Ethical, anatomical and physiological issues in developing vestibular implants for human use

Jean-Philippe Guyot∗, Annieta Gay, Maria Izabel Kos and Marco Pelizzone
Department of Clinical Neurosciences University Hospital, Faculty of Medicine, University of Geneva, Switzerland

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Abstract. Effort towards the development of a vestibular implant for human use are being made. This paper will summarize the first important steps conducted in Geneva towards this ambitious goal. Basically, we have faced three major issues. First, an ethical issue. While it was clear that such development would require the collaboration of human volunteers, it was also clear that stimulation of the vestibular system may produce periods of significant discomfort. We know today how to minimize (and potentially eliminate) this type of discomfort. The second issue was anatomical. The anatomical topology of the vestibular system is complex, and of potentially dangerous access (i.e. facial nerve damage). We choose not to place the electrodes inside the ampullae but close the vestibular nerve branches, to avoid any opening of the inner ear and limit the risk of hearing loss. Work on cadaver heads, confirmed by acute stimulations trials on patients undergoing ear surgery under local anesthesia, demonstrated that it is possible to stimulate selectively both the posterior and lateral ampullary nerves, and elicit the expected vertical and horizontal nystagmic responses. The third issue was physiological. One of the goal of a vestibular implant will be to produce smooth eye movements to stabilize gaze direction when the head is moving. Indeed, after restoring a baseline or “rest” activity in the vestibular pathways with steady-state electrical stimulation, we demonstrated that modulation of this stimulation is producing smooth eye movements.

In conclusion, humans can adapt to electrical stimulation of the vestibular system without too much discomfort. Surgical access to the posterior and lateral ampullary nerves have been developed and, electrical stimulation of the vestibular system can be used to artificially elicit smooth eye movements of different speeds and directions, once the system is in adapted state. Therefore, the major prerequisites to develop a prototype vestibular implant for human use are fulfilled.

Keywords: Bilateral vestibular loss, rehabilitation, vestibular prosthesis, electrical stimulation

1. Introduction

Balance is one of our five sensory modalities. The handicaps associated with blindness or deafness are fa-

miliar to all of us, whereas the difficulties experienced by patients with bilateral vestibular deficit are often underestimated. Balance disorders and oscillopsia produced by such a deficit are relatively well known but other aspects, like the risk to fall, especially among the elderly with all the morbid consequences that implies, are significantly underestimated [14]. Furthermore, a bilateral vestibular deficit can also cause substantial cognitive disorders, like disorders of environmental perception, spatial orientation, and even of the perception of the self [7]. In the U.S., it is estimated that over 40% of the population consults a doctor because of balance problems, on one or more occasions, and that over 6 million people suffer from a chronic
vestibular problem [17]. Given the aging population, balance disorders represent a public health problem of increasing importance in coming decades.

Currently, there is no treatment for vestibular deficits. It has been shown that vestibular exercises were ineffective in 80% of patients with bilateral vestibular deficit [22], and there is no biological way to “repair” the injured vestibular sensorineural structures. In order to help patients suffering from a bilateral vestibular loss, various attempts have been made. For example, the use of tactile cues to substitute the missing vestibular information. Patients would wear a belt around the waist, fitted with actuators that deliver vibrotactile feedback of increasing intensity on the stomach when the posture of the subject begins to deviate significantly from the adequate position [19]. Another approach is to develop a vestibular implant, a prosthesis based on a concept similar to that of the cochlear implant for the rehabilitation of deaf patients. Motion sensors fixed to an individual’s head would capture head movements and, after adequate processing, this information would be transmitted to the central nervous system via electrodes placed in the vicinity of the vestibular end organs or their nerve branches. Suzuki et al. demonstrated long ago that electrical stimulation of the vestibular nerve can elicit responses resembling the normal functioning vestibular apparatus [18]. In recent years, several experiments on animal models have confirmed and extended these findings [2,5,15]. We are now in a position in which the first human experiments are needed to test for the feasibility of an adequate device for human use. This paper will summarize our first important steps towards this ambitious goal.

2. The ethical issue

The first steps of this research were very slow mostly for ethical reasons. It was correctly expected that electrical stimulation of the vestibular system would generate symptoms of dizziness and imbalance. Therefore, the ethical committee of our institution had to be convinced that it was acceptable to have patients (eventually) experience a phase of discomfort while participating in this research protocol. Considering the severe impairment of the quality of life of these patients [8], the ethical committee approved the project. A requirement was that the first volunteer patient be assessed by a psychiatrist, to ensure he had a true understanding of the experience and he was not looking for heroism while participating in such an ‘adventure’. Members of the committee also required to be present during the initial stimulation, to ensure that the disturbances induced by electrical stimulation of the vestibular system were ‘tolerable’. We have now demonstrated that it is possible to stimulate the vestibular system without causing too much discomfort and that the results obtained with this experimental protocol are very promising because they pave the way to the development of future vestibular implants for human use.

3. The anatomical issue

In a cochlear implant the electrodes array is pushed into the cochlea and de facto the electrodes are in the vicinity of the first order auditory neurons located in the spiral ganglion. For a vestibular implant the situation is more complex. The various vestibular sub-modalities are grasped by spatially separated end organs which all converge towards the ganglion of Scarpa. Thus direct electrical stimulation of Scarpa’s ganglion would make it difficult to selectively activate the different vestibular sub-modalities. Furthermore access to Scarpa’s ganglion requires an invasive surgery with a risk of facial nerve damage.

Alternative sites of stimulation are the ampullae of the semicircular canals or the vestibular nerve branches emerging from the ampullae, provided sufficient survival of peripheral axons. Inserting an electrode inside an ampulla presents however a substantial risk to promote a hearing deficit. It has been reported that a total vestibular loss occurs in about 10% of patients undergoing a cochlear implantation, and a partial loss in about 40% [11]. The reverse situation can be expected to occur. Therefore, we deliberately choose not to place the electrodes within the ampullae but close vestibular nerve branches, to avoid any opening of the inner ear and to limit the risk of hearing loss. We also decided to conduct surgery under local anesthesia, a standard technique for most middle ear surgeries [12,21]. Note that the use of local anesthesia is crucial for our concern since under total anaesthesia there is no observable nystagmus (i.e. one observes only a tonic deviation of gaze).

The surgical access to the posterior ampullary nerve was inspired by the seminal work of Gacek in 1974 who proposed to cut this nerve branch for the relief of intractable benign positioning paroxysmal vertigo [6]. Our surgical technique is similar, but instead of cutting the nerve, a little niche is drilled to place the electrode in its vicinity. An anatomical study on 100 hu-
man cadaver heads confirmed that the nerve is accessible via the external auditory canal in 98% of temporal bones (Fig. 1) [3, 13]. The next step was to confirm selective activation of only one vestibular submodality. Acute stimulation trials were conducted in the operating room in 3 deaf patients (with preserved vestibular function) under local anesthesia prior to a cochlear implantation. The characteristics of the electrical stimuli and of the electrode as well as the method of recording and analysis of eye movements have been described in details elsewhere [9, 10]. Briefly, trains of 400 µs biphasic pulses (200–1’000 µA) were delivered with a repetition rate of 200 Hz via an unipolar 125 µm diameter ball electrode made of a 90% Platinum – 10% Iridium Teflon-coated wire. The electrode was maintained by the surgeon during all the experiment. A homemade Matlab® program was used to quantify nystagmic responses. These trials demonstrated that it was possible to elicit a vertical nystagmic response via electrical stimulation of the posterior ampullary nerve (Fig. 2) [20]. The amplitude of the slow component velocity was correlated to the current amplitude and frequency of the stimulation, reaching a maximum of 50°/s at 200 pulses per second [20].

Of course, a vestibular implant will need to act on at least two orthogonal directions of eye movements to be optimally useful. Therefore, encouraged by the positive results obtained in stimulating the posterior ampullary nerve, we have developed an original surgical approach of the branch innervating the lateral semicircular canal (Fig. 3). Briefly, the external auditory canal was anesthetized, and a tympanomeatal flap elevated, using standard techniques of the middle ear surgeries [12, 21]. Then, the attic was opened, and the incus and malleus head removed. To approach the nerve the bone was drilled above the horizontal portion of the facial canal, ventral to the prominence of the lateral semicircular canal [4]. Removal of the incus and malleus head does not represent a serious limitation to the technique given the good results obtained by a functional type III tympanoplasty, with a hearing loss inferior to 20 dB in more than 90% of operated patients [21].

Again, adequate placement of the stimulating electrode was checked via acute stimulation trials which were performed under local anesthesia in 3 patients suffering from intractable episodes of vertigo (Menière’s disease) prior to a labyrinthectomy. These trials demonstrated that it was possible to generate horizontal nystagmic responses despite the proximity of the nerve branch innervating the superior semicircular canal and without stimulation of the facial nerve [9] (Fig. 4).

In conclusion, we demonstrated that it is possible to stimulate selectively both the posterior and lateral ampullary nerves, but we also observed that minute displacements of the electrode drastically modified the amplitude of the eye movements. Therefore it is of utmost importance to allow for refined positioning of the electrode during surgery and this can be done via recording of nystagmic responses provided that surgery is made under local anesthesia.

4. The physiological issue

Under normal physiological conditions, the vestibular system is spontaneously discharging. It is the modulation – by the vestibular end organs – of this baseline or “rest” activity that produces smooth eye movements or posture adjustments. As shown in the previous section, sudden artificial stimulation of the vestibular system elicits nystagmus, and the feeling of vertigo. Since the goal of a vestibular implant is not to produce nystagmus or vertigo, but to drive smooth eye movements to stabilize gaze, the fundamental physiological issue is whether we can restore a baseline “rest” activity in the de-afferented vestibular system without the unwanted nystagmus and vertigo and then modulate it conveniently to elicit smooth eye movements.

Previous animal experiments paved the way to go. For example in guinea pigs when continuous electrical
Fig. 2. Electrical stimulation of the posterior ampullary nerve. The stimulation elicits a vertical nystagmic response.

Fig. 3. Location of the lateral ampullary nerve, right temporal bone. The nerve (arrow) emerging from the lateral semicircular canal (1) can be reached via the external auditory canal (2) after the malleus head and incus (3) are removed. It is close to the facial nerve (4).

stimulation was applied for the first time, animals exhibited a nystagmic response that took about 7 days to subside, and which reappeared in the opposite direction when the stimulation was abruptly stopped. The time required for adaptation however gradually diminished with successive repetitions of “on-off” cycles of stimulation, dropping to a few minutes after four “on-off” cycles [16]. The next steps were thus to check whether this phenomenon of adaptation also existed in humans and that, once in the adapted stage, it was possible to generate smooth eye movements via modulations of the electrical stimulus (note that the term of adaptation is consistent with the terminology used in physiology, and is defined as a phenomenon that serves to minimize a behavioural error [1]).

One totally deaf patient with a bilateral vestibular deficit received a modified cochlear implant for this purpose [10]. One electrode was taken away from the cochlea and used to stimulate the posterior ampullary nerve. It was placed into a small depression drilled near the posterior ampullary nerve on the floor of the round window niche, and fixed with bone wax. Electrical stimuli consisted of trains of 400 µs/phase biphasic pulses, delivered at a repetition rate of 200 pulses per second (pps). When continuous electrical stimulation at 400 µA was turned ‘on’ for the first time, a strong nystagmic response was observed at stimulation onset (Fig. 5 upper panel). The response took several minutes to slow down and it is only after 27 minutes of continuous stimulation that nystagmic beats were almost absent from the recordings. At this point, electrical stimulation was turned ‘off’ and nystagmic beats of reversed direction were observed (Fig. 5 lower panel). This disappearance of nystagmic response upon continuous electrical stimulation and its reappearance (in opposite direction) when stimulation is stopped was (to our knowledge) the first clear demonstration of adaptation to electrical stimulation of the vestibular system in the human.

We waited for the disappearance of the nystagmic “off-response” to the first stimulation attempt and then we cycled the stimulation again ‘on’ and “off” for a few times. At the fourth “on-off” attempt a strong nystagmic response was still observed at onset, but the response already decreased after only about 10–15 s, and disappeared 7 minutes after stimulation onset. Again, when the stimulation was turned “off” nystagmic beats of reversed direction were observed. The time to adaptation dropped further with successive cycles to be less than 1 minute after 7 “on-off” cycles of stimulation [10].

In summary, these results demonstrated that humans can adapt to steady-state stimulation of the vestibular system without suffering too much discomfort. The time needed to reach adaptation appears to be shorter in humans than in some animal models and is progressively reduced by successive “on-off” cycles. However, we recently observed that the reduction gained by repeated cycling does not persist over time. One subject underwent 5 series of 4 successive “on-off” cycles, with periods of 1, 2, 4 and 18 hours of rest (without stimulation) between series. While it is clear that a strong pre-adaptation is still present after only 1 hour of rest, all the benefit of cycling is lost after a period of rest of 18 hours (Fig. 6).
Fig. 4. Electrical stimulation of the lateral ampullary nerve. The stimulation elicits eye movements predominantly in the horizontal plane (2 upper tracings). [Reproduced with permission J.Ph. Guyot, A. Sigrist, M. Pelizzone, G.C. Feigl and M.I. Kos Eye movements in response to electric stimulation of the lateral and superior ampullary nerves Ann Otol Rhinol Laryngol 120 (2011), 81–87].

Fig. 5. Nystagmic response to the first attempt of chronic electrical stimulation of the vestibular system. Upper panel: A strong nystagmus response is observed at stimulation onset. Lower panel: After 27 minutes of continuous stimulation, nystagmic beats are (almost) absent when stimulation is "on", and turning the stimulation "off" elicits a clear nystagmic response of opposite direction. (HL: horizontal left; HR: horizontal right). [Reproduced with permission J.Ph. Guyot, A. Sigrist, M. Pelizzone and M.I. Kos Adaptation to steady-state electrical stimulation of the vestibular system in humans Ann Otol Rhinol Laryngol 120 (2011), 143–149].

The final experiment was to attempt to mimic the natural system – i.e. elicit smooth oscillatory eye movements – by modulating the stimulation signal once the subject was in adapted state. Figure 6 shows clear small oscillatory eye movements upon sinusoidal amplitude modulation (340 µA ± 60 µA) at 3 Hz of the original pulse train. The oscillatory eye response is about 0.5° peak to peak (i.e. well above the noise level) and of approximate sinusoidal shape (Fig. 7). Frequency modulation (200 ppc ± 120 ppc) of the stimulation signal produced similar eye movements, but of weaker amplitude (not shown). To our knowledge, this was the first demonstration in human that smooth oscillatory eye movements could be driven by electrical stimulation of the vestibular system.

5. Conclusions
We master the surgical access to two possible sites of stimulation of the vestibular system: one near the
Fig. 6. Progressive loss of adaptation phenomena when increasing the duration of the rest period. The duration of the nystagmic response to the first cycle of the series increases from about 7 min to about 30 min when the rest period between series is increased from 1 hour to 18 hours. After 18 hours of rest, all adaptation phenomena are lost.

Fig. 7. Eye movements elicited by sinusoidal amplitude modulation of the electrical stimulation (340 µA ± 60 µA; 3 Hz). The modulation of the stimulation elicited clear, smooth and sinusoidal eye movements. (HL: horizontal left; HR: horizontal right). [Reproduced with permission J.Ph. Guyot, A. Sigrist, M. Pelizzone and M.I. Kos Adaptation to steady-state electrical stimulation of the vestibular system in humans Ann Otol Rhinol Laryngol 120 (2011), 143–149].

posterior ampullary nerve to encode movements in the vertical plane, another near the lateral ampullary nerve to encode movements in the horizontal plane. Stimulation at these two sites elicits nystagmic responses in the expected directions. The nystagmic response however disappears upon prolonged steady-state stimulation: the vestibular system progressively enters in an “adapted” state. Once in this adapted state, amplitude and frequency modulations of the stimulation produce smooth eye movements that mimic the modulation envelope. These results are very promising because, theoretically at least, they open the way to the development of vestibular implants for human use.

Notwithstanding the progresses that were made, many steps still remain to develop a device that provides useful functional rehabilitation. First, these experiments in a single patient must be replicated in more subjects to evaluate interindividual variability. Second, all the experiments reported here were conducted very close to stimulation threshold to maximise safety and minimise any possible discomfort. As a consequence for example, the amplitude of the smooth oscillatory eye movements produced by modulation of the stimulation was quite small, about 0.5° peak to peak, which might not be sufficient for functional rehabilitation. Thus the same experiments should be repeated at higher stimulation levels. Third, since it is required to reach an “adapted” state, and that adaptation is lost quickly (i.e. overnight), future vestibular implants will have to find a way to circumvent these unpleasant periods of useless nystagmus (e.g. by delivering a constant background stimulation, even at night, or by very progressively increasing/decreasing stimulation at onset/offset of the device). Finally the question remains whether solely the restoration of the canal function, without restoring the otolithic function is sufficient or not.

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