Monitoring the stress response during general anaesthesia

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Abstract—The major objectives of anaesthetists in the operating theatre are to maintain the hypnosis, the relaxation, the analgesia, and the vital functions during the operation. The aim of this paper is to present an overview of new developments regarding monitoring and control of stress response during general anaesthesia. The applicability of the main parameters to monitor the adequacy of analgesia online will be discussed. Different models based on pharmacokinetic and pharmacodynamic effects in particular the opioid remifentanil and the hypnotic propofol were developed. The response of these anaesthetics on heart rate, different parameters of the heart rate variability and the bispectral index during induction of general anaesthesia were studied. Starting from these models, control strategies in analgesia have been discussed. The developed environment for the assistant system for anaesthesia at the University of Rostock is presented.

I. INTRODUCTION

The main objectives during general anaesthesia are to provide hypnosis, muscle relaxation, and analgesia of patient. Anaesthetists apply various types of drugs to induce and maintain adequate anaesthesia and the vital functions while surgical manipulations and diagnostic procedures. There are interactions between the three main components of anaesthesia in different quantity.

Whereas gold standards are known to monitor automatically states of hypnosis and muscle relaxation there is no standardized method to determine the state of analgesia. Analgesia is defined by the absence of pain in response to stimuli which would be painful under nonanaesthetical conditions. Pain is an individual sensation and during anaesthesia correlated with clinical signs. The stress response to an external stimulus during anaesthesia depends on the intensity of stimulus and the application rate of analgesic drugs. The administration of hypnotic agents is also stabilizing the state of analgesia and vice versa. The anaesthetists control the drug rates with the objective to achieve a balance between analgesia and hypnosis.

The intensity of stimulus can not be standardized and is a consequence of experience of physicians and the sensitivity of patients. Therefore, the level of analgesia can only be determined as a contemporary reaction on a stimulus under known rates of anaesthetics. The quantification of the stress response is therefore restricted to a comparison with the state of the patient without the influence of stimuli or with the response to other stimuli.

II. POTENTIAL MONITORING METHODS

In the clinical practice individual signs of inadequate analgesia can be an increase in heart rate (HR) and arterial blood pressure (ABP), mydriasis - widening of pupils, sweating and lacrimation - tears flow. Analgesic stability is defined according to haemodynamic stability by lack of variation between 20% of the reference heart rate or the arterial pressure [1]. The classically used endpoint in response to painful stimulation is the movement of the patient [2].

In the last years different monitor methods have been tested to quantify the stress response. The Bispectral index (BIS) is a statistical evaluation of different frequency components in the electroencephalogram (EEG). The BIS is used to monitor the depth of hypnosis as reaction on hypnotic drugs. There are also many studies to consider the correlation of the BIS with sedation by the combination of hypnotic and analgesic drugs. Without using of opioids, the BIS predicts movement in response to surgical stimulations [2]. The BIS during total intravenous anaesthesia (TIVA) shows reaction only on a noxious stimulus and does not predict the movement of patients [3].

In Ref. [4] skin conductance monitoring is compared with the BIS to distinguish different clinical states of patients while waking up after total intravenous anaesthesia (TIVA). Skin conductance varies with sympathetic tone and the following sweat gland filling. The authors consider that the BIS is a better predictor than skin conductance but it is characterized by slower response time. The authors of this paper considered, that HR and ABP are not applicable as predictor for arousal, but these parameters have been recorded every 2 min only.

The skin vasomotor reflexes measured by laser Doppler flowmetry detect a reduced skin blood flow induced by noxious stimulation [5]. The pulse wave reflex detected by pulseplethysmography is a better predictor as skin vasomotor reflex [6], but the sensitive suppression of pulseplethysmography amplitude by nociceptive stimuli is influenced by various other terms.

The pulse transit time (PTT) is a further parameter to detect the response on nociceptive stimuli. The value of PTT describes the time from the onset of ventricular electrical activity to the start of the ejection into the aorta. It can easily and continuously be measured using standard monitors in the operating theatre, electrocardiogram (ECG) and pulse oximetry. In conclusion Singham et al. resumed, that PTT reflects the autonomic response independently of HR [7].

None of the described monitor methods is standardized for the use in the operating theatre. HR and ABP are the classical parameters to register the adequacy of analgesia. The known problem of big intra- and intervariability as well as the dependency on the comprehensive state of
patient is evaluated by the anaesthetists with their experience. The non-invasive measured ABP is not suitable for closed-loop control because it supplies the measured values in intervals of several minutes only. The invasive measured ABP is rarely available.

The different parameters of heart rate variability (HRV) offer the possibility to support the autonomic response in HR, without the induction of a further monitor. They visualize both parasympathetic and sympathetic activities of the autonomic nervous system [8]. Our research group developed an online tool for calculating the HRV under MATLAB®. Based on the measured RR-intervals of ECG, the tool supplies continuously parameters in time and frequency domains. First the RR-series are detrended by the method of Tarvainen et al. [9]. Secondly, they are sampled with 4Hz. In the time domain analysis of modified RR-series, the standard deviation of the last minute is calculated in a sliding time window. In the frequency domain the FFT of last 128s is used to achieve the power of the low frequency range (0.04 - 0.15Hz) and of the high frequency range (0.15 – 0.4 Hz). Also the ratio of both parameters is calculated, which is considered to mirror the changing influence of parasympathetic or sympathetic systems respectively, i.e. the sympatho/vagal balance. Nociceptive stimuli activate the sympathetic system [8].

Similar to HRV, respiratory sinus arrhythmia (RSA) was investigated as response to stress stimuli during general anaesthesia. The RSA describes the influence of spontaneous respiration on HR subsequently of stimuli. Blues and Pomfrett concluded, that RSA is related more to depth of anaesthesia, i.e. hypnosis [10].

Experimental pain models were developed to quantify the stimulus response by predetermined stimulus intensity and drug level. Thermal, pneumatic, chemical or electrical inputs have been tested. However, the intensity of experimental pain is not relevant for surgical stimuli, because tissue damage has to be prevented. Therefore, in preparation for control of analgesia, it should be helpful to observe suitable parameters perioperatively.

### III. MODELS FOR ANAESTHETIC EFFECTS ON POTENTIAL STRESS PARAMETERS

There are different options for modelling the body response to drug application. They all describe the pharmacokinetic (PK) and pharmacodynamic (PD) of the body drug response. The PK shows the distribution of drug in the body and the PD summarizes the effects on the body. Empirical models are the simplest models, which formulate directly the reaction of the body on the drug rate. Ordinarily, compartmental models are used, which represent a division of the body into a minimal number of compartments. One compartment is characterized by typical behavior in drug distribution. The mamillary model is the most spreaded compartmental model. It consists of a central compartment reflecting the blood plasma and a different number of peripheral compartments, which are linked to the central compartment only. The most accurate model type in anaesthesiology is the physiological one using several compartments with parameters directly related to the characteristics of the different organs.

Data of HR, ABP, BIS, and HRV have been recorded during induction of anaesthesia in studies at the University of Rostock to investigate the effect of the anaesthetics and the response to different painful stimuli. Therefore, empirical [11] and compartmental models have been developed.

For compartmental models three compartments and an additional effect compartment (Fig. 1) have been used, with the parameters from Minto and Schnider [12] for the analgesic drug remifentanil and with the parameters from Schnider et al. [13] for the hypnotic drug propofol. A software tool was developed under MATLAB® for calculation of the plasma and the effect site concentration by constant infusion rates and the target controlled infusion (TCI) based on the method of Bailey and Shafer [14]. The tool simulates the drug distribution in a patient with optional values in weight, age, height, and gender. The application period of the manually administered bolus of propofol was 10 seconds. The period between the application of the bolus and the start of the continuous infusion of propofol was calculated as the mean value of the recorded periods of patients with 25 sec.

![Figure 1. Pharmacokinetics and Pharmacodynamics of a three compartment model.](image)

The mean of responses of 28 patients is used for modelling. The method for unconstrained nonlinear optimization with a simplex search of Nelder and Mead [15] was applied to find the models, starting at initial estimate for determined model parameters. Therefore, the signal is negated and scaled, so that the signal starts with zero at the beginning of the infusion. Records of 240 sec with a sampling time of 1 sec were analyzed.

When the infusion of remifentanil started, the patients were awake. Therefore, the HR and the HRV were influenced by a number of impressions, such as excitement and anxiety. It could visually be concluded, that the reactions of different HRV parameters and of the BIS on continuous infusion of remifentanil with 0.4 µg/kg body weight/ min are not significant and able to deliver any model. Therefore, HR has been tried to model with the output of PK/PD-model as input (Figure 2). A gain K and the time constants $T_1$ and $T_2$ have been acquired by the initial model structure in (1).

$$G(s) = \frac{K \cdot (1 + sT_2)}{(1 + sT_1)} \quad (1)$$

$K=1.36 \quad T_1=1\ s \quad T_2=159.79\ s$

Propofol is a hypnotic drug and the patient falls to sleep by its application. The body response to propofol appears among the BIS, the parameter of hypnotic state, in drop of ABP, HR and the HRV. The reaction of continuous measured standard deviation (SD) is shown in
Fig. 4 as an example for modelling the body response to propofol. Firstly, a propofol bolus of 2 mg/kg body weight has been applied and than the continuous infusion of 2 mg/kg body weight/h has been started. A slightly signal increase was observed immediately after the beginning of bolus application in HR, the SD of time domain analysis, and the low frequency component of frequency domain analysis. It is probably caused by stinging pain in vein during the beginning of propofol application. It has been ignored for model optimization.

The commonly used limiter function for propofol is a fractional sigmoid $E_{\text{max}}$ model between the effect compartment concentration $c_e$ and the effect on the response parameter [20]. The authors choose an arctangent function, where $K_1$ and $K_2$ are gains optimized also by modelling. The pharmacodynamical model describing the propofol model to changes in SD of HR is shown in Fig. 3, where the limiter function and second order model with delay $T_d$ of body reaction are in series.

$$C_e = \frac{e^{-cT_1}}{(1 + sT_1)(1 + sT_2)}$$

$$c_e' = K_1 \cdot \arctan(K_2 \cdot c_e)$$

$$\Delta SD$$

The parameter set resulted from optimization for the complex model as shown in Fig. 4 is given with:

$$K_1 = -9.105 \quad K_2 = 0.013 \quad T_d = 22.5 \text{ s}$$

$$T_1 = 70.34 \text{ s} \quad T_2 = 14.64 \text{ s}$$

Generally, it seems to be more useful to approach models with an easier structure. First order models with delay of body response have been attempted for modelling of the responses of HR, the low and high frequency total power of frequency domain analysis to the application of propofol.

Fig. 5 demonstrates the evidence of HRV-parameters to distinguish the intensity of stimuli during general anaesthesia. The patient is in steady state after the induction of anaesthesia with the used anaesthetics. The insertion of a laryngeal airway mask or the intubation follows to enable artificial ventilation. The investigators considered that the intubation is the most painful stimulus during anaesthesia. In Fig. 5 the mean values of the responses of SD of the time domain analysis of HR for 14 patients respectively to the intubation and to the insertion of laryngeal mask have been compared [16]. The effect of intubation is significant higher compared with laryngeal mask insertion.

The authors concluded from the results of modelling and the reaction on different painful stimuli, that the combination of HR and the continuously calculated SD of HR will be a significant parameter setting for monitoring analgesia. In the next investigations these parameters should be observed perioperative to evaluate their capability for controlling of analgesia.

**IV. CONTROL STRATEGIES FOR ANALGESIA**

Up to now, a standard measurement for pain or state of analgesia of the patient is not known. Only few relevant approaches of closed-loop controllers for analgesia have been established.

In Ref. [17] a multiple input multiple output predictive controller was presented to regulate the invasive mean ABP by infusion rate of alfentanil through a computer-controlled infusion pump based on TCI-models. The predicted plasma concentration of alfentanil was involved also as an output in the control strategy. The controller is able to avoid under- and overdosing and to keep the ABP on different reference values. A limitation of the method is the application of invasive ABP, because it represents an additional catheter, which is no routine in the operating theatre.
Schwilden and Stoeckel [18] developed a closed-loop controller to maintain the median frequency of EEG at 2-4 Hz using the opioid alfentanil. The EEG is known to reflect the hypnotic state of the patient more than his analgesic state. Therefore, it is not an appropriate procedure for pain control.

The research group of Mahfouf and Nunes [19] linked a multivariable fuzzy controller based on three rules with a patient model. The patient model relates the HR, the systolic ABP, and the auditory evoked potential features with the effect concentrations of hypnotic drug propofol and analgetic drug remifentanil. The effects of surgical stimuli were involved in this model by Mamdani fuzzy models using expert knowledge of anaesthesiologists. The system is characterized by a very complex structure, but so far there are no experiences with applications on humans.

Stadler based the analgesia controller on a physiological PK model using alfentanil and the inputs HR and non-invasive mean ABP [20]. The measurement period of ABP was reduced to the minimal value of 2 min, so that no complication originates for the patient. Hence, the haemodynamic changes in response to stimuli are more rapid. The combined measurement of non-invasive ABP and HR should replace the seldom available invasive ABP. A modified cascade structure was used for the controller. The inner cascade was a TCI system without feedback from the patient. The outer loop influences the target concentration of the inner loop by controlling the changes of HR and ABP. The pain detection is defined by exceeding a relative threshold value of HR, but the target concentration is only increased, if this occurrence is accompanied by a high ABP. So far, the concept was validated in pilot studies with less intense stimuli.

In the research group Anaesthesia Control at the University of Rostock an assistant system for anaesthesia (ASYNARO) was developed [21]. The system controls two major components of anaesthesia, the hypnosis and the neuromuscular block. For controlling the depth of anaesthesia a fuzzy-PD+I (P-proportional, D-differential, I-integral part) controller calculates the amount of hypnotic drug propofol to minimize the error between the actual measured BIS-value and the BIS set point of 40. The developed fuzzy system, with integrated prefiltner, normalization and derivation, is composed of separate PD- and I-part. Therefore, the number of rules was limited: 7 rules for the I-part and 43 for the PD-part. The rules were modified together with the anaesthesiologists. The fuzzy controller uses the Mamdani interference system. For the control of muscle relaxation, an adaptive Generalised Predictive Controller (aGPC) was developed. The controller strategy is divided into two periods. At the beginning of control the patient behaviour is highly nonlinear. Therefore, a modified on-off controller is used to determine a bolus application of the relaxant to the patient. The GPC takes the control in the second period after identifying the linear model. The online identification of a third-order discrete-time ARX-model is implemented to get the actual patient information. The redundant sensor structure with parallel electromyographically and acceleromyographically measurement advances the safety of the control procedure. The system with both controllers was tested successfully for 51 patients during elective surgery under general anaesthesia.

The maintaining of haemodynamic and other vital functions is the forth major objective during general anaesthesia. For neuro- or cardiac surgery it could be beneficial to decrease the blood pressure to limit bleeding and establish better surgical conditions. As mentioned above, the blood pressure is influenced by anaesthetics and could reflect the state of analgesia. Therefore, our research group made an effort to create a blood pressure control system [22]. Based on the model of Slate et al. [23] a fuzzy gain scheduled PID controller for hypotension by the application of sodium nitroprusside was developed.

The next step will be the development of ABP control to keep the blood pressure on a determined level by application of two different drugs for hypotension and hypertension. After integration of blood pressure control into the assistant system for anaesthesia, further studies will taking place in preparation of closed-loop control of analgesia by the HR and the HRV-parameter SD with the fast acting analgesic drug remifentanil and hypnotic drug propofol. The BIS and the ABP are already controlled, but the parameters are strongly influenced by the state of analgesia. Therefore, a new control strategy has to be conceived for a completion of the multiple input multiple output (MIMO) structure of anaesthesia assistant system described in Fig. 6.

![Figure 6. MIMO structure for prospective assistant system for anaesthesia control](image)

### References


Doppler skin vasomotor reflex and pulse wave reflex,” British Journal of Anaesthesia, 89, pp. 389-397, 2002


