GARCH MODELS FOR DRUG EFFECTS ON PATIENT HEART RATE, DURING GENERAL ANAESTHESIA

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Abstract: A model that can describe the effect of anaesthetic drugs on patient's heart rate (HR) is of great importance when considering haemodynamic stability under surgery. A Generalized Autoregressive Conditional Heteroscedasticity (GARCH) model was used to model HR considering the effect concentrations of the anaesthetic propofol and the analgesic remifentanil, using the clinical data of 16 patients. The model was able to capture the HR trend in all 16 patients with very small errors throughout the surgical time. A correlation was found between the GARCH parameters and patient baseline characteristics, leading to the possibility a patient adjusted adaptive model.

Keywords: Biomedical systems, stochastic modelling, modelling errors, pharmacokinetic data

1. INTRODUCTION

Anaesthesia can be defined as the lack of response and recall to noxious stimuli, involving the use of three drugs, a muscle relaxant, an anaesthetic (hypnotic) and an analgesic. The analgesic drug is of great importance since it affects the pharmacodynamics of the anaesthetic drug and there is no clear indicator of the degree of pain. The analgesic and anaesthetic drugs are interconnected, since they interact with each other so as to achieve an adequate level of depth of anaesthesia (DOA) and analgesia (Vuyk, 1999). The possibility of consciousness during surgery is a factor that affects clinicians and patients. The brain signals (e.g. electroencephalogram EEG) are used to indicate the level of DOA, measuring the depression in the central nervous system. But, haemodynamic signals indicate the level of analgesia and stability (McGregor *et al.*, 1998)(O'Hare *et al.*, 1999). The heart rate (HR) (i.e. the number of heart beats per unit of time) is an haemodynamic signal, which as normal values around 72 beat/min. Overall, general anaesthesia consists of both loss of consciousness through the acting of the anaesthetic drugs, and the inhibition of noxious stimuli reaching the brain through the acting of the analgesics. The intravenous anaesthetic drug propofol is used in combination with the analgesic remifentanil.

Propofol and remifentanil have a synergistic relationship. The effect of the combination of these two drugs is greater than that expected as based on the concentration-effect relationships of the in-

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dividual agents (Vuyk *et al.*, 1997). The properties of remifentanil make it a suitable analgesic for use with propofol, and adequate for control in anaesthesia.

A model for heart rate can be very useful to understand the effect of different drugs and drugs' interactions. This model could have in consideration only the effect of remifentanil or remifentanil and propofol. Since remifentanil has a stronger effect than propofol on the haemodynamic signals (McAtamney *et al.*, 1998)(Prakash *et al.*, 2001). However, drug interactions can influence HR. The aim of this study is to develop a model that can describe the characteristics and trend of patient HR under general anaesthesia.

The Generalized Autoregressive Conditional Heteroscedasticity (GARCH) model structure was used, since it is a good model for processes without seasonality and with high variability. Heart rate variability increases in the presence of pain (Toweill *et al.*, 2003).

In this work, a comparative study will be performed on a wide group of patients to evaluate the effectiveness of GARCH models with different input variables (effect concentration of remifentanil or remifentanil and propofol). The clinical data are presented in section 2. Section 3 describes the model that was applied to the clinical data, for the concentration-effect relationship on HR. The results are presented in section 4. And sections 5 and 6 present the discussion and conclusions.

2. CLINICAL DATA

Data collected during 16 neurosurgical interventions were used in this study. All 16 patients were subject to general anaesthesia using the anaesthetic drug propofol and the analgesic drug remifentanil. The level of unconsciousness (DOA) was manually controlled by the anaesthetist using as reference the patient's vital signs and the bispectral index of the EEG (BIS) monitor. The following clinical signs were recorded during the surgery every 5 seconds: BIS, infusion rate of propofol and remifentanil, haemodynamic parameters. The infusion rates were used to calculate the plasma and effect concentration of both drugs, as described in the following subsections. The 16 patients studied were Glasgow 15, ASA 1/2, 46.3±15 years, 64±14 kg, 164±8 cm, 10 female. Anaesthesia started with a constant infusion 200 ml/hr of propofol until loss of consciousness (LOC), thereafter propofol was changed according to the BIS value. The remifentanil infusion started at LOC. The mean duration of surgery was 482.2±195.4 minutes (245.0 - 972.2).

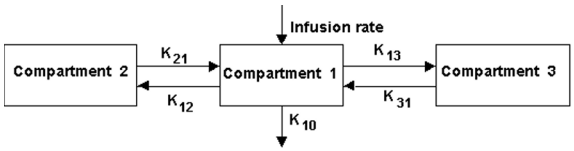

Fig. 1. 3-compartment pharmacokinetic model. The plasma concentration is defined as the concentration in compartment 1.

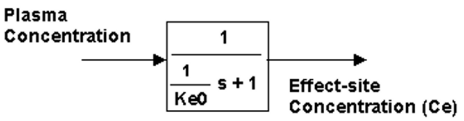

Fig. 2. Effect compartment model

2.1 Pharmacokinetic (PK) Models

The PK models of the two drugs use a 3-compartment model (figure 1). For propofol, the PK parameters from Schnider (Schnider *et al.*, 1998) were used, whereas for remifentanil, the parameters from Minto (Minto *et al.*, 1997a) were used. The PK models have its parameters adjusted to age, gender, weight and height of the patients.

2.2 Effect Compartment

The effect compartment is a hypothetical compartment describing the delay between the plasma concentration and the effect concentration. Figure 2 shows the diagram of the effect compartment relationship. The pharmacodynamic parameters $ke0$ used were described by Schnider (Schnider *et al.*, 1999) for propofol, and for remifentanil by Minto (Minto *et al.*, 1997b).

2.3 Average Patient

The data of an average patient was constructed using the average values of all 16 patients (i.e. their signals, figure 3). This average patient was used to determine the fixed structure of the model for HR.

3. GARCH MODEL

Figure 4 shows the block diagram of the HR model. The objective is to describe the relationship between the drugs effect concentrations and its effect.

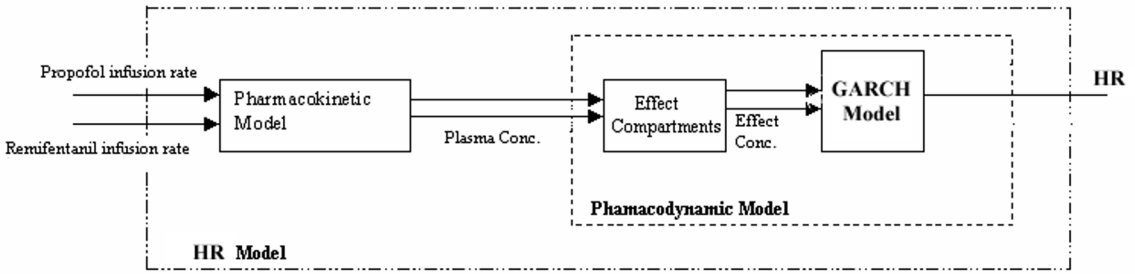

Fig. 4. Block diagram of the HR model.

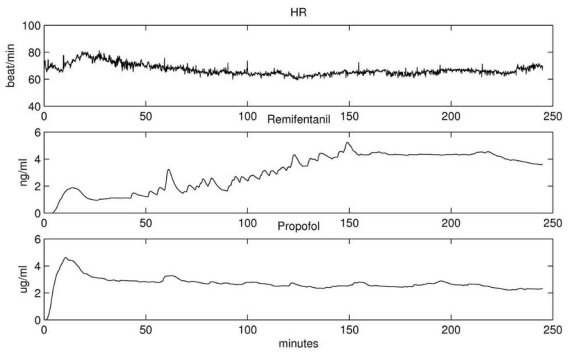

Fig. 3. Average patient mean arterial pressure (MAP), heart rate (HR), and effect concentrations of propofol and remifentanil.

3.1 Model Structure

The Generalized Autoregressive Conditional Heteroscedasticity (GARCH) is a model that predicts the data (time series) and its variance. The change in variability is very important when describing the HR signal. A variance that changes with time has implications in the validity and efficiency of the statistical inference of the parameters that describe HR (y_t) (Hamilton *et al.*, 1994).

A process u_t, that satisfies equation 1 is described by an ARCH(q) model.

$$u_t^2 = \xi + \alpha_1 u_{t-1}^2 + \alpha_2 u_{t-2}^2 + ... + \alpha_m u_{t-q}^2 + \omega_t (1)$$

A generalized model GARCH(p,q) is:

$$u_t = \sigma_t v_t \tag{2}$$

where v_t is an independent random sequence with zero mean and unit variance. And σ_t^2 is the conditional variance of u_t (conditional on all the information up to time $t-1$):

$$\begin{aligned} \sigma_t^2 &= k + \beta_1 \sigma_{t-1}^2 + \beta_2 \sigma_{t-2}^2 + ... \\ &+ \beta_p \sigma_{t-p} + \alpha_1 u_{t-1}^2 + \alpha_2 u_{t-2}^2 + ... \\ &+ \alpha_q u_{t-q}^2 \end{aligned} \tag{3}$$

where $k \equiv [1 - \beta_1 - \beta_2 - ... - \beta_p]\xi$, $\alpha_i \geq 0$ $i = 1, \ldots q$, and $\beta_i \geq 0$ $i = 1, \ldots, p$.

3.2 Implementation

To develop a model it is necessary to specify inputs and outputs, estimation parameters with any optimization technique, evaluate errors and validate the model.

Each patient reacts to pain in a different way. Two GARCH models were implemented: GARCH Model 1 using just the effect concentration of remifentanil; and GARCH Model 2 using the effect concentrations of remifentanil and propofol. A basic fixed structure (equation 4) given by the average patient data was used for the GARCH models.

$$\begin{aligned} y_t &= 70.12 + u_t \\ \sigma_t^2 &= 0.2059 + 0.66922\sigma_{t-1}^2 + 0.30416 u_{t-1}^2 \end{aligned} \tag{4}$$

The HR signal was initially filtered with a moving average filter (6 samples) to remove outliers and then filtered with a lowpass second order Butterworth filter, so as to remove the electrical interference.

The parameters of the GARCH models were individually adjusted to each patient data, so as to capture the interindividual variability. A log-likelihood objective function was used to optimize the parameters, using the software MATLAB 6.5.1

4. RESULTS

The two models (GARCH model 1 using just the effect concentration of remifentanil and GARCH model 2 using the effect concentrations of remifentanil and propofol) were fitted to the data of the 16 patients. The mean absolute errors were calculated for the results of the two models and for each of the 16 patients.

4.1 Results with the GARCH Model 1

The results of GARCH model 1 are good, however in some patients there seems to be constant error between the model result and the real HR (figures

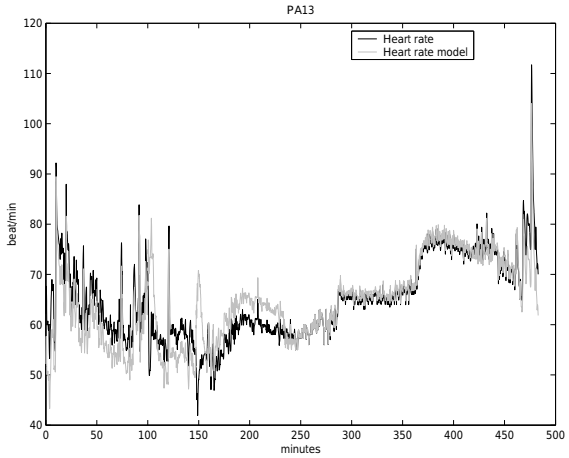

Fig. 5. Results of the GARCH Model 1 for the data of patient PA13.

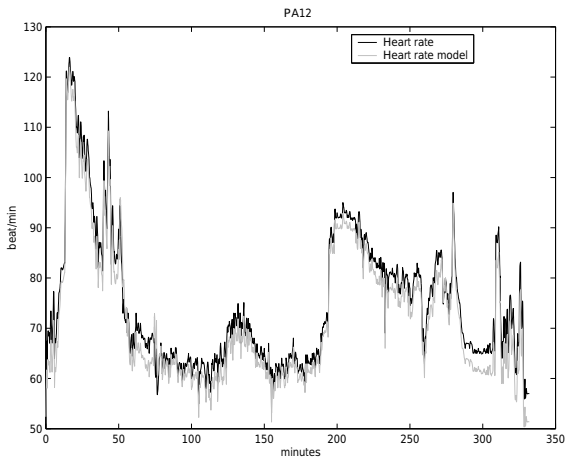

Fig. 6. Results of the GARCH Model 1 for the data of patient PA12.

5 and 6). This constant error, or shift in scale could be the influence of the other drug (i.e. propofol), for which this model does not account for.

The mean absolute error of GARCH Model 1 for the 16 patients was 10.9±9.3. The individual mean absolute errors of the model in all 16 patients are presented in table 1.

4.2 Results with the GARCH Model 2

The results of GARCH Model 2 are good, following the HR trend in all patients. Figures 7 and 8 show the model results for patient PA13 and PA12. The amplitude shift that was present in the

Table 1. Mean absolute errors (MAE) for the results of the GARCH Model 1 in all 16 patients.

Patient	MAE
PA1	5.9
PA2	8.6
PA3	17.0
PA4	16.3
PA5	7.9
PA6	5.2
PA7	5.7
PA8	3.5
PA9	2.9
PA10	16.7
PA11	4.3
PA12	3.0
PA13	3.0
PA14	31.8
PA15	13.3
PA16	30.2

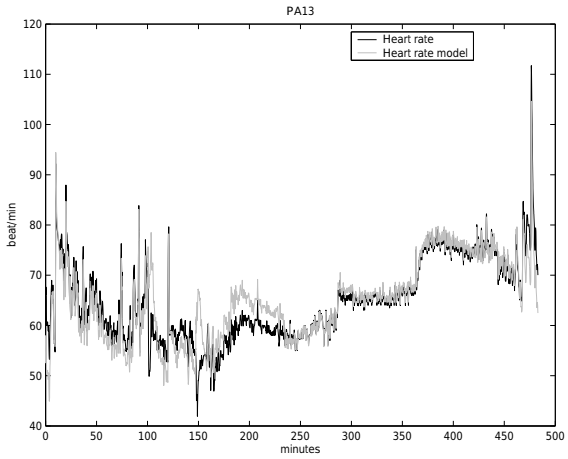

Fig. 7. Results of the GARCH Model 2 for the data of patient PA13.

results of GARCH Model 1 are not present when using GARCH Model 2.

The mean absolute error of GARCH Model 2 for the 16 patients was 11.2±9. The individual mean absolute errors of the model in all 16 patients are presented in table 2.

5. DISCUSSION

Analyzing the figures, the results of GARCH Model 2 do not have any scale shift from the real data. However, the mean absolute error shows that on average a smaller error is associated with GARCH Model 1, which only takes into consideration the effect concentration of remifentanil. Remifentanil is a drug that directly affects the haemodynamic signals (Vuyk, 1999).

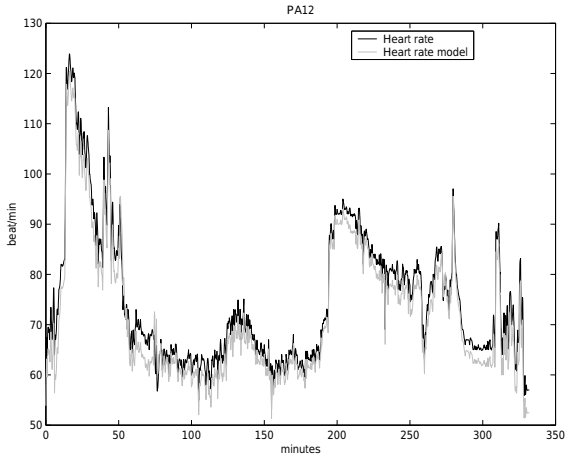

Fig. 8. Results of the GARCH Model 2 for the data of patient PA12.

Table 2. Mean absolute errors (MAE) for the results of the GARCH Model 2 in all 16 patients.

Patient	MAE
PA1	4.6
PA2	8.1
PA3	17.1
PA4	15.2
PA5	10.7
PA6	5.1
PA7	5.2
PA8	10.0
PA9	3.7
PA10	14.7
PA11	4.3
PA12	3.0
PA13	2.4
PA14	31.6
PA15	15.1
PA16	30.2

A correlation analysis was performed between the GARCH Model 1 parameters and the patients' individual characteristics (i.e. age, weight, baseline HR value) (table 3). A high correlation was found between patient's weight and K, GARCH and ARCH parameters. In addition, baseline HR is strongly correlated with the GARCH and ARCH parameters. This high correlation between patients' characteristics and the model parameters can be further used to adapt the model online based on the initial fixed structure.

Table 3. Correlation coefficients between GARCH parameters and patients' individual characteristics.

	K	GARCH	ARCH
Age	-0.1904	0.3982	-0.3982
Weight	-0.5255	0.5385	-0.5385
Baseline HR	0.2937	-0.5581	0.5581

6. CONCLUSIONS

The heamodynamic stability under surgery depends on the patient's individual response to the drugs. The degree of sensitivity/resistance of the patient to the drugs has a great influence on the amount of drugs necessary during surgery, to maintain an adequate level of unconsciousness and analgesia. Information extracted from models can be used to adapt the infusion rates of both drugs, avoiding cases of overdosage or pain. The control system parameters could be adjusted or adapted to individual patient requirements.

The two GARCH models tested in this study proved to be efficient in modeling the HR variation according to the concentrations of the anaesthetic drugs. These models can be used in the operating theatre to predict the HR trend according to the drug concentrations used by the anaesthesiologist, i.e. as an advisor system.

Haemodynamic stability as measured by the HR its clinically important, specially under surgery. HR variations are associated with the level of pain, and depend on the individual patient.

In the future, this model can be automatically adjusted to the patient, identify the degree of pain and subsequently help to adjust the dose of the analgesic, improving the patients' comfort and safety

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