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ORIGINAL STUDY

Changes Over Time of the Refractory Properties Measured from ECAP in Pulsar CI[100] Cochlear Implant Recipients

Isaac Alvarez, Angel de la Torre, Joaquín Valderrama, Cristina Roldán, Manuel Sainz, José Carlos Segura, José Luis Vargas

Department of Signal Theory, Telematics and Communications, University of Granada, Spain (IA, AT, JV, JCS)
Department of Surgery and its Specialities, University of Granada, Spain. ENT Service, San Cecilio University Hospital, Granada, Spain (CR, MS, JLV)

Objective: The aim of this work is to present a longitudinal study of the refractory properties of the population of neurons involved in the generation of the evoked compound action potential (ECAP).

Materials and Methods: The refractory properties of 12 subjects implanted with the Med-El Pulsar CI[100] cochlear implant system have been examined by recording and analyzing ECAP responses collected under the masker-probe paradigm.

Results: Our preliminary results show a statistically significant decrease of the refractory period and a statistically significant increment of the amplitudes of the ECAP responses after 3 months of cochlear implant experience.

Conclusion: The evolution of the parameters describing ECAP responses reveals a decrease of the refractory period and an increment of the amplitudes associated to the use of the cochlear implant system. These changes take place in the first 3 months after the first switch-on of the cochlear implant processor and after this time the refractory period and the amplitudes tend to be stable.

Keywords: Electrically Evoked Compound Action Potential, ECAP, refractory period, cochlear implant

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Introduction

Current cochlear implant systems allow electrically evoked compound action potentials (ECAP) to be recorded [1,2]. These measurements represent the compound action potential associated with the synchronous firing of the neurons in the spiral ganglion evoked by electrical stimulation. The typical neural response waveform is characterized by a negative peak N1 (with a latency of 200-400µs) followed by a positive peak P2 (with a latency of 500-700µs). The electrically evoked compound action potentials are nowadays widely used in clinical and research applications [3-5].

Previous studies in cats examined the refractory properties of the population of neurons involved in the generation of the ECAP response by using a two-pulse masker-probe paradigm. They found a reduced excitability if inter pulse intervals of < 5ms were used and an absolute refractory period (or refractory period of the fastest neuron) between 0.3ms [6] and 0.5ms [7]. Analyzes of the ECAP responses have also been used to infer the refractory properties of cochlear implant users. Brown [8] recorded ECAP data from 11 subjects implanted with the Ineraid cochlear implant and found important differences across subjects in the refractory properties. Morsnowski [9] analyzed the auditory nerve's refractory properties of 14 Nucleus 24 cochlear implant users and found an absolute refractory period of 390µs and a time constant of the recovery function of 425µs.

The refractory properties (and more specially, the refractory period) limit the ability of auditory nerve to

Corresponding address:
Isaac Alvarez
Department of Signal Theory, Telematics and Communications, University of Granada, Spain
C/ Periodista Daniel Saucedo Aranda s/n 18071 (Granada-Spain)
Phone: +34-958 241521 • Fax: +34-958 240831
E-mail: isamaru@ugr.es

accurately encode temporal information [10]. For this reason, measurements related to the refractory properties could provide a reasonable index to estimate the potential benefit that can be obtained from the cochlear implant by a patient [8]. Longitudinal studies analyzing the changes in the refractory properties induced by the use of the cochlear implant are therefore required. Lai [11] analyzed ECAP data from 63 subjects implanted with the Nucleus 24 cochlear implant system and they reported that the patients generally exhibited little changes over up to 4 years, presenting some of them larger changes within the first 15 months. Tanamati [12] studied ECAP features in 13 children during the first year of Nucleus 24 cochlear implant use and found a statistically significant raise of the amplitude, but not significant changes for latency or recovery time were observed.

This paper presents a novel longitudinal study of the refractory properties of 12 Med-El Pulsar CI^{100} cochlear implant users. ECAP responses are used to analyze the changes over time of the refractory properties of the population of neurons involved in the generation of these evoked potentials. Since there are substantial differences of Med-El implant systems compared with other cochlear implant systems [13], the results provided by our study provide interesting information to be compared with studies based on other cochlear implant systems. This paper is organized as follows. Section 2 describes the data acquisition procedure for ECAP recording and the estimation of the refractory properties. Section 3 analyzes the changes across time of the refractory properties of the patients considered in this study. Finally, section 4 summarizes the main contributions.

Materials and Methods

Subjects

Twelve deafened patients, 4 females and 8 males, aged from 0.5 to 65 years participated in this study. All subjects were implanted with the Med-El Pulsar CI^{100} [13,14] implant device at San Cecilio University Hospital, Granada (Spain). Details of the study population are summarized in Table 1. Of a total of 144 electrodes (12 electrodes per patient), 125 were activated. Each patient underwent at least three ECAP recording sessions. The first recording was obtained immediately before the first fitting of the cochlear implant speech processor. In each session one apical electrode, one medium electrode and one basal electrode were evaluated.

Table 1. Profiles of all subjects in this study.

Id	Sex	Active electrodes	Age at implantation (yrs)	Recording sessions
1	M	12	0.51	4
2	M	11	1.16	4
3	F	9	1.92	3
4	M	9	2.00	5
5	F	9	2.67	3
6	M	12	2.75	3
7	M	11	2.75	4
8	M	9	15.16	4
9	F	10	33.51	4
10	M	10	47.51	4
11	M	12	65.08	3
12	F	11	65.25	3

Each prospective subject was given an informed-consent form explaining the purpose and procedures involved in the study. If the patient agreed to participate, the form was signed and the subject was provided with a copy. The experimental protocol was approved by the Ethic Committee of San Cecilio University Hospital, Granada (Spain).

ECAP acquisition

The ECAP recording system integrated into the Med-El Pulsar CI[100] cochlear implant system allows different configurations to be used for stimulation and recording. The stimulation configuration used in this study was set up in masker-probe mode [6,8,15]. This mode acquires three registers corresponding to three different stimulation patterns. Figure 1 shows the stimulation patterns for obtaining each register: S_a, S_b and Sc. In order to obtain each register, we averaged 50 responses for each stimulation pattern by the conventional ensemble-averaging method. The response is measured after a blanking time interval of 125µs. The stimulation rate used was 50Hz (a response was recorded every 20ms). Biphasic pulses were set up with durations of each phase between 30 and 45µs, and amplitudes smaller than 1200µA. The first biphasic pulse of the stimulation pattern is the masker and the second one is the probe pulse. The "Inter Pulse Interval" (IPI) represents the time interval between both pulses. In this study, IPI was ranged from 0.3 to 8ms.

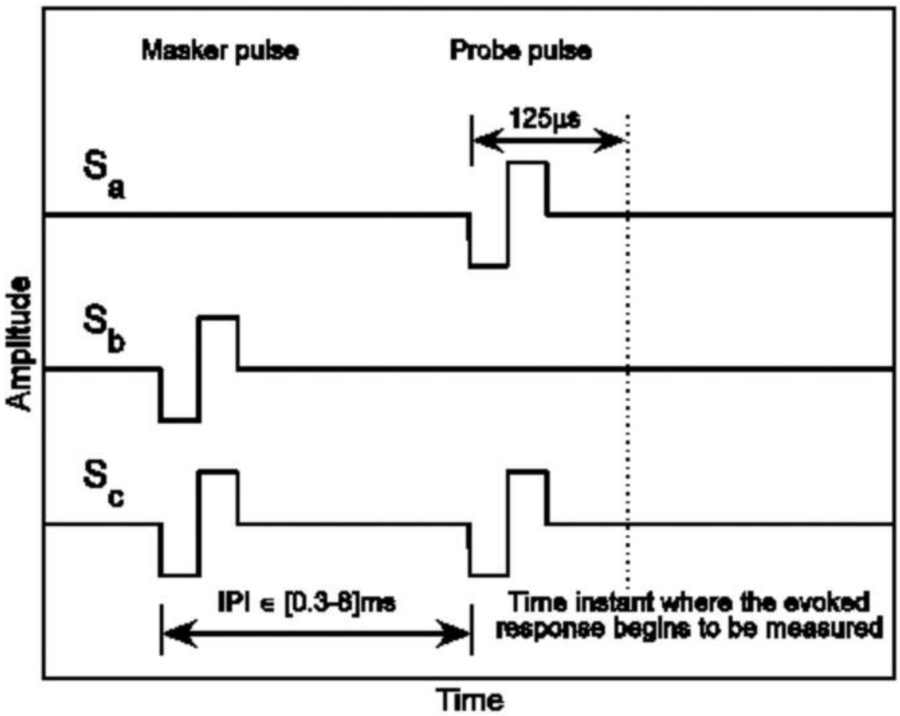

Figure 1. Stimulation patterns associated with the masker-probe paradigm.

Assuming the linearity of the system, we can describe the register R_a corresponding to the stimulation pattern S_a (containing only the probe pulse) as:

$$R_a \approx A_p + B_p \quad (1)$$

where A_p and B_p are the artifact and the biological response corresponding to the probe pulse, respectively.

Register R_b contains the artifact and the biological response associated with the masker pulse (A_m and B_m, respectively):

$R_b \approx A_m + B_m$ (2)

Register Rc contains the artifacts associated with the masker and probe pulses (A_m and A_p, respectively) and the biological response associated with the masker pulse (B_m). If IPI is smaller than the refractory period of the fastest neurons, all neurons remain in a refractory state when the probe pulse is presented and register Rc does not contain the biological response of the probe pulse. On the other hand, if IPI is higher than the refractory period of the slowest neurons, the register R_c contains the full biological response of the probe pulse [8,16]. Depending on the inter pulse interval, the biological response to the probe pulse changes, and the content of register R_c can be expressed according to the following equation:

$R_c(\tau) = A_m + A_p + B_m + B_p(\tau)$ (3)

where $B_p(\tau)$ is the biological response to the probe pulse for an inter pulse interval τ. The following limits are verified:

(4)

According to these definitions and assuming the linearity of the system, the masker-probe register (R_{mp}) [6,8] combines the registers R_a, R_b and R_c:

$$R_{mp}(\tau) = R_a + R_b - R_c(\tau) = A_p + B_p + A_m + B_m - A_m - A_p - B_m - B_p(\tau) = B_p - B_p(\tau)$$

(5)

The biological response associated with the probe pulse for a given value of IPI ($\tau = \tau i$) can then be calculated as:

(6)

Characterization of the refractory properties

Figure 2a shows a series of ECAP responses recorded under the masker-probe paradigm (according to equation 6) for different inter pulse intervals (for one of the patients included in this study). From the amplitude of the ECAP responses, the recovery function (amplitude as a function of the IPI) can be represented (Figure 2b).

The behavior of the recovery function is similar to that described for other cochlear implant systems [9]: the amplitude is null for IPI smaller than a threshold value; then, a fast growth is observed; finally, for high IPI values, the amplitude tends to saturate. Since all neurons are in refractory state for small IPI values, a null amplitude portion is expected in the recovery function for IPI values smaller than the refractory period of the fastest neuron involved in the generation of the ECAP response. For this reason, the threshold of IPI value for which the recovery function starts to grow is usually interpreted as the refractory period of the fastest neuron [9,10]. As the IPI increases, more and more neurons have a refractory period smaller than the IPI and contribute to the ECAP response. For very high IPI values, all neurons have a refractory period smaller than the IPI and, since all the neurons contribute to the ECAP response, the amplitude tends to saturate.

If the ECAP response is assumed to be the result of the additive contribution of all the neurons that are not in refractory state for a given IPI value, then the recovery function normalized to the maximum value could be interpreted as the cumulative density function of refractory periods for the population of neurons involved in the generation of the ECAP response.

In order to characterize the refractory properties of the population of neurons, we have modelled the recovery function by fitting an exponential model according to the following expression [9]:

(7)

where A_0 represents the amplitude limit for very high IPI values, τ_0 is the IPI threshold (that can be interpreted as the refractory period of the fastest neuron) and α is the constant of the exponential fitting. Based on this model, the recovery function can be parameterized with three parameters (A_0, τ_0 and α).

From equation 7 the cumulative density function of refractory periods can be obtained by normalizing:

(8)

and the probability density function of refractory periods can be obtained as:

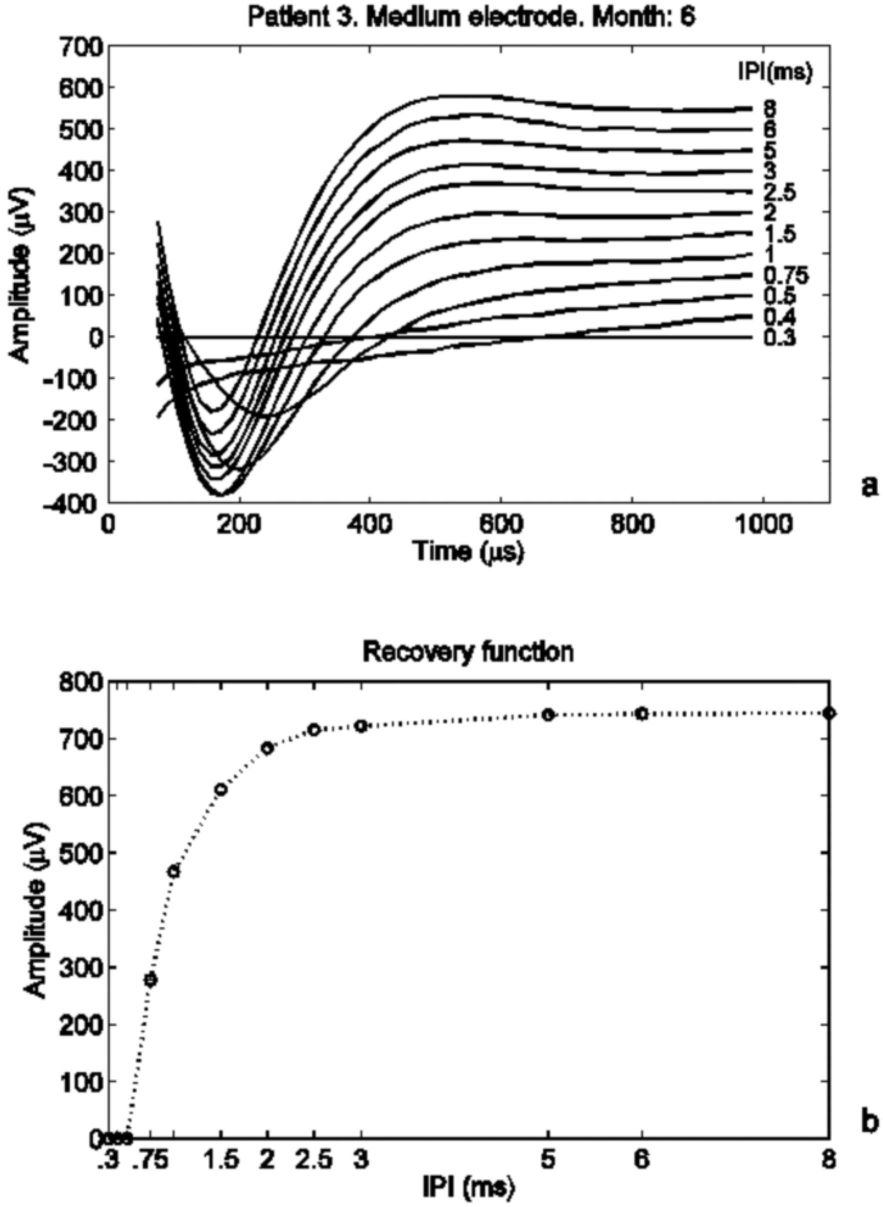

Figure 2. ECAP responses obtained for different values of IPI (upper panel) and the corresponding recovery function (lower panel).

(9)

Finally, from equation 9, the mean and the standard deviation of refractory periods can be estimated as:

(10)

Figure 3a presents the function A(τ) that optimally adjust (using a least square criterion) the measured recovery function according to the equation 7. The probability density function of the refractory periods is represented in Figure 3b. In order to study the refractory properties and their evolution over time for the population of patients included in this study, each recovery function has been characterized by the following parameters: A_0 (amplitude of the ECAP response for high IPI values); τ_0 (refractory period of the fastest neuron); τ_{20}, τ_{50} and τ_{80} (20th-, 50th- and 80th- percentiles, respectively); and finally, μ_τ and σ_τ (mean and standard deviation of the refractory period for the population of neurons involved in the ECAP response, respectively).

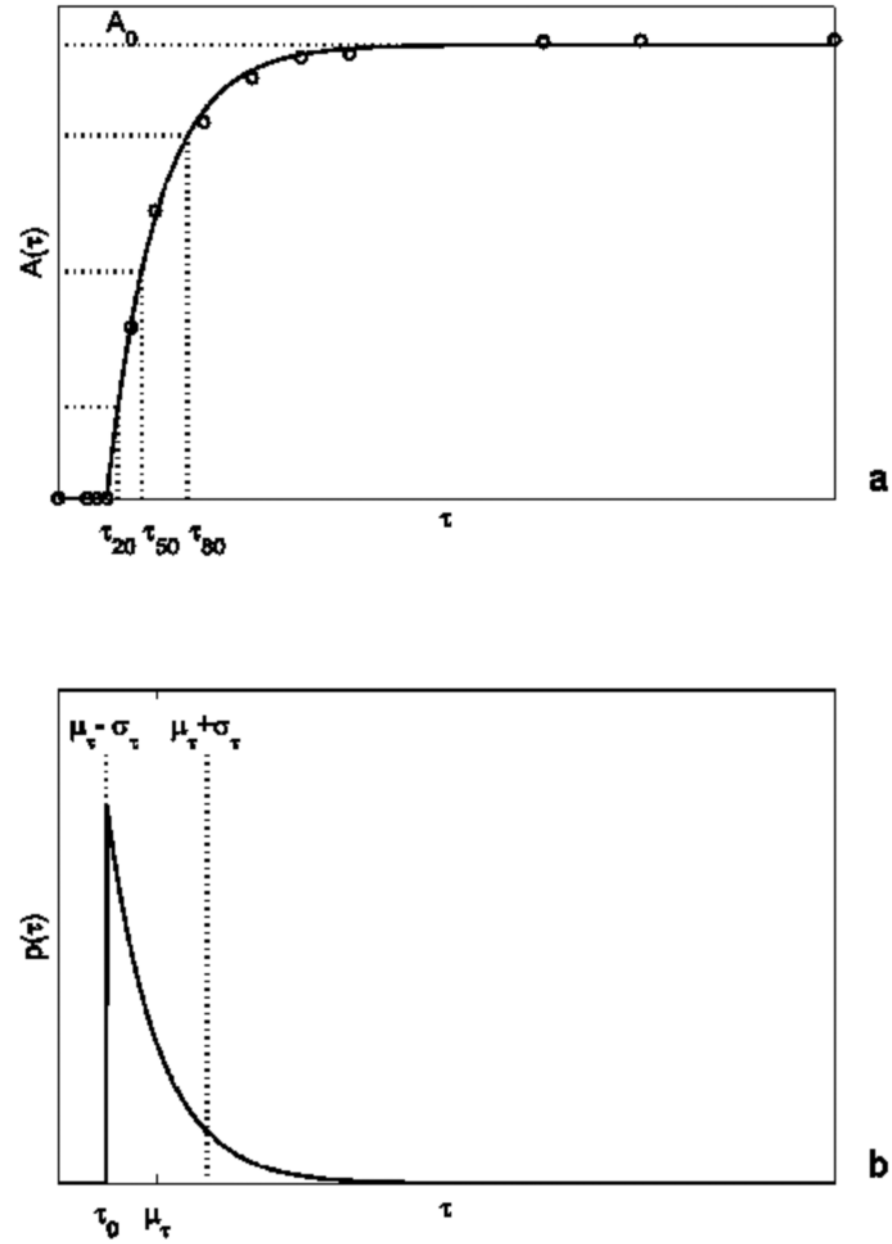

Figure 3. Fitted function $A_{(\tau)}$ (upper panel) and probability density function $p^{(\tau)}$ (lower panel) of the refractory periods for the same patient shown in Figure 2. The parameters A_0, τ_0, τ_{20}, τ_{50}, τ_{80}, μ_τ and σ_τ are indicated.

Results

Figure 4 shows the variations over time of the parameters A_0 (4a), τ_0 (4b), $\mu\tau$ (4c) and $\sigma\tau$ (4d) for the average patient. The plots represent the evolution for apical (circles), medium (squares) and basal (diamonds) electrodes, averaged for all the patients included in this study. We acquired the recovery function of each electrode immediately before the first switch-on of the cochlear implant processor (month 0) and for at least in two months more. For the rest of months, a linear interpolation was used. We can observe that the amplitude of the evoked response (parameter A_0) is increased with the use of the cochlear implant. The refractory period of the fastest neuron (parameter τ_0) is higher during the first months and decreases until a constant value is reached at approximately 3-4 months post first switch-on of the cochlear implant processor for apical and medium electrodes and approximately at the sixth month for basal electrodes. It can also be observed that the mean of the refractory periods (parameter μ_τ) for the population of neurons analyzed in this study is reduced with the use of the cochlear implant. No clear tendency is observed for the standard deviation of the refractory periods (parameter σ_τ). No statistically significant differences were found between apical, medium and basal electrodes ($p>0.05$ in all cases), except when comparing apical and basal electrodes for the parameters τ_0, τ_{20}, τ_{50}, τ_{80} and μ_τ ($p<0.05$). Table 2 shows the mean and the standard deviation for all the parameters considered in this study, evaluated in three different moments: month 0 (first switch-on), and months 3 and 6 post switch-on. We can observe that the parameter A_0 is increased and the rest of parameters (τ_0, τ_{20}, τ_{50}, τ_{80}, μ_τ and σ_τ) are reduced with the use of the cochlear implant. After six months of cochlear implant experience, the mean value of the refractory period of the fastest neuron is 0.57ms, the mean of refractory periods is 1.32ms and the 80% of neurons present a refractory period smaller than 1.78ms.

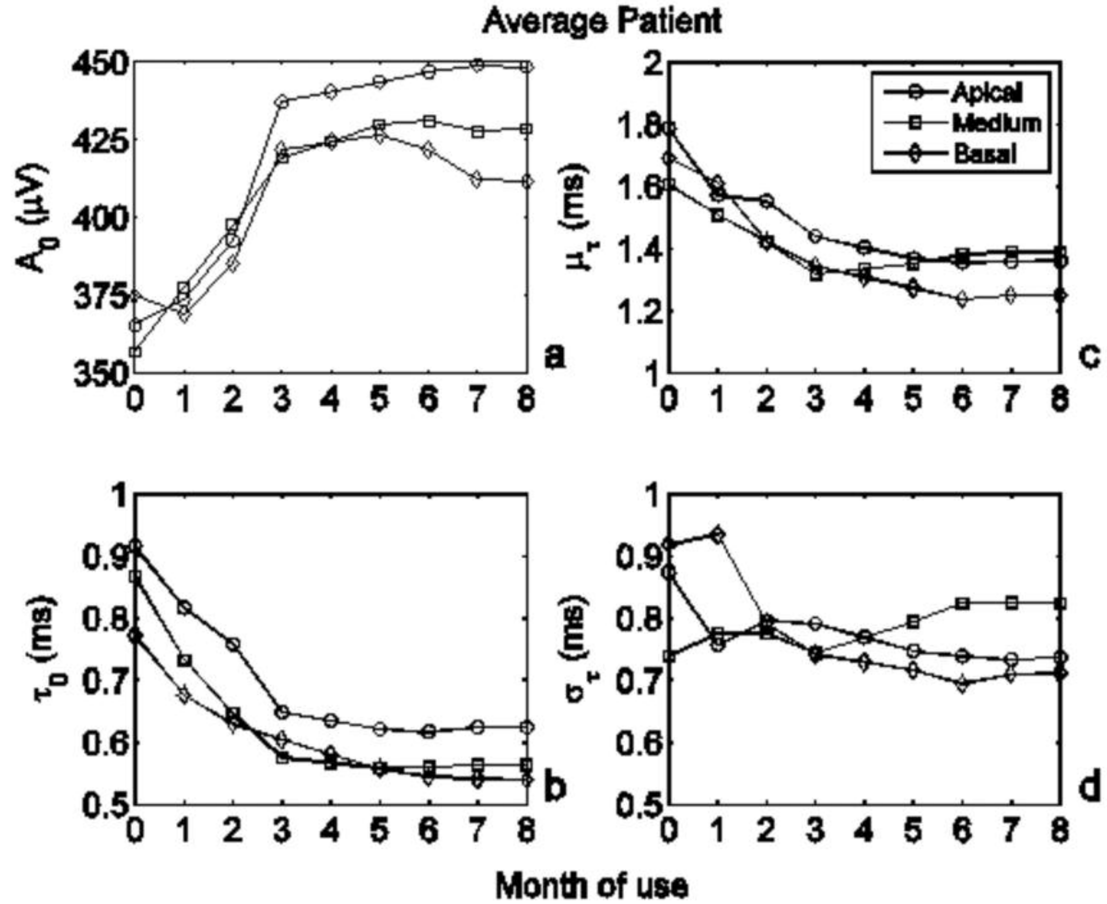

Figure 4. Variations over time of A_0, τ_0, μ_τ and σ_τ parameters for the basal, medium and apical electrodes of the average patient.

Table 2. Mean and standard deviation of the parameters considered in this study for the months 0 (switch-on of the cochlear implant processor), 3 and 6.

Parameters	month	mean	std dev
A_0 (μV)	0	365.50	172.17
	3	426.01	197.53
	6	433.15	175.83
τ_0 (ms)	0	0.85	0.33
	3	0.61	0.19
	6	0.57	0.17
τ_{20} (ms)	0	1.04	0.31
	3	0.78	0.19
	6	0.74	0.17
τ_{50} (ms)	0	1.44	0.40
	3	1.14	0.29
	6	1.10	0.27
τ_{80} (ms)	0	2.21	0.75
	3	1.83	0.60
	6	1.78	0.58
μ_τ (ms)	0	1.69	0.50
	3	1.37	0.39
	6	1.32	0.37
σ_τ (ms)	0	0.84	0.48
	3	0.76	0.38
	6	0.75	0.38

In order to analyze the statistical significance of the changes across time, a Wilcoxon rank sum test [17] was applied. Table 3 (left panel) shows the p-values when comparing the proposed parameters for the first switch-on (month 0) and the months 3 and 6 post switch-on. We can observe that the increased of the parameter A_0 with the use of the cochlear implant is not statistically significant ($p>0.05$ in all cases). The parameters (τ_0, τ_{20}, τ_{50}, τ_{80} and μ_τ) are statistically significant ($p<0.05$) when comparing the months 3 and 6 respect the month 0, but not for the month 6 with respect to the month 3. We can also observe that the changes across time of the σ_τ parameter (or constant α in the exponential fitting) are not statistically significant. The small significance levels (p-values) indicated by these global results are due to a great inter-patient variability [3,8]. To deal with this issue, a normalization procedure is proposed. Normalization is performed by dividing each parameter by the average level of the electrode across the different ECAP recordings sessions. Table 3 also shows the p-values for the normalized parameters (right panel). We can observe that no statistically significant differences for the standard deviation of refractory periods (parameter σ_τ) were found. However, smaller significance levels (p-values) were obtained for the rest of parameters after applying normalization for removing inter-patient variability. A statistically significant raise of the amplitude of the evoked response (parameter A_0) and a statistically significant decrease of parameters τ_0, τ_{20}, τ_{50}, τ_{80} and μ_τ were observed. All these changes across time were statistically significant at 3 months after the first switch-on of the cochlear implant processor. Changes from 3 to 6 months of cochlear implant experience were found to be not significant.

Table 3. p-values provided by Wilcoxon Rank Sum test when comparing the parameters (left panel) for the months 0, 3 and 6 post switch-on of the cochlear implant processor. The normalized parameters are also indicated (right panel).

	M3-M0	M6-M0	M6-M3		M3-M0	M6-M0	M6-M3
A_0	0.188	0.107	0.765	A_0-norm	5.23e-4	1.73e-5	0.166
τ_0	1.49e-3	1.87e-4	0.412	τ_0-norm	9.01e-8	1.02e-9	0.111
τ_{20}	3.00e-4	2.86e-5	0.437	τ_{20}-norm	2.74e-9	6.24e-11	0.193
τ_{50}	8.92e-4	1.73e-4	0.589	τ_{50}-norm	7.76e-8	1.74e-9	0.336
τ_{80}	1.97e-2	6.99e-3	0.719	τ_{80}-norm	1.23e-4	5.51e-6	0.656
$\mu\tau$	4.23e-3	1.11e-3	0.660	μ_T-norm	5.08e-7	1.52e-8	0.468
$\sigma\tau$	0.573	0.408	0.875	σ_T-norm	0.195	0.111	0.933

Discussion

This study uses the masker-probe paradigm to estimate the behavior of the refractory properties for the population of neurons involved in the generation of the evoked compound action potential and its evolution over time after the first switch-on of the cochlear implant. A longitudinal study over 12 deafened patients implanted with the Pulsar CI[100] cochlear implant system reveals that the amplitude of the evoked response increases and the refractory period decreases with the use of the cochlear implant. The dispersion of refractory periods of the population of neurons activated by the same electrode does not present statistically significant changes across time.

No statistically significant differences were found among apical, medium and basal electrodes in this preliminary study, except when comparing apical and basal electrodes for the refractory period of the fastest neuron, the 20th-, 50th- and 80th- percentiles and the mean of refractory periods. The refractory period of the fastest neuron decreases until a constant value is reached at approximately 3-4 months of cochlear implant experience for apical and medium electrodes and approximately at the sixth month for basal electrodes. Although it is assumed that the basal electrodes exhibit a higher degree of degradation than the apical ones, a statistically significant higher value of the refractory period of the fastest neuron was found for apical electrodes in this preliminary study.

The changes observed in the population of neurons between the instant of switch-on of the cochlear implant processor and the third and sixth months are statistically significant. Our results are in accordance with other studies related with the fitting of the cochlear implant processor. Some authors showed that fitting levels in the Nucleus device were not stable until 6-12 months after cochlear implant activation [18,19], while other studies considered stable fitting levels with 3-4 months of cochlear implant experience [4,5].

At the sixth month after the activation of the cochlear implant processor, the 80% of the population of neurons involved in generation of the ECAP responses exhibit a refractory period smaller than 1.78ms, the mean value of the refractory period of the fastest neuron is 0.57ms and the mean of refractory periods is 1.32ms. These preliminary results are slightly higher than those reported in other studies [9,10]. The results presented in this study are based on a small sample and therefore more statistic is required to perform a more detailed analysis of the relationship between neural refractoriness and cochlear implant experience.

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