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Closed-loop control of anesthesia

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Abstract :Purpose of review:

Closed-loop systems are able to make decision on their own and try to reach and maintain a preset target. As a result, they might help the anesthesiologist in optimizing the titration of drug administration without overshoot, controlling physiological functions and guiding monitoring variables. Thanks to the development of fast computer technology and more reliable pharmacological effect measures, the study of automation in anesthesia has regained popularity.

Recent findings:

This short review focuses on the most recent developed and tested feed-back systems in anesthesia. Various new approaches for controlling the administration of intravenous and inhaled hypnotic-anesthetic drugs are published recently. For the analgesics, a framework for further research has been presented in the literature. For the other drugs like muscle relaxants and hemodynamics, a short review can be found.

Summary :

Until now, most of these systems are still under development. The challenge is now to establish fully safety, efficacy, reliability and utility of closed-loop anesthesia for its adoption into clinical setting. Beside the optimization of the controlled variables and control models, these systems has to be tested in extreme circumstances.

Keywords :

Closed-loop, drug administration techniques, feed-back, automation

Introduction :

In contrast to “open-loop” control of drug administration, where the anesthesiologist makes a decision to maintain or change a desired target drug dose or concentration or a desired clinical effect (e.g., the depth of the hypnotic or analgesic component of anesthesia), “closed-loop” controllers are designed to maintain a targeted effect by adapting the administered amount of drugs. In closed-loop control, the anesthesiologist only enters the desired variable to be maintained. Thanks to the development of fast computers and related technology, automated systems might improve the administration of drug delivery [1].

A number of basic components are required to develop a satisfactory closed-loop drug delivery system: 1) a system under control, which is the patient; 2) a controlled variable that measures the relevant drug effect; 3) a set point for this variable, which is the chosen target value specified by the user; 4) an actuator which is, in this case, the infusion pump/vaporizer driving the administration of drug; 5) a controller to control the actuator, which comprises an algorithm to translate a measured value of the controlled variable to a particular action for the actuator to steer the controlled variable closer to the target value[1].

Controlling the hypnotic component of anesthesia

Several closed-loop systems for hypnotics have been proposed in the literature. The effectiveness of such controllers strongly depends on the reliability of the physiological signal to be controlled [2**] and on the optimization of the control algorithms. As “depth of hypnosis” is not measurable, surrogate measures have to be applied as controlled variable. Using the electro-encephalogram (EEG), several computerized univariate parameters like

spectral edge frequency (SEF) and median frequency (MF) can be extracted and have been used as controlled variables for closed-loop systems in the past [3]. However, several investigators have found disadvantages when using these indicators [4, 5]. More recently, the bispectral index (BIS[®], Aspect Medical Systems Inc. Newton, MA) has been tested and validated as a promising measure of the hypnotic component of anesthesia [6]. BIS combines several features extracted from EEG including higher order spectra of the signal which can reveal phase coupling of single waveforms. Multivariate statistics were used to combine the different features into a single indicator [2**]. BIS values lie in the range of 0-100. BIS in the 90-100 range represents fully awake patients and ranges around 60-70 and 40-60 indicate light and moderate hypnotic state, respectively. When lower than 40, BIS indicates a too excessive level of hypnosis. Although not ultimately perfect, BIS offers a sensitivity of 100% and a specificity of around 55 % to measure loss of consciousness at values lower than 53 during propofol administration [7**].

Initially, Sakai et al. [8] performed some preliminary tests with a BIS (version 1.22) controlled closed-loop system and concluded that their system provided intraoperative hemodynamic stability and a prompt recovery from sedative-hypnotic effects of propofol. As it is always aimed at optimizing anesthetic performance by applying closed-loop systems compared to manual (human) control, Morley et al. [9**] investigated the performance of a closed-loop system for administration of general anesthesia, using BIS (version 3.1) as a target for control in combination with a modified proportional-integral-derivative (PID) controller for drug administration (see below). Anesthesia was maintained by intravenous infusion of a propofol/alfentanil mixture or an isoflurane/nitrous oxide based technique was used. The intravenous drugs were given via an infusion pump, the inhaled anesthetics were injected in the inspiratory limb of the breathing circle. For each technique, patients were

randomly allocated to receive either closed-loop or manually controlled administration of the relevant agents. Closed-loop and manually controlled administration of anesthesia resulted in similar intra-operative conditions and initial recovery characteristics. Convenience aside, the closed-loop system showed no clinical advantage over conventional, manually adjusted techniques of anaesthetic administration. The main problem of this study might be the use of a PID control algorithm (see below).

Absolom et al. [10**] developed a similar closed-loop anesthesia system using BIS as the control variable, a proportional-integral-differential control algorithm, and a propofol target-controlled infusion system as the control actuator. Closed-loop performance was assessed in 10 adult patients undergoing major orthopedic surgery under combined general and epidural anesthesia. Induction was done manually by a plasma compartment controlled infusion system. After the start of surgery, when anesthesia was clinically adequate, automatic control of anesthesia was commenced using the BIS as the control variable. Thanks to the optimization of the PID controller with a pharmacokinetic based infusion system, the system was able to provide clinically adequate anesthesia in 9 of 10 patients. The authors concluded that further studies are required to determine whether control performance can be improved by changing the gain factors or by using an effect site-targeted, target-controlled infusion propofol system.

Various control strategies exist to guide closed-loop drug administration [11]. As illustrated above, proportional-integral-differential (PID) controllers are used in several automated control systems and require some explicit understanding of the input-output relationship in terms of some mathematical solution. PID controllers are essentially “ignorant”, i.e., without knowledge of the drug metabolism and the realized (potentially dangerous) concentration

values. Without fine tuning for the specific situation these general controllers can be slow to establish control and can be dangerous to use because of possible oscillations. Fine tuning of a PID controller is difficult in this particular setting because the human body is very complex. This may lead to several clinical difficulties due to the complex pharmacological behavior of the products used, interindividual pharmacological variability and patient's reactions to external surgical stimuli. The model-based controller may be a better alternative. Here, the administration of drugs in response to clinical effect (surgical manipulations) is based on knowledge of the fate of the drug and its effect in the human body, concentrated in a mathematical model. Several different parametric and non-parametric pharmacokinetic-dynamic (PK-PD) models have been described in the literature as basic predetermined models for anesthesia applications. During control, the model might be updated to meet the patient's individual pharmacological behavior. Then, the controller is called "model-based and adaptive".

Knowledge-based systems, like for instance fuzzy control, have the ability to control a process without the determination of an explicit mathematical model of the input – output relationship. It is therefore a suitable system when little is known about the patient [11]. To the best of our knowledge, fuzzy logic systems were never used for automated administration of hypnotics in human.

Model-based adaptive control of propofol administration with BIS was previously used in a closed-loop system for sedation during spinal anesthesia by Mortier et al. [12] and , more recently, during general anesthesia by Struys et al. [13**].

The last two reports (from the same research group) describe a new closed-loop control system for propofol that uses the BIS as the controlled variable in a patient-individualized,

adaptive, model-based control system. This means that a specific pharmacodynamic profile of the individual patient is explored during induction. Thereafter, this pharmacodynamic model is adapted during control. The pharmacokinetic-dynamic model applied in this system used an effect compartment controlled infusion of propofol previously validated by the same authors [14*]. An artifact tolerant controller was also build in this system. When BIS data are corrupted, open-loop effect compartment control is automatically switched on. When BIS is back on line, the loop is closed again. In the most recent report, the authors compared their system with manually controlled administration of propofol (in combination with the same fixed dose of remifentanil in both groups) using hemodynamic and somatic changes to guide anesthesia. Performance of control during induction and maintenance of anesthesia were compared between both groups using BIS as the controlled variable in the closed-loop controlled group (group I) and the reference variable in the manually controlled group (group II), and, conversely, the systolic blood pressure as the controlled variable in group II and the reference variable in group I. At the end of anesthesia, recovery profiles between groups were compared. Although patients undergoing manual induction of anesthesia in group II at 300 ml/h reached a BIS level of 50 faster than patients undergoing open-loop, computer-controlled induction in group I, manual induction caused a more pronounced initial overshoot of the BIS target. This resulted in a more pronounced decrease in blood pressure in group II. During the maintenance phase, better control of BIS and systolic blood pressure was found in group I compared with group II. Recovery was faster in group I. The authors were able to conclude that this closed-loop system for propofol administration using the BIS as a controlled variable together with a model-based controller is clinically acceptable during general anesthesia.

Gentilini et al. [2**] developed a model and closed-loop system of hypnosis by means of BIS with isoflurane. The automated administration of inhaled anesthetics yield to a more complex situation than intravenous drug administration as the control of the complete respiratory function has to be included in the system. These investigators created a model for control consisting of three parts: a model for the respiratory system, a pharmacokinetic and a pharmacodynamic model. A cascaded internal model controller is employed. This controller consists of a master controller which compares the actual BIS and the reference value set by the user and provides expired isoflurane concentration references to the slave controller. The slave controller maneuvers the fresh gas anesthetic concentration entering the respiratory system. Additional control functions (like artifact tolerant control) are implemented to optimize safety. The system was tested preliminarily during some clinical cases and performed accurately.

Beside BIS, other EEG derived indicators are currently developed such as approximate entropy [15*] and Shannon entropy [16]. Until now, no closed-loop systems are created using these indicators as controlled variable. Previously, Kenny et al. used a derived indicator from the mid-latency auditory evoked potential (MLAEP), called AEPindex, as controlled variable [17]. Unfortunately, this system is only available from the authors. Until now, one other MLAEP derived indicator is commercially available, namely the Alaris AEP monitor (Alaris Medical Systems, Basingstoke, UK). They used a new method for extracting the MLAEP from the EEG signal by employing an autoregressive model with an exogenous input (ARX) adaptive method. This method allows extraction of the AEP signal within 15-25 sweeps of 110-ms duration, resulting in only a 6-s response delay time. A new variable, called the AAI (A-Line ARX-Index), is then calculated from this fast extracted MLAEP wave [7**]. However, no closed-loop application with this monitor has been tested until now.

Controlling the analgesic component of anesthesia.

The application of closed-loop control for analgesics (mostly opiates) encounters the problem of a lack of an optimal measurement method. Clinical scoring systems and observations like the Visual Analogue Scale (VAS) are available for the measurement of pain, however, when the patient loses consciousness, pain becomes only nociception. So far, limited expertise exists on direct measures for nociception. Some years ago, Larson et al. used pupillometry to measure reflex pupillary dilatation in response to noxious stimulus. They concluded that alfentanil blocks this dilation [18].

Although it is known that most of the hypnotic drugs will also alter the hemodynamic status of the patient, anesthesiologists mostly use these autonomic and somatic changes to guide their administration of per-operative opiates. As a result, a single-input-single output controller for opiate control based on hemodynamic changes is clinically not feasible. More complex systems are required. Gentilini et al. [19**] designed a Model Predictive Controller (MPC) for the control of the mean arterial blood pressure (MAP) during anesthesia. Alfentanil was selected as opiate drug. Three innovative features in their algorithms are worth to be mentioned. First, opiate concentrations predicted by a pharmacokinetic model are used together with Mean Arterial Pressure (MAP) by the controller algorithm to determine future opiate infusion drug. This feature is particularly important when MAP signal is either corrupted by artifacts or unreliable for the assessment of the analgesic state of the patient. Second, the system is able to cope with user-specified constraints on both input (drug infusion rate) and output (MAP and opiate plasma concentration) variables. For instance, the controller will not administer opiates as long as this results in overshooting user-defined predicted plasma drug concentration. Third, the controller determines opiate infusion rates at each step using an optimization algorithm which aims at reaching target levels for both output variables,

minimizing the drug consumption and maintaining the output and input variables within constraints. Their system was used in 13 volunteers and will be validated more in detail.

Controlling other drug administration by means of closed-loop systems.

There are many closed-loop control systems for muscle relaxants reported in the past [20], but only a few could cope with the introduction of the latest shorter acting neuromuscular blocking drugs. Geldner et al. [21] published the most recent one using mivacurium. A closed-loop system using a neural network as a predictor could be established. The system proved to be reliable for a closed-loop infusion of mivacurium in order to maintain a predefined degree of neuromuscular blockade of 95% during routine surgery.

Hoeksel et al. [22] investigated the effects of computer control of blood pressure with sodium nitroprusside and nitroglycerin on hemodynamic stability when compared to conventional manual control. They could conclude that, compared with manual control, computer control of systemic hypertension significantly improved hemodynamic stability during cardiac surgery.

Multiple input – multiple output systems.

In a recent editorial, P. Glass [23] stated that the interaction of hypnotics and opioids for achieving two major endpoints in general anaesthesia (loss of consciousness and inhibition of movement at skin incision) are based on the evidence that loss of consciousness and response to skin incision are not a single continuum of increasing “anaesthetic depth” but rather are two separate phenomena, nevertheless interfering with each other. Using response surface methodology [24], Gentilini et al. proposed a framework for multiple input – multiple output control systems [25**]. Although the interaction models have been applied during

pharmacological investigations, several other trials are required before these automatic interaction controllers can be applied in closed-loop systems. Also, one has to realise that the side-effect of the hypnotic drug (for example, hypotension) might be the measured effect of the analgesic.

Discussion :

The study of the performance of the anesthesiologists and models of the cognitive tasks demands during anesthesia shows that increasing the complexity and shortening the response time of anesthesia delivery and monitoring systems may create new demands for clinicians attention and cognitive resources[26]. Also, new long-lasting surgical procedures (micro-surgery, ...) might decrease the vigilance level of the anesthesiologist during the maintenance phase of anesthesia [27]. As the overall complexity of the anesthesia systems might be too extended for the human user, the application of automated feedback systems, also called “closed-loop systems”, might allow better control. Automated systems are able to make decision on their own and try to reach and maintain a preset target. As a result, they might help the anesthesiologist in optimizing the titration of drug administration without overshooting, controlling physiological functions and guiding monitoring variables. Moreover, they may take advantage of the drug synergies, for which now proper modeling framework was developed [24]. Furthermore, if tuned properly, closed-loop systems should be able to compensate the interindividual variability and to tailor the drug administration profile to the particular stimulation intensity of each surgical procedure. Also, closed-loop systems can be used for research as a “reference” anesthesiologist during clinical studies. [28]

A disadvantage of all the actually developed systems is their limited scope of action and their extent of authority. The human operator is accepted to accommodate these limitations by

employing the automation only when appropriate and by recovering control when automation's limits are reached. Intelligent alarms might help in these circumstances. [29].

The ultimate goal of the closed-loop controllers is their general acceptance in clinical practice. So far, all developed closed-loop systems have been used in well controlled scientific trial environment. In a recent editorial, Glass et al. [30**] questioned about the essential requirements of closed-loop technology. They stated that closed-loop delivery systems are no longer esoteric. Rather, the challenge is now to establish fully safety, efficacy, reliability and utility of closed-loop anesthesia for its adoption into clinical setting. Beside the optimization of the controlled variables and control models, these systems has to be tested in extreme circumstances. Glass et al formulated some questions regarding this : Will the control system work well if large adjustments have to be made and will it be fast enough without causing under- or overshoot in control hereby creating dangerous side-effects? These are questions that require to be answered in future research.

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