Interaction between EEG and Drug Concentration to Predict Response to Noxious Stimulation during Sedation-Analgesia: Effect of the A118G Genetic Polymorphism

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Abstract— **The level of sedation in patients undergoing medical procedures is affected by the interaction between the effect of the anesthetic and analgesic agents and the pain stimuli. The presence of the A118G single nucleotide polymorphism (SNP) in the OPRM1 gene affects the requirements of opioids for patients undergoing sedation-analgesia. The purpose of this work is to evaluate the influence of the SNP A118G in OPRM1 on EEG measures for the prediction of the response to pain stimulation during endoscopy procedure. The proposed measures were based on power spectral density and auto-mutual information function. It was found that the statistical performances of the EEG measures improved when the presence of the SNP was taken into account (prediction probability *Pk*>0.9).**

I. Introduction

To determine appropriate requirements for administration, monitoring and control of sedation and / or analgesia in invasive medical procedures has been an active research topic during the past decade [1-4]. The main purpose has been to minimize the impact of the aggression in the patient. Parameters extracted from the electroencephalogram (EEG) have demonstrated to be extremely useful for noninvasive assessment of the hypnotic effect during general anesthesia or during sedation [5-10]. Changes on the EEG signal are directly related to the biochemical variations of a drug induced in the brain and the effects on individual behavior. The hierarchical model of the interaction of hypnotic and analgesic effects, such as propofol and remifentanil, proposes that opioids could act at different levels in the nervous system attenuating how the noxious stimuli get to the cortex [11,12].

Several factors have been demonstrated to affect the pharmacokinetics–pharmacodynamics of propofol and remifentanil [13,14]. For example, differences in genetic factors might affect the disposition or the sensitivity of the patients to either propofol or remifentanil. However, the influence of genetic variability in drug dosing of anesthetic drugs has not been widely studied. It is well known that the OPRM1 gene encodes the μ-opioid receptor, which is a member of the G protein-coupled receptor family [15]. Genetic variations in exon 1 of the OPRM1 gene, located at chromosome 6, have been associated with changes in the spatial conformation of the μ-opioid receptor as a result of amino acid changes in the receptor protein and thereby altering its function. The single nucleotide polymorphism (SNP) of the OPRM1 gene called A118G (rs1799971) results in an amino acid substitution from asparagine to aspartate at mutant receptors (N40D) [15,16].

Borrat *et al.* [17] assumed that a genetic trait such as the A118G SNP in the OPRM1 gene can affect the requirements of remifentanil in patients undergoing procedures under sedation-analgesia. Then, they used it as a covariate factor in the modeling process to optimize dosing of an anesthetic drug. They demonstrated that when an expected decrease in bispectral index (BIS) value is not observed after adequate dosing of analgesics, one of the factors to be considered might be the presence of the A118G variant in OPRM gene in chromosome 6. Furthermore, other works have shown that the A118G SNP affects the requirements of opioids to control postoperative pain [16] and chronic pain [18].

From these considerations, we assume that the A118G SNP might influence the performance of EEG measures in the assessment of the sedation level. Thus, in the present paper, the prediction of the response to pain stimulation during endoscopic procedures is studied taking into account the presence (OP=1) or absence (OP=0) of the SNP A118G in OPRM1. The statistical performances of linear and non-linear measures of EEG in the prediction of responding to nail bed compression were evaluated in both OP groups, together and independently. Furthermore, multivariate discriminant functions were built taking into account the OP value and the drug concentration.

II. Materials and Methods

A. EEG Database and Preprocessing

The database belongs to the Department of Anesthesiology, Hospital Clínic de Barcelona (Spain). This database contains data recorded from 200 patients who underwent ultrasonographic endoscopy of the upper gastrointestinal tract under sedation and analgesia with propofol and remifentanil. For each patient, the following information is available: predicted concentrations of propofol (Ce_{Prop}) and remifentanil (Ce_{Remi}), bispectral index (*BIS*), information about the presence (OP=1) or absence (OP=0) of the SNPA118G in OPRM1, and electroencephalogram (EEG) signal. The observed categorical responses after applying noxious stimuli include the evaluation of the Ramsay Sedation Scale

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(RSS) level [19] after nail bed compression. All patients belong to 1-3 ASA classification. Patients with altered central nervous system, medicated with analgesics or drugs with central effects on the perception of pain, from moderate to severe cardiomyopathy, neuropathy or hepatopathy that needed control during the anesthetic process were not included in the database.

The EEG was recorded using the Auditory Evoked Potential AEP monitor/2 from Danmeter (Odense, Denmark). Sampling frequency was 900 Hz, with a resolution of 16 bits and a recording time of about 60 minutes. All information Ce_{Prop}, Ce_{Remi}, BIS, and RSS were annotated with a resolution of 1 s. After the application of a FIR band pass filter of 100th order, with cut-off frequencies of 0.1-45Hz, the EEG signals were resampled at 128 Hz. Then, the EEG signals were segmented in windows of length of 1 minute between 30 s and 90 s before the response annotation of RSS. The annotated RSS was assigned to the previous 1 minute length window if the differences ΔCe_{Remi} and ΔCe_{Prop}, between the first and the last second of the window, were ΔCe_{Remi}<0.1 ng/ml and ΔCe_{Prop}<0.1 μg/ml. Otherwise, the window was cut at the sample where the conditions were satisfied. Windows of EEG containing high amplitude peak noise were processed with a filter based on the analytic signal envelope (ASEF) [20]. If the difference between adjacent samples were higher than 10% of the averaged differences of the previous samples, the windows were cut. In this way, the smallest window resulted to be of 50 s. The windows of interests were filtered into the characteristic frequency bands of the EEG signal: δ, 0.1-4 Hz; θ, 4-8 Hz; α, 8-12 Hz; β, 12-30 Hz, *TB*, 0.1-45 Hz.

B. Genetic Determination of A118G SNP

Before starting the endoscopic procedure, a venous blood sample was drawn from every patient for posterior genetic analysis to detect A118G SNP. Genomic DNA was isolated from blood using the QiaAmp® DNA Mini kit (Qiagen, Courtaboeuf, France) according to the manufacturer's instructions. Genotyping for A118G SNP was performed by TaqMan® (Invitrogen, Life Technologies Ltd., Paisley, United Kingdom) allelic discrimination using a predesigned SNP Genotyping Assay in the 7300 Real-Time PCR System (Applied Biosystems, Foster City, CA) following the manufacturer's instructions. Genotyping was scored manually and blindly by two independent operators to avoid errors.

C. Traditional EEG Analysis

The following traditional EEG measures were calculated in each window:

- Standard deviation (*std*) of the EEG windows filtered in each frequency band.
- Power spectral density (PSD) of the EEG windows in the *TB* band using the Welch method.
- Spectral power in each band (P_δ , P_θ , P_α , P_β) as the area under the PSD curve, normalized by the total PSD area.
- Mean frequency (*mF*) in each band (*TB*, δ, θ, α, β), as the centroid of the PSD curve.
- Spectral edge frequencies (*SEF50*, *SEF75*, and *SEF90*) in each band. The *SEFx* was calculated as the frequency below which *x* % of the total EEG spectral power is located.

D. Auto-Mutual Information Function

Auto-mutual information function (*AMIF*) [21] derived from Shannon's (*Sh*) information theory is defined as

$$AMIFSh(\tau) = \sum_{x_i \epsilon X} \sum_{x_{i+\tau} \epsilon X} P_{xx}(x_i, x_{i+\tau}) \, log_2 \left(\frac{P_{xx}(x_i, x_{i+\tau})}{P_x(x_i) P_x(x_{i+\tau})} \right) \quad (1)$$

The probabilities P_{xx} and P_x were constructed on the series x_i and their delayed series $x_i+\tau$, for τ = {1,2,…,128} samples. This function describes how the information of a signal (*AMIF* value at τ =0) decreases over a prediction time interval (*AMIF* values for τ>0). In the case of a completely regular and deterministic signal, the *AMIF* would remain at the maximum value of τ=0 for all τ. In the case of an uncorrelated random signal, the *AMIF* would become zero for all τ apart τ=0. Increasing information loss is related to decreasing predictability, and increasing complexity of the signal.

AMIF can be also defined from Rényi information theory as

$$AMIFRe_q(\tau) = \frac{1}{q-1} log_2 \sum_{x_i \epsilon X} \sum_{x_{i+\tau} \epsilon X} \frac{{P_{xx}}^q(x_i, x_{i+\tau})}{{P_x}^{q-1}(x_i) P_x^{q-1}(x_{i+\tau})} \quad (2)$$

where q is the control parameter that defines Rényi information, and was selected as q = {0.1, 0.2, 0.5, 2, 3, 5, 10, 30, 50, 100}. *AMIF* was normalized by the maximum value *AMIF*(0).

Several measures were defined on the *AMIF* with respect to the time delay τ: mean (*m*), first relative maximum (*max*) and first decay for τ=1 (*FD*). These variables were calculated from the EEG signal filtered in each one of the characteristic frequency bands.

E. Statistical Analysis

A non-parametric test, U of Mann-Whitney test, was applied considering two groups: segments associated with responsive levels of RSS (RSS<6) and segments associated with unresponsive level of RSS (RSS=6). A significance level p-value <0.05 was taken into account. Measures that satisfy this condition were considered for building univariable and multivariable discriminant functions, in order to predict the pain responses. The leaving-one-out method was performed as validation method. Sensitivity (*Sen*) and specificity (*Spe*) were calculated for testing the performance of all the measures. *Sen* measures the proportion of responsive state (RSS<6) correctly classified and *Spe* measures the proportion of unresponsive state (RSS=6) correctly classified.

In order to analyze the influences of the SNP on the results, the analysis was performed in 3 sets of data: 1) OP01, measures of EEG windows from the entire dataset; 2) OP0, measures of EEG windows from patients with

OP=0; 3) OP1, measures of EEG windows from patients with OP=1.

The ability of the measures to describe pain responses was evaluated using prediction probability (P_k), which compares the performance of indicators [22]. A P_k of 1 represents a perfect prediction. The P_k avoids the shortcomings of other measures being independent of scale units and it does not require knowledge of underlying distributions.

III. Results

In general, the measures that yield the best P_k in all the analyzed sets were found to be P_β , $max(Re_{q=2})_\delta$ and $FD(Sh)_\beta$ combined with Ce_{Prop}.

Fig. 1 shows the averaged $AMIFRe_2(\tau)$ in δ band derived from the EEG segments in responsive states (RSS<6) and unresponsive states (RSS=6) in the two SNP sets, OP1 and OP0. The curves exhibit an initial fast decrease at short time scales followed by a slow increase and then a decrease to nonzero stable values at longer time scales. It can be observed that AMIF from responsive state windows in which the SNP is present (OP1) has the highest relative maximum ($max(Re_{q=2})_\delta$), denoting a less complexity behavior of the EEG around the time scales that correspond to δ band.

Fig. 2 shows the boxplot of the distribution of P_β , $max(Re_{q=2})_\delta$, $FD(Sh)_\beta$ and Ce_{Prop} of the two sets OP0 and OP1 from responsive and unresponsive segments. Comparing the RSS states, as it can be seen in Fig. 2a, P_β presents higher values for responsive states (RSS<6) than unresponsive states (RSS=6). These trends are also reflected in the values of $max(Re_{q=2})_\delta$ (Fig. 2b) and $FD(Sh)_\beta$ (Fig. 2c). Comparing the two sets, the responsive windows in OP1 set have higher values of P_β and $max(Re_{q=2})_\delta$ than in OP0. A similar behavior is observed in unresponsive windows of P_β. On the contrary, $FD(Sh)_\beta$ presents higher values in OP0 than OP1 for both RSS states. The values of Ce_{Prop} are shown in Fig. 2d where it is denoted that patients with SNP (OP1) need higher concentration of propofol in order to reach unresponsive level.

Table I shows the univariable results of the measures that gave the highest P_k , *Sen* and *Spe* in the entire dataset OP01 and in the OP0 and OP1 sets. The statistical performances of BIS [5] were also calculated.

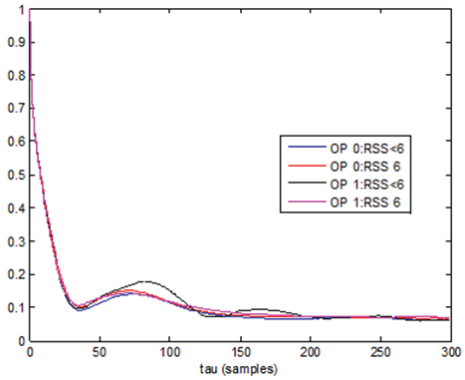

Fig. 1 Averaging of $AMIFRe_2(\tau)$ function

TABLE I
RSS RESPONSE TO NOCICEPTIVE STIMULATION: SINGLE VARIABLE

Dataset OP01	P_β	$max(Re_{q=2})_\delta$	$FD(Sh)_\beta$	*BIS*	Ce_{Prop}
P_k	0.717	0.749	0.710	0.786	0.700
Sen (N=561)	56.5	60.4	58.3	77.5	70.7
Spe (N=349)	76.5	78.4	69.1	65.5	56.4
Set OP0					
P_k	0.715	0.747	0.701	0.774	0.680
Sen (N=511)	56.6	60.3	59.3	75.6	70.5
Spe (N=320)	75.2	77.5	66.6	63.6	54.0
Set OP1					
P_k	0.737	0.784	0.864	0.931	0.827
Sen (N=50)	56.0	64.0	72.0	88.0	72.0
Spe (N=29)	79.3	89.7	100	75.9	82.0

N= number of analyzed windows; P_k: prediction probability; Sen: (%) sensitivity; Spe: (%) specificity; p-value<0.05

TABLE II
RSS RESPONSE TO NOCICEPTIVE STIMULATION: MULTI VARIABLES

Dataset OP01 *Measures f(•)*	P_k	*Sen* N=561	*Spe* N=349
$max(Re_{q=2})_\delta$, P_β	0.809	70.1	76.5
$FD(Sh)_\beta$, P_β	0.794	65.4	78.8
$max(Re_{q=2})_\delta$, $FD(Sh)_\beta$	0.771	65.1	75.4
Ce_{Prop} , P_β	0.794	67.9	75.4
Ce_{Prop} , $max(Re_{q=2})_\delta$	0.776	64.5	76.5
Ce_{Remi} , $FD(Sh)_\beta$	0.722	60.1	69.6
OP , P_β	0.716	56.3	74.2
OP , $max(Re_{q=2})_\delta$	0.751	60.4	78.5
Ce_{Prop} , $max(Re_{q=2})_\delta$, P_β	0.841	72.5	78.8
Ce_{Prop} , Ce_{Remi} , $max(Re_{q=2})_\delta$	0.781	65.0	75.4
Ce_{Prop} , Ce_{Remi} , $FD(Sh)_\beta$	0.750	68.6	68.1
Ce_{Prop} , *OP* , $max(Re_{q=2})_\delta$	0.777	64.5	76.2
Ce_{Prop} , *OP* , P_β	0.793	67.0	74.8
$max(Re_{q=2})_\delta$, $FD(Sh)_\beta$, P_β	0.829	70.4	77.4

N: number of analyzed windows; P_k: prediction probability; Sen: (%) sensitivity; Spe: (%)specificity; p-value<0.05

TABLE III
RSS RESPONSE TO NOCICEPTIVE STIMULATION: MULTI VARIABLES

Measures f(•)	Set OP0			Set OP1		
	P_k	*Sen* N=511	*Spe* N=320	P_k	*Sen* N=50	*Spe* N=29
$max(Re_{q=2})_\delta$, P_β	0.804	69.7	76.3	0.868	70.0	82.8
$FD(Sh)_\beta$, P_β	0.786	64.6	77.8	0.923	78.0	89.7
$max(Re_{q=2})_\delta$, $FD(Sh)_\beta$	0.750	61.3	71.9	0.870	74.0	93.1
Ce_{Prop} , P_β	0.786	75.6	63.6	0.867	66.0	82.8
Ce_{Prop} , $max(Re_{q=2})_\delta$	0.764	64.3	73.4	0.900	80.0	79.3
Ce_{Prop} , $FD(Sh)_\beta$	0.725	65.3	65.9	0.925	78.0	86.2
Ce_{Remi} , $FD(Sh)_\beta$	0.717	61.5	68.1	0.863	73.0	100
Ce_{Prop} , $max(Re_{q=2})_\delta$, P_β	0.832	71.9	78.1	0.960	84.0	89.7
Ce_{Prop} , $FD(Sh)_\beta$, P_β	0.812	69.5	76.3	0.954	80.0	89.7
Ce_{Prop} , Ce_{Remi} , $max(Re_{q=2})_\delta$	0.773	62.9	77.3	0.960	84.0	85.7
Ce_{Prop} , Ce_{Remi} , $FD(Sh)_\beta$	0.740	67.3	67.5	0.956	80.0	89.3
Ce_{Prop} , $max(Re_{q=2})_\delta$, $FD(Sh)_\beta$	0.745	61.3	71.9	0.930	80.0	79.3
$max(Re_{q=2})_\delta$, $FD(Sh)_\beta$, P_β	0.822	69.5	76.9	0.935	82.0	93.1

N= number of analyzed windows; P_k: prediction probability; Sen: (%) sensitivity; Spe: (%) specificity; p-value<0.05

Tables II and III show the combined measures that gave the best classification percentages. A maximum of three uncorrelated variables were taken into account. The highest P_k in the OP01, OP0 and OP1 was obtained with Ce_{Prop} , $max(Re_{q=2})_\delta$ and P_β. When also $FD(Sh)_\beta$ was considered, the *Sen* and *Spe* in the OP1 set were significantly improved (Table III) compared to set OP0. The combination of EEG measures with Ce_{Prop} and Ce_{Remi} gave the best results in OP1 set. This can be related to the fact that equal dose of analgesic has less effect on EEG in patients with SNP than in patients without SNP [17]. In this way the interactions between EEG measures and drug concentration become a more significant factor in the assessment of the sedation level in patient with SNP.

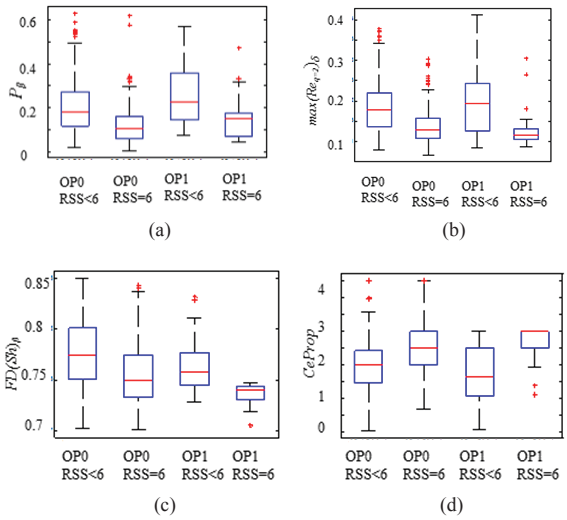

Fig. 2 Distribution of (a) P_β , (b) $max(Re_{q=2})_\delta$, (c) $FD(Sh)_\beta$, and (d) Ce_{Prop}. On each box, the central mark is the median and the edges of the box are the 25th and 75th percentiles.

IV. Conclusions

The influence of the SNP A118G in OPRM1 on the prediction of the response to pain stimulation during ultrasonographic upper gastrointestinal endoscopic procedure based on EEG measures was evaluated studying two groups of patients with and without the SNP. The statistical performances of the proposed EEG measures in the prediction of responding to nail bed compression improved when the presence or absence of the SNP was taken into account, permitting to obtain performances better than BIS.

The combination of the propofol concentration (Ce_{Prop}) with the spectral power and auto-mutual information measures in δ and β bands yielded P_k>0.8 , *Sen*>70% and *Spe*>75 % in the group without SNP and P_k>0.9, *Sen*>80% and *Spe*>85 % in the group with SNP. However, the quantity of the analyzed windows in the set of patients with SNP was low; then, these preliminary results need further validation with a higher number of patients.

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