation, a regular and particularly frequent point of resistance is the fear that automation may replace skilled anesthetists in the operating room. "Will closed-loop systems eventually replace providers?" is a question each of the authors has been asked when we give lectures on this topic around the world. While understandable—automation has been feared in virtually every form in which it was initially introduced—any practitioner familiar with the current and future state of these technologies will likely agree that such fearful propositions are severely overstated. The future of anesthesia is not "man versus machine" but rather man with machine. A more appropriate question would be: "What benefit could automation have on my daily clinical practice and how could this system improve patient care while also reducing mundane clinical tasks?" We do not yet have a complete answer to this question but research on the subject is being reported at an unprecedented rate, and recent evidence shows that combining several robots together could potentially have an impact on patient outcome.[109]

Robotic anesthesia, closed-loop feedback control of anesthesia, has been used in numerous research settings. There is obviously still a significant step from performance in these settings to daily performance, particularly in the hands of clinicians with little or no experience with such technologies. Like robotic technology in manufacturing industries, rigorous testing needs to be done before such commercial products are available, especially in the medical field. Because closed-loop systems have different components, each component might fail, connectivity might be compromised, software failure might occur, and above all human failure might lead to system failure, for example, wrong input of initial patient or surgery-related data. Safe checks could be the presence of a human controller, operator to continuously check for plausibility, the possibility to manually override the system—including going back to fully automated mode—and continuous internal safety checks of the system itself. One can imagine that these are important safety considerations, which will require significant manpower and financial resources to address.

CONCLUSIONS

The integration of robots into clinical practice aims at assisting the clinician. The goal is to increase treatment accuracy, improve patient safety, and reduce workload. The final objective is to allow the anesthesiologist to focus on tasks requiring human intelligence. Autonomous systems for general anesthesia, sedation, and manual tasks in combination with cognitive help are not inferior to the performance of anesthesiologists and may eventually allow superior performance. Robots in anesthesia are made to assist anesthesiologists providing a technological mental and physical "augmentation" to the clinician allowing a "smart" distribution of the workload. The goal of automation is not to replace a qualified care provider normally required for a particular task or intervention, but rather to assist a standard provider in application of an intervention ensuring that the highest quality of care is being used consistently and effectively for all patients.

Future studies will determine whether they could have a clinical impact on outcomes compared to anesthesia conducted without the help of autonomous systems.

DISCLOSURES

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