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Neuromonitoring of cochlea and auditory nerve with multiple extracted parameters during induced hypoxia and nerve manipulation

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Abstract

A system capable of comprehensive and detailed monitoring of the cochlea and the auditory nerve during intraoperative surgery was developed. The cochlear blood flow (CBF) and the electrocochleogram (ECoChGm) were recorded at the round window (RW) niche using a specially designed otic probe. The ECoChGm was further processed to obtain cochlear microphonics (CM) and compound action potentials (CAP). The amplitude and phase of the CM were used to quantify the activity of outer hair cells (OHC); CAP amplitude and latency were used to describe the auditory nerve and the synaptic activity of the inner hair cells (IHC). In addition, concurrent monitoring with a second electrophysiological channel was achieved by recording compound nerve action potential (CNAP) obtained directly from the auditory nerve. Stimulation paradigms, instrumentation and signal processing methods were developed to extract and differentiate the activity of the OHC and the IHC in response to three different frequencies. Narrow band acoustical stimuli elicited CM signals indicating mainly nonlinear operation of the mechano-electrical transduction of the OHCs. Special envelope detectors were developed and applied to the ECoChGm to extract the CM fundamental component and its harmonics in real time. The system was extensively validated in experimental animal surgeries by performing nerve compressions and manipulations.

1. Introduction

1.1. Neuromonitoring during surgery of the posterior fossa

Neuromonitoring of cochlear nerve and auditory pathway for surgeries involving structures in the posterior fossa has been used for over 20 years (Fischer and Bertrand 1993, Winzenburg *et al* 1993, Moller 1996, Fischer *et al* 1997, Colletti and Fiorino 1998, Guerit 1998, Yokoyama *et al* 1999, Mullatti *et al* 1999, Yamakami *et al* 2003). Typically, such monitoring is performed through three techniques: the monitoring of auditory brain stem responses (ABRs), direct recording of cochlear nerve action potential (CNAP) and electrocochleogram (ECoChGm). ABRs are far-field responses which signal the functioning of the ascending auditory pathway. ABRs have very low signal-to-noise ratio (SNR) and require a high number of sweeps (around 1024 in good environmental conditions and 2048 in difficult environments such as the

operating room or ICU) or advanced filtering (Bertrand *et al* 1990, Fischer and Bertrand 1993, Moller 1996) to grant interpretable responses. Using adaptive Wiener filtering on 200 sweeps, it is possible to obtain interpretable ABR recordings every 15–20 s (Bertrand *et al* 1990, Fischer and Bertrand 1993). The intra-surgical monitoring of ABR ordinarily uses sub-dermal electrodes attached to the patient's head in ipsi-lateral configuration. Clicks are used as acoustical stimuli delivered to the patient through insert earphones. CNAPs are also elicited by click stimuli and are recorded using Teflon-insulated silver electrode wires placed directly in the proximal region of the eighth nerve. CNAP signals have higher SNRs and amplitudes than ABR (around 20 μ V), and require fewer sweeps (100) at high rates (31 s⁻¹). Only 2- to 3-s intervals are needed to obtain a new signal (Colleti and Fiorino 1998).

In posterior fossa surgery ECoChGms are recorded using three techniques (cf Ferraro 1992, 1993, Winzenburg *et al* 1993, Moller 1996, Mullatti *et al* 1999, Yokoyama *et al* 1999): extratympanic electrode (ET), tympanic membrane electrode (TM) and transtympanic (TT) capture. ECoChGm recorded from the ear canal (i.e., extra-tympanic) have small amplitudes, and so require a high number of averaging sweeps. TM recordings have larger amplitudes and are easier to define than those acquired from the ear canal (Ferraro 1992). TT ECoChGms acquired from the promontorium (i.e., transtympanic) have even higher amplitudes requiring only few hundreds of sweeps to acquire an interpretable response. ECoChGm have proven very useful in monitoring blood supply to the cochlea (Moller 1996). Winzenburg *et al* 1993 report successful TM and TT ECoChGm recordings during acoustic neuroma removal surgeries.

1.2. Laser-Doppler measurement technique

Laser-Doppler (LD) blood flow measurement technique is based on the Doppler effect created by moving particles, which are irradiated with a laser beam. LD measurement systems generally use a low-power, infrared laser diode as the coherent light source. In clinical systems, the laser source is usually coupled to an optical fiber that is placed in contact with the vascularized tissue of interest (Levine *et al* 1993). Following the Doppler principle, upon contact with moving red blood cells (RBCs) light undergoes a frequency shift related to the velocity of RBCs. A portion of the scattered light returns to a collecting fiber which delivers the incidental Doppler-shifted signal to a photodetector connected to a signal-processing unit. Flow is calculated as the product of velocity and volume, utilizing units of milliliters per minute for every 100 g of tissue to measure the speed of RBCs moving in random directions (Vasamedics Inc. 1993).

In small animals, such as guinea pigs and gerbils, the laser beam can be delivered to the capillary bed of the stria vascularis through the promontory bone of the cochlea (Miller *et al* 1983, Asami *et al* 1995). In humans and larger animals, such as rabbits, however, whose cochlea is surrounded by dense otic capsule bone, the penetration depth of the laser is greatly attenuated, which decreases the measurement capability and results in unreliable CBF values (Miller *et al* 1991, Mom *et al* 1999). Methods that provide an increased penetration depth, like thinning of the bone, not only increase the invasiveness of the procedure but also increase the risk of damage to fine structures of cochlea, as well. The round window (RW) represents a more suitable site to obtain reliable recordings of CBF (Mom *et al* 1999, Telischi *et al* 2003).

1.3. Project description

Simultaneous use of CBF measurement and click-elicited ECoChGm has provided surgeons with real-time access to a correlation of the electrical cochlear function and the CBF (Yavuz *et al* 2003). The ECoChGm elicited by frequency specific stimuli can be analyzed to obtain data on cochlear microphonics (CM), compound action potential (CAP) and summing potential (SP). CM mainly offers information about the status of the outer hair cells (OHC) in the basal region of the cochlea and the stimulus specific frequency region; CAP provides

information about the physiological status of the inner hair cells (IHC) and their initial stimulation of the neurons in the spiral ganglion. The aim of this project was to develop a real-time, interactive monitoring system to achieve long-term functional assessment of the cochlea and nerve during surgery involving eighth-nerve manipulations. Cochlear blood flow is recorded in real time, providing the surgeon with prompt feedback. The system includes means for a detailed assessment of the electrophysiological cochlear function at three different cochlear regions. For each specific stimulating frequency, the system independently analyzes the behavior of the OHC (CM) and the IHC and their synapses (CAP). The assessment of the eighth-nerve status is achieved through simultaneous recording of CNAP with an electrode located in the posterior fossa. The system is also able to track the nonlinear behavior of the OHC (through CM) following nerve manipulations and compressions.

The implementation of such a system, capable of real-time recording and analysis, demanded the development of specific stimulation, instrumentation and signal-processing techniques. The system must display detailed relevant information about the physiological state of the cochlea and auditory nerve with minimal delay, so the surgeon can react as called for to avoid damage to the cochlea and/or the auditory pathway. This paper is focused on the new methods developed to assess the detailed cochlear functional state.

2. Methods

Figure 1 shows the instrumentation implemented to perform the experimental recordings. In this study, the information regarding CBF is gathered directly via the otic probe which contains an electrode and the LD system. The state of OHC, IHC and synapses is coded in ECochGm recorded at the RW. In addition to the RW electrode for assessing the cochlear state, a second electrode, located at the posterior fossa, is used to record the cochlear compound nerve action potential (CNAP). The posterior fossa electrode was placed as close as possible to eighth-nerve complex but not touching it. In general it was about 2–3 mm from the eighth-nerve complex between internal auditory canal and entrance to the brainstem. This second channel assesses the conduction state of the auditory nerve.

2.1. Experimental set-up

The neuromonitoring system developed in this study was validated with animal experimentation using anesthetized albino rabbits. The posterior fossa was exposed via sub-occipital posterior craniotomy. Using a surgical microscope, the internal auditory canal (IAC) porus was exposed and identified for nerve compression and manipulation using a glass pipette. A specially designed otic probe (Telischi *et al* 2003) was placed in the RW niche, enabling simultaneous acquisition of CBF and ECochGm. An ER2 (Etymotic) insert earphone placed in the external ear canal delivered the stimulus. A second electrophysiological channel, amplifying the signal recorded from an electrode placed in the posterior fossa, was also used. This electrode mainly recorded the CNAP signal. The smart-EP evoked-potential acquisition system (Intelligent Hearing Systems, Miami, FL) was used for all recordings (figure 1).

Previous studies using distortion product otoacoustic emissions (DPOAE) (Morawski *et al* 2003) showed different cochlear regions are affected differently by ischemic insults. It appears that high frequency regions tend to be more affected by ischemia than low frequency ones. In this study, the spatial cochlear selectivity is obtained using narrow band stimuli at specific frequencies. We designed the system to deal with successive stimuli at three different frequencies. In the animal experiments, we tested the system with three tone-bursts stimuli shaped with a Blackman window (70dB SPL, 5 ms duration) at frequencies 4 kHz, 8 kHz and 12 kHz. The left column of figure 3 shows the spectral characteristics of the stimuli used.

The bioelectric signals were amplified 5000 times and band-pass filtered (30 Hz–16 kHz, 6 dB/octave). 64 sweeps of each stimulus type were presented to the cochlea, as shown in figure 2. Each stimulus type is presented at a rate of 49.3 s^{-1} and 64 sweeps are averaged. Alternating stimuli polarity is used to make the CAP–CM separation in ECoChGm easier. Using this protocol, the system took approximately 9 s to gather ECoChGm recordings for the three frequencies in, obtaining a new sample of the cochlear functional state. The protocol was repeated continuously along the whole surgical intervention.

The two-channel electrophysiological signals were sampled at 40 000 samples/s with a 16-bit resolution analog to digital converter. 512 sample responses (12 ms) were used for the data analysis. Responses to alternating stimuli were collected in two average buffers, corresponding to 32 sweeps each one. Each buffer held the average response for stimuli having one specific polarity.

2.2. Signal analysis

Before developing the automatic, real-time, analysis system, real recordings were obtained from rabbits to perform preliminary signal analysis. Spectral analyses of the different ECoChGm signals are presented in figure 3. When the 4 kHz stimuli were presented, the corresponding ECoChGm showed rich information in both the time and frequency domains. In the frequency domain, four spectral regions can be identified. The low frequency region, from 0 Hz to 2500 Hz, contains primary information from the CAP–SP components. Like the stimulus envelope, the SP signal is bell shaped and has its main energy in the 0–500 Hz band. The CAP spectrum overlaps the SP spectrum in the very low frequencies. A second spectral peak, around 4 kHz—corresponding to the CM component—can be identified. At 8 kHz a frequency peak corresponding to the second harmonic of the CM, referred to as CM2, is also observed. Finally, a peak at 12 kHz corresponding to the third harmonic of the CM (CM3) is present. During the experiments CAP, CM and CM2 were tracked, the noise-to-signal level of the third harmonic was often rather small; this made it difficult to track. Each of the tracked signals showed a particular dynamic behavior in response to the nerve manipulations and compressions, giving complementary information in response to surgical maneuvers that occurs during the intervention such as nerve manipulations and artery compressions. The ECoChGm elicited by the 8 kHz tone-burst stimulus showed three spectral regions: a low-frequency one, corresponding to the CAP–SP; a frequency peak around 8 kHz, corresponding to the CM and a small peak corresponding to the second harmonic. This component is attenuated by the analog filters used for acquisition, and has small SNR. The ECoChGm elicited by 12 kHz tone bursts showed two main activations: one at low frequencies (CAP–SP) and the other at around 12 kHz (CM). This ECoChGm also has a minor activation at 4 kHz.

SP, CAP and CM components are extracted from ECoChGm using alternating stimuli, as shown in figure 4. Adding and subtracting the responses elicited by the positive and negative polarity stimuli enabled us to separate the complex CAP–SP and CM2 from CM and CM3.

2.3. Automatic real-time feature extraction

Table 1 summarizes the different traces and measurements the system allows us to extract automatically. For all three stimuli, the CAP latency and amplitude provided us with information about the state of IHC and synapses of a specific cochlear region; the amplitude of the envelope of CM mainly provides information about the physiological state of the OHC and CM2 can provide additional information of OHC transduction function. This information is presented to the surgeon in real time to supply a detailed feedback of the cochlear state.

Figure 5 shows the real-time ECoChGm feature extraction technique. The system automatically extracts CAP–SP, CM and CM2 for each of the stimuli frequencies. The signal processing

begins from the very stimulus delivery. Alternating phase stimuli are sent to the subject to obtain two average traces: even average corresponding to cochlea response to condensation stimuli and odd average containing the average of the response to rarefaction stimuli. These two averages are added and subtracted to obtain two new curves. Given that the CM ‘copies’ the acoustical stimulus, it is eliminated in the added curve and enhanced in the subtracted one. The CAP+SP trace is assumed to be equal to rarefaction and condensation stimuli so it is enhanced in the added curve and does not affect the subtracted one. With this simple data operation we are making an initial separation of CM and a trace containing both CAP and SP. Were the cochlea a linear system, this separation should be enough, but due to the nonlinear transduction function of OHC, CM2 shows added in the CAP+SP trace and so the CM3 in the CM trace. Further processing is required to complete the signal analysis and feature extraction: CM2 must be eliminated from the CAP+SP trace before a peak-tracking algorithm could be applied to the CAP. CM and CM3 envelope magnitudes must be computed from the CM+CM3 trace. CM2 envelope magnitude must be also computed from the added average.

2.3.1. CAP detection and peak tracking—Using a zero phase shift, spectral low-pass filter, the CAP+SP signals are extracted from the added average. A fast Fourier transform (FFT) is applied to the signal; the CAP+SP are obtained by computing the inverse FFT, after the high frequency coefficients (higher than 2500 Hz) were zeroed (eliminating the CM2 component and high frequency noise). When the functional state of the cochlea was normal, this signal was useful to extract CAP’s latency and amplitude. Following nerve manipulations and compressions, CAP and SP were severely affected. In these cases the CAP was embedded in the SP, which makes the automatic detection of the peaks difficult. To factor the SP energy out from the CAP–SP signal, an additional digital high-pass filter was applied (600 Hz cut-off frequency) which enhanced the CAP peaks as shown in figure 5. After filtering, peak detection and tracking algorithm were applied to the CAP signal to compute the N1 peak latency and amplitude. The algorithm detects N1 peak as the signal’s maximum in a search window.

2.3.2. CM analysis—The CM fundamental signal, originating primarily from the OHC, gives an electrical signal that replicates the waveform of the acoustical stimulus. Consequently with the stimulation strategy, it was expected the CM fundamental wave to be an amplitude-modulated signal, having the same stimulus frequency and time envelope (Blackman window) of the stimulus signal. In addition to anticipated fundamental CM waveform, several CM harmonics originating from the nonlinear transduction function of OHC with similar temporal waveforms were also present as expected. Thus, the measurement of the envelopes of the CM fundamental and harmonics is a reliable and stable measurement of the OHC activity.

(a) Envelope detectors: To detect and measure the CM, CM2 and CM3 amplitudes for all the stimulation frequencies, we developed the envelope detectors presented in figure 6(a). Each filter is tuned to detect a specific frequency (w). When the input to the filter is an amplitude-modulated arbitrary phase sinusoidal signal superimposed with noise and additional signals, having different frequencies than the tuned frequency, $[s(t) = a(t) \cos(wt + \varphi) + s_1(t) + n(t)]$, the filter produces the envelope magnitude of the input signal $[z(t) = a(t)]$. In the upper branch of the filter, the incoming signal is multiplied by a windowed cosine wave whose frequency equals the carrier frequency. This product is integrated over an integer number of carrier cycles and squared. In the lower branch, a similar process is performed, but multiplying the incoming signal by a windowed sine wave instead of a cosine wave. The envelope magnitude is computed as proportional to the square root of the sum of the two branches. The two windowed sine and cosine signals are wavelets, which are well localized in time and frequency. As the wavelet temporal length increases, the correlation between it and the incoming signal integrates more activation, canceling the noise not correlated with the stimulus. The wavelets can be tuned so as to produce envelope detectors with high frequency specificity and high signal-to-noise ratio,

making it even possible to measure the CM from a posterior fossa electrode (Morawski *et al* 2004).

Mathematical background: To analyze the behavior of the envelope detection filter, first assume as the input signal a cosine wave of known frequency (w), having unknown amplitude and phase:

$$s(t) = a(t) \cos (wt + \varphi). \quad (1)$$

The Blackman window (figure 8) has the following expression:

$$W(t, \tau) = 0.42 + 0.5 \cos (2\pi t / \tau) + 0.08 \cos (4\pi t / \tau) - \tau \leq t \leq \tau. \quad (2)$$

We can compute the intermediate filter outputs of the coherent filter as

$$\begin{aligned} y_1(t) &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} s(t) W(t, \tau) \cos (wt) dt \\ &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} a \cos (wt + \varphi) W(t, \tau) \cos (wt) dt \end{aligned} \quad (3)$$

and

$$\begin{aligned} y_2(t) &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} s(t) W(t, \tau) \sin (wt) dt \\ &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} a \cos (wt + \varphi) W(t, \tau) \sin (wt) dt. \end{aligned} \quad (4)$$

These integrals have a short closed form when the Blackman window length is an integer multiple of the carrier signal period, N , and the envelope is almost constant inside the window:

$$\tau = 2\pi N / w \quad N = 1, 2, \dots \quad (5)$$

In these cases the intermediate filter outputs are

$$\begin{aligned} y_1(t) &= 0.23a(t) \cos (\varphi) \quad y_2(t) = -0.19a(t) \sin (\varphi) \\ N &= 1 \\ y_1(t) &= 0.21a(t) \cos (\varphi) \quad y_2(t) = -0.21a(t) \sin (\varphi) \\ N &= 2, 3, \dots \end{aligned} \quad (6)$$

When $N \geq 2$, the output of the coherent filter is proportional to the envelope of the input signal. When the integral is performed on only one carrier signal period ($N = 1$), the coherent filter output is sensitive to the input signal phase:

$$z(t) = \sqrt{y_1^2(t) + y_2^2(t)} = a \sqrt{0.0084 \cos (2\varphi) + 0.0445} \quad N = 1 \quad (7)$$

$$z(t) = \sqrt{y_1^2(t) + y_2^2(t)} = 0.21a(t) \quad N = 2, 3, \dots \quad (8)$$

The amplitude of the input signal can be computed as:

$$a(t) = \frac{z(t)}{0.21} \quad N = 2, 3, \dots \quad (9)$$

Equation (9) shows how the coherent filter can extract the envelope of a signal when it is tuned to have the same frequency as the input signal. Since the input signal is not a pure sine wave but an amplitude-modulated signal it has a spectral split around the carrier frequency. When the input signal $s(t)$ does not have the same frequency as the demodulating filter as shown below:

$$s(t) = a(t) \cos(\alpha \omega t + \phi). \quad (10)$$

The upper and lower branch outputs of the coherent filter become

$$\begin{aligned} y_1(t) &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} s(t) W(t) \cos(\omega t) dt \\ &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} a(t) \cos(\alpha \omega t + \phi) W(t) \cos(\omega t) dt \end{aligned} \quad (11)$$

$$\begin{aligned} y_2(t) &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} s(t) W(t) \sin(\omega t) dt \\ &= \frac{1}{\tau} \int_{-\tau/2}^{\tau/2} a(t) \cos(\alpha \omega t + \phi) W(t) \sin(\omega t) dt. \end{aligned} \quad (12)$$

These integrals can be computed to obtain the following closed form expressions:

$$\begin{aligned} y_1(t) &= a k_1(\alpha, N) \cos(\phi) \quad N = 1, 2, \dots \\ y_2(t) &= a k_2(\alpha, N) \sin(\phi) \quad N = 1, 2, \dots \end{aligned} \quad (13)$$

where $k_1(\alpha, N)$ and $k_2(\alpha, N)$ are functions of the frequency deviation (α) and the number of carrier frequency periods (N). As in the case with input signal having the same frequency of the demodulating filter, we realize that the upper branch of the detector is proportional to the amplitude of the input signal multiplied by the cosine of its phase. The lower branch is proportional to the amplitude of the input signal multiplied by the sine of its phase. The absolute values of the proportion factors (k_1 and k_2) are not the same for the two branches, but their difference is very small. After some mathematical computations, the filter output, $z(t)$, can be computed as

$$z(t) = a \beta_1(\alpha, N) + a \beta_2(\alpha, N) \cos(2\phi) \beta_2 \ll \beta_1, \quad N \geq 2. \quad (14)$$

The filter output has two terms: one dominant term that depends only on the input signal amplitude; and a second term which is also influenced by the input signal's phase. Figure 6(b) shows the behavior of the filter constants as functions of the input frequency deviation (α) and the wavelet temporal length (N). Figure 6(b) shows that the coherent filter works as a band pass envelope detector. The pass-band width is controlled by (N). We also verify that, for filters with (N) greater than 3, the dominant term in equation (14) $[\beta_1(\alpha, N)]$ is more than 1000 times larger than the phase-dependent term $[\beta_2(\alpha, N)]$, so the approximation to the envelope is rather good. In the ECoChGm analysis presented in this study, N is adjusted to set the integration window to 1.5 ms ($N = 6$ for 4 kHz, $N = 12$ for 8 kHz and $N = 18$ for 12 kHz stimuli).

Envelope detector computer implementation: In this study a discrete-time version of the envelope detector of figure 6 is implemented. The integrals are substituted by moving averages. The number of samples in the moving average is selected to cover multiple periods of the carrier frequency. Equations (15)–(19) present the envelope detection algorithm as an integration of two finite impulse response (FIR) filters $h_1(i)$ and $h_2(i)$.

$$y_1(k) = \sum_{i=0}^{M-1} s(k-i)h_1(i) \quad (15)$$

$$y_2(k) = \sum_{i=0}^{M-1} s(k-i)h_2(i) \quad (16)$$

$$h_1(i) = \frac{1}{M} \cos\left(2\pi \frac{f_0}{f_s} i\right) W_M(i) \quad (17)$$

$$h_2(i) = \frac{1}{M} \sin\left(2\pi \frac{f_0}{f_s} i\right) W_M(i). \quad (18)$$

Using $W_M(i)$, Blackman window of length M , the signal envelope is then estimated as

$$a(k) = \frac{1}{0.21} \sqrt{y_1^2(k) + y_2^2(k)}. \quad (19)$$

(b) Application of envelope detectors to CM analysis: The envelope detector filter presented above provides an efficient real-time processing of the raw data directly, because it removes the signal energy outside the main pass-band. Its band-pass characteristic enables the use of the raw ECochGm signal as input to extract the CM envelope without preprocessing. Tuning the length of the filter, time and frequency selectivity can be easily performed to achieve a good signal-to-noise ratio. In this study envelope detection filters were constructed and tuned to compute CM envelope magnitude for 4 kHz, 8 kHz and 12 kHz stimuli. These filters process the corresponding CM+CM3 signal (figure 4). For the second harmonic detection, the envelope detectors were tuned to a frequency twice that of the stimulus frequency and use as input the SP+CAP+CM2 buffer.

2.4. Trend generation and interactive tools

The signal processing provides the user with information about the auditory functional state in the form of visual displays of signals and numerical measurements extracted from the different components. In the neuromonitoring system developed in this study, a new set of measurements are obtained every 9 s in real time.

This high rate of information must be presented adequately to the person in charge of neuromonitoring who must assess the functional state of the cochlea without delay. The design of an ergonomic computer screen layout and relevant alarms are then necessary to present the relevant information. This goal is achieved by trend generation and interactive tools implemented in the final monitoring software.

The extracted signals were presented to the user in two different ways: (a) time-recorded traces of CAP and CM and (b) computed trend curves for the different measurements. The system provides three pages of trend analysis: the first one shows trends for CBF, CM amplitudes for the three frequencies and CM2; the second one shows the latency of CAP and CBF and the last page presents the CAP amplitude and CBF. CBF is presented in all the trend curves since it is to the measurement of blood supply to the cochlea to which all measurements are contrasted.

The signal processing and display are performed concurrently for two recording channels. This is done by running the monitoring program twice in two separate windows (which can reside in a second computer monitor) simultaneously.

3. Results

The neuromonitoring system described in this study has been used to assess the cochlear function in 62 rabbit experiments, involving auditory nerve manipulation and compression. Reliable, real-time recordings of CBF, through the round window, were achieved in all the experiments. The RW electrode of the otic probe provided high signal-to-noise ratio ECochGm recordings obtained with only 64 sweeps. Tone-burst stimuli elicited CAP amplitudes of tens of microvolt and CM amplitudes up to hundreds of microvolt. A detailed, multi-frequency, functional state of cochlea monitoring was achieved with delays of only 10 s. For each stimulation frequency, an effective monitoring of the activity of OHC and IHC was performed. Figure 7 below presents an example of signal trends of the system during a 3-min nerve compression. The dynamics of CBF, CAP amplitude and latency (N1 peak) and CM amplitude are presented for the 4 kHz stimulus. All measurements are very stable and the physiological state of cochlea can be followed in a fast and reliable fashion. Once the artery is compressed, the CAP decreases rapidly in amplitude and increases in latency until the N1 peak is not clearly identifiable. CM has a different behavior, requiring more time to achieve its minimum value but having a somewhat faster recovery time.

The CM harmonics enable the possibility of monitoring the nonlinear functioning of OHC in response to nerve manipulations and compressions. Figure 8 presents the modifications of CBF simultaneously plotted with CM, CM2 and CM3. 100% is arbitrarily defined as the normalized baseline before the nerve compression. CM, CBF and CM3 present quite similar trends, following the blood supply to the cochlea. The second harmonic (CM2), plotted in an independent trace, shows a totally different pattern presenting an over activation of almost 600% at the onset and offset of the nerve compression.

4. Discussion

The long-term real-time monitoring system developed in this study provides high resolution information on cochlear dynamics that cannot be achieved in traditional recording setups. This system provides the recording of many physiological variables in a rapid and reliable way, simultaneously with CBF. In this study, different components of the ECochGm recorded in the RW niche are extracted and analyzed in real time. CAP shows the dynamics of synapses of IHCs. CM mainly provides information about the behavior of OHCs. CM2 shows significant modifications as responses to the surgeon's manipulations of the auditory nerve.

According to common consensus, the RW ECochGm records mainly the contribution of the electrical activity from the cells close to the basal part of the cochlea. Therefore, the frequency specificity of CM recordings is significantly limited. However, we observed in our experiments (Morawski *et al* 2004a) that CM patterns of reduction just after internal auditory artery (IAA) compression and patterns of recovery for the 60 s post release period are different for different stimulation frequencies. This observation suggests that CM response has measurable contributions from frequency specific cochlear locations that may be useful in monitoring.

Current intraoperative systems for hearing mainly monitor latency or amplitude of CAPs (from ECochGm or direct eight-nerve (CNAP) recording) or ABRs. A retrospective evaluation of 65 patients with usable preoperative hearing showed that out of these three intraoperative monitoring techniques, CAP monitoring from the eight nerve showed the best but not statistically significant performance (Batista *et al* 2000). This is not very surprising since all these techniques primarily reflect the status of the IHC and the auditory nerve. In these intraoperative systems, the status of the OHC and cochlear blood flow is not monitored. The present system provides more complete information about cochlear structures and should be

used in addition to CAP or ABR recordings. OHC monitoring using CM is especially important since OHC are known to be very sensitive to any traumatic manipulations and hypoxia.

The present system extracts the nonlinear information of OHC. The spectral properties elicited from tone-burst stimuli, CM, can be explained by the Boltzman function determining the mechano-electrical transduction of the OHC (Holton and Hudspetch 1986, Patuzzi and Moleirinho 1998). The modification of CM2 following nerve manipulations is also compatible with the SP anoxia recordings of Konishi *et al* 1961. Their studies indicate that using the Boltzmann transfer function, it is possible to show the high correlation between the modifications of SP and CM2. Systematic analysis of this nonlinear behavior during nerve manipulation is the object of present studies in our research team and will be the object of further publication. Because of its stability during normal conditions and sensitivity to hypoxia and nerve manipulations, this nonlinear behavior appears to be a promising variable to produce prompt alarms during surgical interventions.

In this study, CAP is separated from CM by averaging rarefaction and condensation responses. This assumes that CMs for opposite polarity stimuli are opposite in phase but equal in amplitude and CAP, on the other hand, is exactly similar. Several studies in animals and humans, however, show that this assumption is not entirely true and in some cochlear pathologies, notably Meniere's disease (e.g. Johansson *et al* (1997) and Sass *et al* 1998), there are significant differences in responses to opposite phase stimuli. In such cases CAP and CM cannot be successfully separated from each other. Other adaptive numerical methods have been developed for such special cases (Arslan *et al* 2000) and these methods can be easily incorporated into our system.

The computational implementation of the neuromonitoring system is still complex to use and must be better thought out to be used in the routine surgical practice. Work must be done to define which of the variables are more relevant and to find precise correlations between surgical maneuvers and physiological variable modifications. This work will complement the results of Colletti *et al* 1997, 1998 who correlated many causes of auditory impairment with electrophysiological measurements. In human clinical environments, similar neuromonitoring systems will contribute to better surgical outcomes in posterior fossa neurosurgeries.

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Figure 1. Schematic diagram showing instrumentation for ECoG and CBF recordings and eight-nerve compression with a glass pipette.

Figure 2.

Stimulation protocol showing presentation patterns of three sound stimuli. 64 sweeps of each frequency stimulus are presented and corresponding responses are averaged. The stimulus phase is alternated to make the CAP–CM separation possible.

Figure 3. Sound stimuli and their spectra (left column) and the corresponding ECoGm recordings with their spectra (middle column). Extracted time waveforms of CAP+SP, CM, CM2 and CM3 corresponding to each ECoGm response are shown on the right column.

Figure 4.

Signal processing methods used to extract information from ECoGm recordings. Right side illustrates a general block diagram of the process, while left side illustrates the signals' waveforms along different phases of processing: the first row shows the waveform of the stimulus used on each frequency: in the middle a time zoom is presented to see the stimulus phase relation. After sending 64 alternating stimulus, the EP machine produces two different average traces (second figure row). As the CM 'copies' the stimulus waveform, an initial separation between CAP+SP and CM can be achieved via simple addition and subtraction of the two raw averages. Additional processing, using with digital low pass filters and envelope detectors, is necessary to extract the CM higher harmonics.

Figure 5.

Example of CAP+SP processing to enhance N1 peak during two clinical situations. The low frequency signal, coming mostly from the summing potential modification, should be removed to enable a reliable automatic N1 peak detection and tracking. (a) CAP+SP before auditory nerve manipulation: dotted line shows the SP+CAP signal extracted from ECochGm, solid line shows the signal after a digital 600 Hz high pass filter is applied (b) CAP+SP with low frequency increase due to auditory nerve manipulation. Dotted line shows the SP+CAP signal as extracted from EcochGm; solid line shows the signal processed high a digital 600 Hz high pass filter. In the original signal, N1 can be only identified as an inflection of the CAP-SP trace, but after the high pass filtering the signal is enhanced.

Figure 6.

Continuous time envelope detector: (a) block diagram, (b) frequency response of the filter coefficients β_1 and β_2 with respect to frequency deviation α . Carrier frequency corresponds to 1. N represents the number of periods of the carrier signal. For more information, see the text.

Figure 7.

30 min trend curve of 4 kHz ECoGm signal around 3 min nerve compression. At time 0 the nerve is compressed and the blood flow to the cochlea restricted. The compression lasts 3 min (cross-hatch indicates cochlear artery compression). The system automatically detects and displays the trend curves for CBF, CAP amplitude, CAP latency and CM amplitude in real time. The asterisk (*) denotes the moment when the CAP signal is lost and restored after the nerve compression.

Figure 8.

Normalized plot of nonlinear 4 kHz ECochGm behavior around a 3 min nerve compression. The data recorded during the 5 min before compression were averaged to obtain a normalization baseline corresponding to 100%. The behavior of the CBF and CM amplitude and its harmonics are plotted among the CBF. The second harmonic CM2 is plotted in a different figure because it has drastic modifications, reaching a value of more than 600% its baseline after nerve manipulations. Cross-hatch indicates cochlear artery compression.

Table 1

Summary of physiological recordings and automatically extracted measurements from ECochGm with their most prominent physiological significance.

Stimulus	Recordings	Measurements	Main physiological significance
All	LD	LD	Cochlear blood flow
4 kHz	CAP+SP	Latency–amplitude	State of IHC and synapses in 4 kHz region
	CM (envelope)	CM amplitude	State of OHC in the basal part of cochlea plus a specific contribution of the 4 kHz region
8 kHz	CM2	Harmonic amplitude	Nonlinear behavior of OHC in 4 KHz region
	CAP+SP	Latency–amplitude	State of IHC and synapses in 8 kHz region
	CM (envelope)	CM amplitude	State of OHC in the basal part of cochlea plus a specific contribution of the 8 kHz region
12 kHz	CAP+SP	Latency–amplitude	State of IHC and synapses in 12 kHz region
	CM (envelope)	CM amplitude	State of OHC the basal part of cochlea plus a specific contribution of the 12 kHz Region