New Advances in the Understanding of the Current Sources of Epileptic Activity in Mesial Areas

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1 Introduction

Epilepsy is one of the most common neurological conditions, with an estimated prevalence of approximately 0.4%-1.0%. Most patients with epilepsy experience seizures that are well controlled with antiepileptic drugs. Medical intractability, also known as drug-resistant epilepsy, occurs in 40% of patients with focal epilepsy (Téllez-Zenteno & Ladino, 2013), of which temporal lobe epilepsy (TLE) is the most frequent and most difficult to treat using antiepileptic drugs. Surgical treatment for these patients is typically a safe, effective and well-established option, with a success rate between 70 and 90% (Sola et al., 2005). The best surgical outcomes are obtained when the epileptic zone (EZ) (Luders & Awad, 1991) is accurately localised through a presurgical evaluation, where patients are subjected to a number of noninvasive ancillary tests: video-electroencephalography (v-EEG), magnetic resonance imaging (MRI), single photon emission-computed tomography (SPECT) and positron emission tomography (PET). When the results from these tests are not functionally and anatomically consistent, invasive recordings are required, such as foramen ovale, subdural or depth electrodes. Activation through drugs that induce or increase interictal activity is often used as a complementary method together with v-EEG (Schmitt et al., 1999; Brockhaus et al., 1997; Krieger et al., 1995; Pastor et al., 2010). Etomidate, a selective modulator of the g-aminobutyric acid receptor A (GABA_A), is a hypnotic agent with a rapid speed of onset, a short duration of action, and minor side effects associated with intravenous perfusion. Etomidate might activate seizure foci, manifesting as a selective increase in the spiking activity on the EEG. In recent studies, we described the many benefits of etomidate-induced activation during the presurgical evaluation of patients with TLE, as this drug facilitates the reliable identification of the ictal onset zone (IOZ) and could be used to diagnose patients who do not experience seizures during v-EEG recordings or to influence decisions regarding the placement of intracranial electrodes. Moreover, the regional cerebral blood flow (CBF), assessed using SPECT with ^99m^Tc-HmPAO, changed after perfusion with etomidate (Pastor et al., 2010; Herrera-Peco et al., 2010). Thus, it is necessary analyse the electrophysiological properties of the etomidate-induced irritative activity to ensure that this effect is generated through the same cortical regions observed at basal conditions. Therefore, the accuracy of this model to the biological system must be determined before drawing conclusions about its application.

Recently, we described a method to localise and evaluate current sources in mesial regions, combining the classical electrostatic approach with pharmacological activation through etomidate (Herrera-Peco et al., 2010). However, several questions still remain. In this study, we specifically address the theoretical and topographical aspects of current sources.

2 Methods

2.1 Patients

A total of 13 patients (6 men and 7 women) were included in this study. The mean age and time of intractable epilepsy were 37.5 ± 4.3 and 30.6 ± 5.8 years for men and 39.8 ± 5.6 and 29.8 ± 4.4 years for women, respectively. Two patients had seizures during etomidate perfusion and were not included in the analysis.

The Ethical Committee of the Hospital de la Princesa approved this research. Informed consent was obtained from all patients. The patients were evaluated pre-surgically in accordance with the protocol of the Hospital de La Princesa (Pastor et al., 2005; Sola et al., 2005). Briefly, all patients were studied
through scalp electroencephalography (EEG), interictal SPECT, MRI 1.5 T and v-EEG, using 19 scalp electrodes according to the international 10-20 system. Six-contact platinum foramen ovale (FO) electrodes, with 1-cm centre-to-centre spacing (AD-Tech, Racine, USA), were inserted bilaterally under general anaesthesia (Wieser & Moser, 1988; Pastor et al., 2008). In all cases, the correct implantation was assured using fluoroscopic imaging in the operating room. The most rostral electrode in the foramen ovale was referred to as FO#0, and the most occipital electrode was referred to as FO#5. During the v-EEG recording, antiepileptic drugs were progressively removed from the second to the fourth day, at approximately one-third of the dose per day. The digital EEG (NeuroWorks, XLTEK®, San Carlos, USA) and FO electrodes data were sampled at 256 Hz and filtered at 0.5-50 Hz for scalp and 1-100 Hz for FO electrodes recording. The IOZ was defined as the region where the seizures originated according to the v-EEG + FO recording. An expert neurophysiologist (JP), blinded to the results of the etomidate injection, identified this area.

2.2 Etomidate Administration

Under the continuous supervision of an experienced anaesthesiologist, etomidate (Janssen-Cilag, Spain) was intravenously applied (0.1 mg/kg) under inactive conditions, with the patient lying in the supine position (Herrera-Peco et al., 2009; Pastor et al., 2010). Supplementary oxygen was administered through nasal prongs at a 5-L/min rate. The electrocardiogram (EKG), capillary oxygen saturation (SaO2) and respiratory rate (RR) were continuously monitored during the entire process, although these variables were not analysed in this study. The analysis with intravenous etomidate was performed between the third and fourth days in the v-EEG unit, except in one case performed on the fifth day. Discrete measurements of all variables were obtained at 30-s intervals at 5 min before (basal level) and 15 min after etomidate application.

The kinetics of the etomidate-induced activity was assessed using an expression equivalent to the first derivative for the discrete time-series of the frequency of spikes:

$$\Delta f = \frac{f(t+\Delta t) - f(t)}{\Delta t},$$  

where $\Delta f$ is the change in frequency (spikes/min), and $\Delta t$ represents the time increment (min).

Lateralisation induced through etomidate perfusion was assessed, comparing the frequency in the left and right areas and the frequency in the mesial and lateral areas. We defined the lateralisation coefficient (lc) using the following expression:

$$lc = \frac{1}{15} \sum_{i=1}^{15} \frac{v_l - v_r}{v_l + v_r},$$  

where $v_l$ signifies the left frequency (either from the mesial or lateral areas) and $v_r$ represents the right frequency for $i =$ 1, 2 ...13 on the time-series of spike instantaneous frequencies. According to this method, etomidate activity lateralises to the left if $0 < lc < 1$ and to the right if $1 < lc < 0$. A bolus of $^{99m}$Tc-HmPAO (740 MBq) was intravenously injected immediately after etomidate administration.

2.3 Measure of Cerebral Perfusion

The regional cerebral blood flow (CBF) was determined using SPECT imaging. The analyses were performed using $^{99m}$Tc- HmPAO, with a low-energy high-resolution collimator, a simple-head camera
(Starcam 3200, General Electric®, Milwaukee, WI, U.S.A.), and 96 projections of 22 s each, with a 64 x 64 matrix. The slices were reconstructed through filtered back-projection using a Butterworth filter (order 10 with a 0.6 cut-off). The brain SPECT images were acquired in the 30 min following the complete recovery of the patient.

The quantitative analysis of the brain perfusion was performed using NeuroGam software (General Electric®) to compare several areas of interest, including the frontal, temporal, parietal, and occipital lobes, and the putamen, globus pallidus, and thalamus, as defined using the software. Moreover, we defined the following areas according to the Talairach and Tournaux atlas (1998): the laterobasal temporal cortex, amygdaloid body, anterior hippocampus, and posterior hippocampus.

To evaluate changes in CBF, we defined the next variable using the following equation:

$$\Delta = \text{CBF}_{\text{etom}} - \text{CBF}_{\text{basal}},$$

where $\text{CBF}_{\text{etom}}$ and $\text{CBF}_{\text{basal}}$ are measures of the regional CBF after etomidate administration and under basal conditions, respectively.

### 2.4 Monopole Model

We applied a classical electrostatic theory to derive mathematical expressions for interictal epileptiform discharges (IED, i.e., spikes and sharp waves) recorded using FO (Malmivuo & Plonsey, 1995). We assumed an infinite and homogenous volume conductor and an isotropic medium, according to the following equation:

$$V = \frac{i_{\text{equiv}}}{4\pi\sigma r}.$$  \hspace{1cm} (4)

(See Pastor et al., 2006 for further details). However, we modified our theoretical framework, replacing the equivalent charge ($q_{\text{equiv}}$) with the equivalent current ($I_{\text{equiv}}$) at coordinates ($z_0$, $r_0$) responsible for a particular spiking activity ($V$). This voltage was recorded from two consecutive FOs, $n$ and $n + 1$ (bipolar linkage), and is given by the following expression:

$$i_{\text{equiv}} = k \frac{\sqrt{(n+1)L-z_0}^2 + r_0^2 \sqrt{(nL-z_0)^2 + r_0^2}}{(nL-z_0)^2 + r_0^2 - \sqrt{(n+1)L-z_0}^2 + r_0^2},$$ \hspace{1cm} (5)

where $r_0$ is the radial distance to the charge, $k = \frac{1}{4\pi\sigma}$, $s$ is the conductivity tensor and $L$ is the inter-electrode distance in mm. In all cases, the $z=0$ corresponds with the position of FO#0, placed at the inner face of the foramen ovale.

The three-equation system ($r_0$, $z_0$ and $i_{\text{equiv}}$) was solved numerically using the IED amplitude data from three consecutive channels. For this purpose, we first identified IED simultaneously recorded using three consecutive differentially arranged electrodes, namely $V_1$ (posterior by definition), $V_2$ and $V_3$ (anterior). The spikes were identified according to the IFSECN criteria (Chatrian et al., 1974) and were only included when a phase reversal between two consecutive channels was observed (Pastor et al., 2006; Herrera-Peco et al., 2009). The spike amplitude was measured from the base line to either the positive or negative peak. Some bioelectrical activity, representing $40 \pm 4.3\%$ of the recorded activity, did not fit with our criteria (spikes with multiple peaks, asynchronous spikes, etc.) and were not included in the
analysis. For the rest of the activity, under the conditions specified, a single source approximation was reliably applied, and the most common spike profile is included in the study.

Typically, more than fifty spikes per patient were collected for analysis in each state (awake, sleep and after etomidate). Non-REM sleep was scored according to the conventional rules for sleep staging (Rechtschaffen & Kales, 1968). For each patient, the following variables for interictal, ictal and pharmacologically induced activity were examined:

1. The relative position \((z_0, r_0)\) in the \(zr\)-plane defined by the FO.
2. The equivalent current \((i_{equiv})\)
3. The mean scattering of the current sources in the \(zr\) plane. This measure is an estimate of the scattering of current sources from all spikes examined. We estimated the mean scattering using a centre-of-mass approach.
4. The relative frequency of activity (% of spikes) along the \(z\)-axis.
5. Relative topography of the different states: wakefulness, sleep, ictal and pharmacologically induced activities. See below.
6. The CBF immediately after etomidate administration.

### 2.5 Topographical Analysis of Current Sources

It is important to establish the degree of superposition among sources obtained from interictal, ictal and pharmacologically induced activity. Thus, the \(zr\)-plane, or configuration space, was divided into small non-overlapping patches of:

\[
\Delta x \times \Delta y,
\]

where \(\Delta x = 1\) mm, \(\Delta y = 1\) mm and \(\text{area} = 1\) mm\(^2\). This tessellation covers the entire theoretical surface. We have defined the active area (where current-source appears, irrespective of the functional state) in two steps: (i) patches where spiking activity \(1\) spike/mm\(^2\); and (ii) spikes less than a minimum distance \((d_{min})\) from other spikes. We have chosen:

\[
d_{min} = \sqrt{\Delta x^2 + \Delta y^2} = 1.4\ \text{mm}.
\]

In this way, spurious spikes were excluded from the active area. Therefore, for each pair of activities, e.g., interictal and etomidate induced, we obtain the total area where the current sources appear for each type of activity and the superposition between them. Moreover, the degree of superposition for the number of sources was also computed. This analysis was performed using a homemade script in MATLAB\(^\text{TM}\) (R2008b).

### 2.6 Numerical Model

To address the behaviour of different source configurations, we implemented a simple numerical model. We assumed a simplistic approach, according to the following hypotheses:

1. A current source is placed in a model of the cortex.
2. The dynamics of the spike (whose mechanism is negligible) are generated in the source and scaled at different points according to the voltage generated for each source configuration.
3. The medium is considered homogeneous and isotropic. Real values for conductance are consciously ignored because we are only interested in relative, not real, magnitudes.

We have assessed three different configurations:

1. Monopolar, with a current \( i \) placed 3 mm below the cortical surface.
2. Dipolar, with two currents \((i \text{ and } -i)\), oriented vertically and located 6 mm apart (d).
3. Quadripolar source, with a current \( i \) placed at the same point as the dipole, but with a negative source \((-i)\), divided into three currents, \(-i_j, j = 1, 2, 3\), where:
   \[
   i + \sum_{j=1}^{3} -i_j = 0
   \]  
   (8)

   According to the cable theory (see below), the relationship between these currents is \(-i_1 < -i_2 < -i_3\).

This model was implemented in Matlab(R) 9.0 and run using a personal computer. Briefly, the dynamics for the interictal epileptiform discharge was simulated from a model of spike obtained from two opposite and partially overlapped Gaussian curves, with different constants. We considered that the spike dynamics did not change with position, but amplitude should be scaled for every position according to the voltage induced for every configuration, e.g. equation 10 for monopolar and modified accordingly for quadripolar, and equation 11 for dipolar configurations.

2.7 Statistical Analysis

Statistical comparisons between groups were performed using Student's t-test or Mann-Whitney's rank sum test if normality failed. Groups that did not fit to normality were subjected to the Kruskal-Wallis one-way ANOVA on ranks. In cases of more than two records per patient, Dunn's multiple pair-wise comparison was used.

Significant changes in regional CBF (\(\Delta\)) were assessed using the z-score, according to the following (null and alternative) hypotheses:

\[
\text{H}_0: \mu_1 = 0 ; \text{H}_1: \mu_1 \neq 0.
\]

Pearson's correlation coefficient was used to study dependence between variables. Linear regression was calculated using the least square sum. A contrast hypothesis against the null hypothesis \(r = 0\) used the following statistic:

\[
t = \frac{r \sqrt{N - 2}}{\sqrt{1 - r^2}}.
\]  
(9)

This statistic describes a Student's t-distribution with \(N - 2\) degrees of freedom (Spiegel, 1991). SigmaStat 3.5 software (SigmaStat, Point Richmond, CA, USA) was used for the statistical analysis. The significance level was set at \(p = 0.05\). The results are shown as the means ±SEM, except where otherwise indicated.
3 Results

All the patients were operated by anterior medial temporal resection. The main clinical features of the patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>vEEG</th>
<th>RM</th>
<th>SPECT</th>
<th>lc. mesial</th>
<th>lc. lateral</th>
<th>Surgery / Engel</th>
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<tr>
<td>1</td>
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<td>M</td>
<td>L-TM</td>
<td>TMS-L</td>
<td>AMT-L</td>
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<td>1</td>
<td>L/I</td>
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<td>AMT-L</td>
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<td>1</td>
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<td>TMS-R</td>
<td>Mes-R</td>
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<td>-0.97</td>
<td>R/I</td>
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<td>Bi-T (L&gt;R)</td>
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<td>-0.27</td>
<td>R/I</td>
</tr>
<tr>
<td>5</td>
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<td>TMS-R</td>
<td>Bi-T (R&gt;L)</td>
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<td>-0.47</td>
<td>R/I</td>
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<tr>
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<td>AMT-R</td>
<td>-0.97</td>
<td>-0.29</td>
<td>R/I</td>
</tr>
<tr>
<td>7</td>
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<td>R-TM</td>
<td>TMS-R</td>
<td>AMT-R</td>
<td>-0.91</td>
<td>-0.80</td>
<td>R/I</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
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<td>Mes-L</td>
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<tr>
<td>9</td>
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<td>AMT-L</td>
<td>1</td>
<td>1</td>
<td>L/I</td>
</tr>
</tbody>
</table>

Table 1: Clinical features of analysed patients. AMT: anterior mesial temporal. L, left; R, right. TMS: temporal mesial sclerosis. Mes: mesial. ATR, anterior temporal resection. lc, lateralisation coefficient.

3.1 Bioelectrical Activity Induced Through Etomidate

The changes observed in the scalp EEG after etomidate administration were characterised by small increases in the amplitude and frequency of the activity recorded (stage 1), followed by generalised, large-amplitude delta activity (stage 2) (Figure 1). In terms of irritative activity, the frequency (spikes/min) of high-voltage spikes and sharp-waves increased in temporal areas, particularly in the mesial areas. These activities only appeared in areas included among the ictal zone (IZ), i.e., etomidate induced this activity only in areas where spikes were recorded under basal conditions (Figure 2).

3.2 Effects Of Etomidate During Cerebral Perfusion

We observed a significant increase in the regional CBF with respect to basal state in the thalamus (p < 0.05, z-score, n = 13), the posterior hippocampus (p < 0.05, z-score), and putamen (p < 0.05, z-score), and these changes occurred bilaterally. However, the only brain structure in which the regional CBF differed between epileptic and nonepileptic hemispheres was the posterior hippocampus (Figure 3). In this area, a CBF was significantly increased in the nonepileptic lobe compared with the epileptic lobe (p < 0.05, paired Student’s t-test).
Figure 1: Shortly after completion of etomidate administration, (arrow) increases in the amplitude and frequency (stage 1), followed by generalized large amplitude delta activity (stage 2) is observed in the bioelectrical activity recorded on scalp EEG.

Figure 2: Activity recorded using FO electrodes after administration of etomidate. A) Basal activity. B) Activity at 30 s and C) 2 min after etomidate administration.

Figure 3: Effects of etomidate on CBF. The graph summarizing the CBF changes by etomidate in regions pertaining to the epileptic hemisphere (black box) and nonepileptic hemisphere (empty box). # p < 0.05, z-score test (n = 13); *p < 0.05, paired Student’s-t-test. Ctx: cortex. Hippoc: hippocampus.
3.3 Fitting The Data To The Monopole Model

To analyse the proper fit of our data to the single source model, we calculated the percentage of spikes recorded in three consecutive channels, with fitting errors >5%. The spikes observed showing an error greater than 5% during interictal (awake and sleep states) and ictal activities, representing approximately 10% of the cases. However, the scattering and the $i_{equiv}$ were similar for interictal and pharmacologically induced activities (Figure 4), suggesting that the single source model could reliably explain interictal and etomidate-induced spiking recorded using FO electrodes in MTLE. No differences were observed between the characteristics of the interictal activity recorded from either wakefulness or sleep with respect to the interictal activity in the presence of etomidate. Therefore, both physiological states can be used for the study of basal interictal activity.

Figure 4: Biophysical properties of current sources from the mesial temporal lobe. The scattering, $i_{equiv}$, was similar during both interictal and pharmacological induction.

3.4 Voltage Source Distribution And Scattering

We analysed the anterior-to-posterior distribution in the z-axis for the entire group compared with the distribution obtained for etomidate. The spatial distribution of the voltage sources responsible for interictal baseline activity was similar to that obtained for etomidate-induced activity. Moreover, there was a close correlation between areas where irritative activity occurred under basal conditions and those induced through etomidate (Figure 5). We attempted to determine whether there were interindividual differences in the irritative activity distribution in the patients sampled. The analysis of the normalised sources showed that 76.9% of the patients did not show the localised distribution of voltage sources at either the interictal baseline or in the presence of etomidate. A more scattered distribution along the axis z, with $\text{IP}_{20-75} > 20$ mm (Rank: 21.5-28.3 mm), was observed in 22.1% of the patients.

We compared the antero-posterior current source distribution for different pairs of functional states, e.g., interictal vs ictal, interictal vs etomidate and ictal vs etomidate. Therefore, we plotted the percentage of frequency of spikes for each segment along the z-axis. The results were fitted to a linear regression using the least square method. We observed a linear relationship among the three functional states.
3.5 Current Topography Sources

Considering the importance of the specificity of activation using etomidate, we analysed the topographical relationship between pharmacologically induced activity and the IOZ in 6 patients. We previously demonstrated that current sources obtained during wakefulness and sleep share common biophysical properties; hence, both types of activities can be considered as similar from a biophysical point of view. However, it remains unknown whether these activities are generated from the same cortical structures. To address this question, we analysed the topographical distribution of current-sources in the configuration space.

The active area (mm²), where the current-sources appears for each of the functional states (interictal, ictal and etomidate induces), was 33.3 ± 5.8; 4.0 ± 0.6 and 10.7 ± 1.4, respectively. Similarly, the occurrence of spikes (spikes/mm²) was 63.3 ± 11.5; 16.7 ± 3.1; and 20.0 ± 3.3, respectively. For each pair of activities, the area and the spikes of superposition were interictal-ictal: 10.0 ± 1.5 mm², (31%) and 74.7 ± 12.6 spikes/mm² (12%); interictal-etomidate induced: 7.3 ± 1.4 mm² (24%) and 74.7 spikes/mm² (12%) and ictal-etomidate induced: 4.7 ± 1.0 mm² (24%) and 30.0 spikes/mm²(45%), respectively.

Thus, there is a great degree of superposition for the current-source topography for interictal, ictal and pharmacologically induced activity.

3.6 Theoretical Approach To Mesial Sources

An electric field (E) is a vectorial magnitude, whose calculation, even in a simple system, is laborious and usually difficult. To overcome these problems, physicists and, subsequently, neurophysiologists have extensively used the following potential approach.

Briefly, the electric field generated through an electrical charge (q, in coulombs -C) can be theoretically related to a scalar potential (f) using the following expression:
Figure 6: Example of topography for current source density locations in different states. A) Interictal epileptiform discharge, B) ictal onset and C) pharmacologically induced activity.

\[ \tilde{E}(r) = -\frac{\partial}{\partial x} \left( \frac{q}{4\pi \varepsilon_0 R} \right) \]  

(10)

where \( \varepsilon_0 \) represents the permittivity in a vacuum (in F/m), and \( R \) is the magnitude of the relative position between the source \( r' \) and the field point \( r \), typically measured in centimetres (cm) for the central nervous system (CNS). For simplicity, we have reduced this problem to a monodimensional problem, assuming that the charge is placed in the vacuum. While this situation does not actually occur in the central nervous system (CNS), this formalism is still frequently used.

As discussed above, this expression is vectorial. However, the expression between brackets, which represents the potential, is scalar. Thus, several charges placed at different points can be defined using the following equation:

\[ \phi(r) = \sum \frac{q}{4\pi \varepsilon_0 R_i} \]  

(11)

This magnitude represents the potential generated through several charges \( q_i \) placed (at vacuum) at \( r_i' \) and measured in \( r \). This theoretical magnitude is relative; thus, we can only measure differences in the potential between pairs of points, and there is not any point where we can define an absolute value. To overcome these flaws, we define a value of zero as infinity. The main advantage of potential is the scalar character, as we can perform easier calculations and subsequently convert these results to the real physical magnitude \( E \) using Equation 10.

There is a powerful approach in electromagnetism called multipolar potential development. Using this approach, we can decompose the potential generated from any source in different polar components, which retain the main features of source distribution and the distance to the point of the field. Therefore, using the most adequate polar component of our system, we can simplify the (usually) extremely tedious and difficult calculations.
The formal features of the multipolar approach are out of the scope of this study, but these features can be represented using this general expression (Wangness 1986; Pastor et al., 2002):

$$\phi(r) = \phi_M(r) + \phi_D(r) + \phi_Q(r) + \cdots$$  \hspace{1cm} (12)

where \(M, D\) and \(Q\) represent monopole, dipolar and quadripolar components, respectively. For systems, such as those studied by Clinical Neurophysiology, orders greater than dipolar are not of interest. Therefore, we can focus on the first two simpler components of this approach.

The following equations show the formal expressions for both terms.

$$\phi_M(r) = \frac{q}{4\pi \varepsilon_0 r},$$ \hspace{1cm} (13)

$$\phi_D(r) = \frac{\vec{p} \cdot \vec{r}}{4\pi \varepsilon_0 r^2}.$$ \hspace{1cm} (14)

In these expressions, \(Q\) represents the monopolar moment, defined (for discrete sources) as:

$$Q = \sum_i q_i,$$ \hspace{1cm} (15)

and \(p\) is the dipolar moment, defined as:

$$\vec{p} = \sum_i q_i \vec{r}_i,$$ \hspace{1cm} (16)

where \(r_i\) represent the places for charges \(q_i\). As shown in Equation 14, there is a dot product for \(p \cdot r\). Therefore, we can simplify this equation:

$$\phi_D(r) = \frac{p \cos \theta}{4\pi \varepsilon_0 r^2},$$ \hspace{1cm} (17)

where \(q\) represents the angle between the dipolar moment \(p\) and the radio-vector of the field. When two charges are equal in magnitude (\(q\)) and opposite in sign and placed at \(d\) cm apart, the dipolar moment is \(p = qd\), oriented from \(-q\) to \(+q\).

Traditionally, theoretical considerations and some empirical facts have favoured the dipolar approach in neurophysiological recordings in humans. It is assumed that there is a charge conservation strictly applied to the CNS; therefore, where a charge source appears, a sink of the same magnitude must counterbalance the appearance of the charge. This model has been empirically corroborated in several models on both microscopic and macroscopic levels (Ramon et al., 2009; Plummer et al., 2010; Campi et al., 2011; Lelic et al., 2012). A dipolar model has been proposed between the upper and lower layers of the cortex (Dümpelman et al., 2012). This model assumes that a source (sink) in a distal location from an apical dendrite of a pyramidal neuron must have a sink (source) of the same magnitude in the soma. Nevertheless, recent data have shown that cortical sources cannot be precisely represented through a single equivalent dipole, and the existence of monopolar components must also be considered at the mesoscopic level (Riera et al., 2012).

Thus, there are several considerations about this model. First, this approach captures only a portion of the actual definition of potential (equation 11) and cannot be considered as true potential. Secondly, although there is a charge counterbalance in a real system in the CNS, the simple soma-dendrite dipolar model (SDDM) is not completely true.
To approach to the SDDM, we have to implement the core-conductor theory and the related cable theory of current propagation. The application of Kirchhoff’s laws to the core-conductor model network generates the cable equations. These equations are the basic mathematical relationships used to study the electrical response of a uniform fibre to subthreshold stimuli (Plonsey & Barr, 2007). The model is represented in the next figure.

Figure 7: Linear core-conductor model for a single fibre of radius a. A schematic electrical circuit of membrane is superimposed. \( I_e \) and \( I_i \) are extra and intracellular currents, respectively, while \( \phi_e \) and \( \phi_i \) represent potentials for the same compartments, \( I_m \) means transmembrane current density and \( \Delta x \) refers to a length unit. The intracellular and extracellular resistances are given as \( r_i \) and \( r_e \), respectively.

The extra and intracellular axial currents are associated with the potentials through the following expressions:

\[
\frac{\partial \phi}{\partial x} = -r_e I_e, \quad \frac{\partial \phi}{\partial x} = -r_i I_i
\]  

(18)

The intracellular axial current decreases along the axis path because there is a current flowing from the fibre through the membrane (\( I_m \), in A/cm). Thus, the relationship between intracellular and transmembrane current is expressed as:

\[
\frac{\partial I_e}{\partial x} = -I_m
\]  

(19)

The transmembrane potential (\( V_m \)) is the difference among intra and extracellular potential; therefore, from Equation 18, we obtain the following equation:

\[
\frac{\partial V_m}{\partial x} = \frac{\partial \phi_i}{\partial x} - \frac{\partial \phi_e}{\partial x} = -r_i I_i + r_e I_e
\]  

(20)

However, from Kirchhoff’s first law, we know that \( I_i + I_e = 0 \); therefore, the above equation can be written as:

\[
\frac{\partial V_m}{\partial x} = -(r_i + r_e) I_i
\]  

(21)

Assuming that \( r_i >> r_e \) and using equation 21, we obtain the equation:
\[
\frac{1}{r_i} \frac{\partial^2 V_m}{\partial x^2} = -i_m \tag{22}
\]

This important equation relates the transmembrane current density along the axial path (typically not measured) with the transmembrane voltage (the magnitude is typically measured). Transmembrane voltage can be obtained from the cable equation (Davis & Lorente, 1947):

\[
v_m(X, T) = \frac{r_i I_0 \lambda}{4} \left[ e^{-X} \text{erfc} \left( \frac{X}{2\sqrt{T}} \right) - e^{-X} \text{erfc} \left( \frac{X}{2\sqrt{T} + \sqrt{T}} \right) \right]. \tag{23}
\]

Equation 23 is an extraordinary equation whose meaning we will try to clarify. Notably, this equation is dimensionless, as the dimensions of space (x) and time (t) have been replaced with the dimensionless variables:

\[
X = \frac{x}{\lambda}; \quad T = \frac{t}{\tau_m}. \tag{24}
\]

The constant \( \lambda \) (cm) or length constant and \( \tau_m \) space (s), the time constant of the membrane can be determined using these expressions. The magnitudes observed in the first fraction are axial resistance \((r_i = \Omega/cm)\), the injected current \((I_0 = \text{A})\) and the constant \(\tau_m\) and \(\lambda\) view. The expression erfc \((x)\) is the complementary error function. This equation can be solved easily for simple theoretical situations stationary, yielding the potential along the dendrite \((V_m(x))\), in response to a current injection, resulting in a maximum potential at the injection site \((V_0)\):

\[
V_m(x) = V_0 e^{-x/\lambda}. \tag{25}
\]

This expression shows a single exponential decay for the voltage, as the injected current flows from the dendrite at a constant rate. Therefore, we can use this expression, obtained from an extremely simplified (and not real) situation, in Equation 23 to obtain the transmembrane current density along the fibre path.

The numerical model demonstrates that the amplitudes of the spikes for dipolar and monopolar sources are similar for points close to the source. However, when the distance increases, the difference between dipolar and monopolar spikes increases and the dipolar spike becomes more similar to the quadripolar source.

**Figure 8:** Spikes generated using different current sources configurations at different distances from the source, indicated above the traces. Blue: monopolar source; red: dipolar source; and black: quadripolar source.
Another important fact obtained from this model is that we cannot resolve Equation 11 with an error $< 5\%$ when using spikes generated from a dipolar or a quadrupolar current source. Thus, the important point of this analysis is that the current density along the fibre cannot be strictly considered as a dipole, with an equal source and sink located far apart, and a current (and voltage, consequently) that exponentially decays along the fibre. This analysis particularly applies to the cell soma and dendrites, which are not myelinated, and the sources generated in the cerebral cortex. Therefore, this monopolar approach could be used in some cases, which remain to be accurately determined.

4 Discussion

In previous studies (Pastor et al., 2010; Herrera-Peco et al., 2010), we showed that the administration of etomidate is a safe and efficient pharmacological method for patients suffering from TLE during presurgical evaluation. However, the changes observed in regional CBF, specifically in areas associated with the EZ, are more difficult to explain.

Traditionally, several different drugs are used to induce brain activity. As previously discussed, it is clinically important that the patient tolerate the drug side effects (Herrera-Peco et al., 2009). For etomidate, the primary side effects observed were myoclonus and moderate pain. Etomidate is a very fast acting agent, inducing a loss of consciousness within 10 s and a state of anesthesia in 3-5 min and is rapidly eliminated due to hepatic extraction (Van Hamme et al., 1978). Therefore, etomidate has optimal pharmacokinetics characteristics to induce the EEG activity. Moreover, it has been described as a safe hypnotic (Vanlersberghe & Camu, 2008). Indeed, no significant hemodynamic effects have been observed (Gooding et al., 1979), although higher doses $(0.35 \pm 0.17 \text{ mg/kg})$ induce tachycardia and increase the mean arterial pressure (Arden et al., 1986).

In contrast to other anaesthetics, etomidate has a specific target at clinical concentrations (Voss et al., 2008). Indeed, etomidate almost exclusively acts on the the $\beta_2$ and $\beta_3$ subunits of the GABA$_A$ receptor. This specificity might be important for diagnosis in pre-surgical evaluation. The exact mechanism by which etomidate activates the irritative area is not completely understood. However, several lines of evidence might explain this effect. Studies in cultured astrocytes have shown that etomidate inhibits glutamate uptake, increasing the extracellular glutamate concentration to a level that can escape the synaptic cleft and activate extra-synaptic receptors. As a consequence, irritative activity would be increased (Räth et al., 2008). However, an examination of slices obtained from epileptic patients revealed a decrease in the reversal potential for Cl$^-$ anions (Cohen et al., 2002). This change could induce depolarisation, not hyperpolarisation, following GABA release, thereby driving irritative activity.

Several biophysical properties of spontaneous and pharmacologically induced activities are similar, including the $i_{\text{equiv}}$, scattering and rate-to-monopolar fitting. However, in this study, we addressed two important questions concerning topography and theoretical considerations about the current-source model. First, we showed that interictal, ictal and etomidate-induced activities greatly overlap, indicating that the biophysical mechanisms are similar, and the cortical areas where all types of activity appear are likely the same or closely related. This fact suggests that this technique can be used to better define the region resected during surgery. Theoretically, the current-source model demonstrates that monopolar and dipolar sources are similar in the vicinity of the source; therefore, we can consider this monopolar model as a good approach to a dipolar source. However, when the distance from the source increases, the potential induced through both configurations clearly differs, suggesting that a dipolar source cannot be fitted to a
set of potentials obtained from a monopolar source at a certain distance. However, neither monopolar nor dipolar theoretical sources can be fitted to real current sources from the cortex (Riera et al., 2012). Cortical macro-columns are a complex set of current sources (Nunez & Srinivasan, 2009), and the best theoretical model will likely be different for different configurations. Notably, there is a high degree of accuracy (> 95%) for most of the sources concerning the monopolar model in current sources from the mesial temporal lobe. Thus, we cannot consider this fact as a demonstration, as this empirical fact emphasises the use of a monopolar approach to bioelectrical sources in humans. Indeed, much more work remains, both theoretical and empirical, before completely elucidating this aspect.

Etomidate perfusion induces a brief increase in the amplitude and frequency of brain activity, recorded using scalp EEG, followed by generalised high-voltage delta activity. The latter activity resembles that observed during non-rapid eye movement (NREM) delta sleep. Etomidate is a potent GABA agonist, and GABA plays an important role in NREM delta sleep (Gottesmann, 2002). These results might explain the increased thalamic regional CBF induced by etomidate. Although we cannot exclude the fact that increases in CBF in the basal ganglia might be associated with ictal patterns in epileptic patients (Norden & Blumenfeld, 2002). Traditionally, an intense increase in regional CBF is a hallmark of partial-onset seizures, potentially reflecting the increase in regional synaptic activity and changes in neurotransmission. During the ictal SPECT, the $^{99m}$Tc-HMPAO infusion is performed briefly after the seizure starts, and a delay must be overcome before the radiotracer reaches the brain. Thus, ictal SPECT, likely shows an increase in regional cerebral perfusion associated with the seizure (Van Paesschen, 2004), and almost certainly indicates propagation from the area of ictal onset. Indeed, a true ictal SPECT recording has corroborated the increase in CBF induced through epileptic activity (Pastor et al., 2008).

Considering the significant increase in the IED induced through etomidate, we expected an increase in the regional CBF in the IOZ. Surprisingly, however, we observed a relative decrease in the regional CBF in the posterior hippocampus of the EZ. Recently, we showed that there is a consistent and highly significant reduction of micro-blood vessels, particularly in the CA1 field in the sclerotic hippocampus (Kastanauskaite et al., 2009). This reduction might be associated with the relative inability of the epileptic posterior hippocampus to increase CBF locally in response to etomidate. However, it is also reasonable to conclude that etomidate increases the CBF more significantly in the structures spared through epileptic discharges. Although further experiments are needed to fully elucidate the mechanisms underlying etomidate-induced increases in CBF and brain activity, from a clinical point of view, these findings demonstrate significant methods of pre-surgical evaluation. Indeed, differential SPECT perfusion could be used to identify the EZ in TLE patients with a dubious lateralisation.

To conclude, etomidate-induced bioelectrical activity in mesial structures of patients under presurgical evaluation is a powerful and confident technique to validate hypotheses concerning the location of the epileptic zone. Moreover, this activity facilitates the identification of different patients regarding the activity topography, and we can use this technique for new surgical approaches, e.g., high-definition radiosurgery, in patients with well-localised sources.

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