UNIVERSITÁ DEGLI STUDI DI MILANO
FACOLTA' DI MEDICINA E CHIRURGIA

DOTTORATO DI RICERCA IN FISIOLOGIA

SETTORE SCIENTIFICO DISCIPLINARE BIO-09 – CICLO XXV°

A BIONIC EYEBLINK

MANAGEMENT OF FACIAL PALSY

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Anno accademico 2011-2012

Editing and layout by Giusepp da Rigina.

Printed in Milano, Italy, in January 2013.

Part of this research has been conducted at the
Facial Nerve Center of the Harvard Medical School,
Massachussets Eye and Ear Infirmary, Boston MA, USA.

The cover shows the *Homo Vitruvianus* – Leonardo da Vinci (Milano) around 1490.

Ai miei alleli (e tre..)
Ai miei fratelli (e due..)
..e questa volta anche a Linda ☺

acknowledgements

Many people contributed to this work. With their unwavering trust and confidence in me, when at times I felt lost or off-track, they remained my true believers and ensured that we, together, would move on to complete the project.

First and foremost, my advisor Paolo Cavallari gave me the opportunity to pursue the challenge of developing this cutting-edge technology. By inspiring me with his vision, he also allowed me to take a bold step forward and develop different aspects of myself that I will carry into my professional career and life.

Thank you Tessa Hadlock, for welcoming me in the Facial Nerve Team. Tessa is well versed in both clinical and bench research, which, coupled with her facial plastics background, made her an invaluable support to this research. Plus, her humanity, enthusiasm and leadership make her one in a million.

I specially acknowledge James Heaton for his uncompromising commitment to excellence. Thanks for your support throughout the journey of clinical trials, for tirelessly editing my work and for teaching me how to play the carpenter/electrician in the lab ;)

I also acknowledge the influence that Federico Biglioli has had throughout my surgical education: he planted the seed and inspired me to pursue a PhD.

Special Thanks to my family for giving me wings big enough to fly the unconventional route, soaring on their love.

Thanks to all the closest friends who have supported me in the last years. I hesitate to list names since there is no order of priority, but hopefully those who have touched my life realize the impact they have had and will forgive me for not mentioning them. Thanks to my guiding light, you know who you are.

Now, wherever my journey leads from here... this doctoral experience will influence my final destination.

INDEX

1. FOREWORDS

Facial nerve disorders encompass a broad spectrum of dysfunction, ranging from subtle dynamic facial asymmetry to a complete dense paralysis. Unilateral peripheral facial palsy affects 0.4% of the population per year in Western Europe and the United States (*Bleicher et al. 1996; Schrom and Bast, 2010*). Bell's palsy (idiopathic) accounts for approximately two-thirds of all new facial paralysis cases, with the incidence of about 20-30 people per 100000 per year (*Kennedy, 2010*).

The impact of a facial nerve disorder can be dramatic and substantial effort has been put forth by scientists toward rehabilitation of the paralyzed face. This thesis highlights the current gold-standard surgical procedures for the rehabilitation of mimicry in individuals with facial paralysis and explores the potential application of *functional electrical stimulation* (FES) as a novel treatment restoring the face mimicry.

Closed-loop facial pacing represents an innovative solution for prosthetically assisted movements. In particular, blinking is typically symmetrical, enabling healthy eye blink on one side of the face to serve as a trigger to pace assisted blinks on the contralateral side, in case of unilateral peripheral facial nerve palsy.

The goals of this research are developing an eye-blink detection system and advancing the understanding of performing surface FES of the facial branch innervating the *orbicularis oculi* muscle in order to elicit artificial eyeblinks. The application of a biomimetic device to individuals with acute reversible facial paralysis would provide immediate restoration of the periocular function and could be used until either the patient recovers sufficient function to no longer require assistance for eye closure, or the decision is made to proceed with further surgery.

This work will hopefully lay the groundwork for a future technological transfer and create the premises for the development of an implantable neuroprosthesis for the rehabilitation of irreversible facial paralysis.

2. CLINICAL INTRODUCTION TO FACIAL PARALYSIS

Facial paralysis may have devastating effects, both because of physiological and psychological sequelae.

The long-term clinical presentation typically includes some combination of synkinesis, disuse atrophy, soft tissue adhesions and muscle lengthening of the affected side. Furthermore, typical clinical findings include complete paralysis up to atrophy of the muscle fibers that remain denervated, or paresis of muscles where partial reinnervation was established spontaneously or through surgical intervention.
Additional impairments may include drooling, tearing, muscle spasm, recurrent eye drying, and infections. Associated disabilities typically include difficulties in eating, drinking, dental hygiene, and speech. Emotional and social consequences affect a number of these patients, causing many of them to become socially isolated, less productive at work, and depressed. The clinical literature also suggests that long-standing damage to the facial nerve is irreversible and that the residual impairments or disabilities or both may deteriorate further over time. While nasal obstruction, oral incompetence, and articulation difficulties are of paramount importance, it is the periocular complications of facial paralysis that the clinician must address first, in order to prevent irreversible damage to the affected eye. When the *orbicularis oculi* muscle (*OO*) is incapable of meaningful contraction, lagophthalmos and ectropion may develop, leading to keratitis and corneal ulceration. Additionally, loss of the lachrymal pump may cause epiphora, and when the *frontalis* muscle is also involved, the brow and upper eyelid descend. This ptosis not only obstructs the upper visual fields, but may result in injury from the chronic sloughing of epithelial cells onto the corneal surface.

Current management of periocular facial paralysis consists of short-term and long-term strategies, both of which have significant disadvantages. In the setting of acute facial paralysis, artificial tears and hydroxypropyl cellulose ointment are applied to moisten and lubricate the cornea. This regimen does not restore a natural blink and, therefore, must be repeated every 1 to 2 hours, leading to a constantly wet periocular area, blurry vision, and significant inconvenience. When a longer-term solution is required, numerous surgical options may be employed to restore a blink; these usually are described in chapter 3. The use of *functional electrical stimulation* (FES) to reactivate the paralyzed *OO*, has the potential to provide an elegant and effective means of eliciting eye closure, without implanting lid weights nor harvesting autologous nerves or muscles.

3. SURGERY OF FACIAL PARALYSIS

The choice of the surgical treatment of irreversible facial paralysis depends on many different factors. The physician must accurately evaluate and examine the patient and determine the etiology, duration, and the scale of the paralysis. Only a precise assessment of the paralysis and health status dictates the potential for recovery and the most appropriate reconstructive scheme. Also the patient and the surgeon should thoroughly discuss the patient's expectations. As part of patient's education, surgeons need to establish realistic expectations and determine whether the patient is willing to expend the time and resources required for a successful result.

The favorable solution is a dynamic reconstruction of the mimetic function. *Facial reanimation* procedures refer to interventions that restore facial symmetry, resting tone, voluntary movement, or a combination of these. Several broad categories of facial re- animation techniques exist, each appropriate to a specific set of clinical, anatomic, or outcome-related circumstances.

Dynamic reconstructions tend to be more successful and fruitful to improve cases of severely impaired mimicry, and should be offered to each patient considering reconstruction, unless health risk contraindications exist. The most common approaches for reconstruction are direct facial nerve repair with or without cable grafting, nerve transfer, cross-facial nerve grafting, and muscle transfer. No current reconstructive stratagem can reproduce every facial expression and movement. Timing of the paralysis is crucial in the clinical decision-making, since a longer period of denervation translates into a lesser degree of recovery after rein-nervation. There is a decrease in efficiency of muscle reinnervation after 12-18 months of paralysis/denervation. Muscles that are reinnervated may not undergo full recovery or respond to regenerated nerves. The goals of facial reanimation include the following:

- facial symmetry at rest;
- symmetrical smile;
- voluntary, coordinated, spontaneous facial movements;
- oral competence and eyelid closure with corneal protection;
- absence or limitation of synkinesis and mass movement.

3.1. Direct repair of the facial nerve

When facial nerve discontinuity is encountered, the first approach is to attempt to reestablish direct neural continuity between the facial motor nucleus and the distal facial nerve through either primary repair or autografting techniques.

Direct repair represents the most effective procedure to restore the function of the facial nerve. This produces an intact motor nerve supply from the facial motor nucleus in the pons to the muscle endpoint and is preferable whenever possible. Repair is indicated in patients who have experienced acute disruption or transection of the nerve from an accident, trauma, resection during extirpation, or any iatrogenic damage during surgery. If direct repair without tension is possible, it should be performed. Mobilization of the nerve

may add some relative length but also may result in devascularization and further neural injury. For any defect greater than 2 cm, a *cable graft* may be inserted to produce a tensionless coaptation of the proximal nerve stump to the distal branch or branches. Several cable graft options are available when the length of the residual facial nerve is not sufficient for a direct tensionless repair. ***Supplement A*** *and* ***B*** reports the Author's experience with the primary reconstruction of multiple branches of the facial nerve via thoracodorsal nerve cable grafting in oncologic surgery.

3.2. Reinnervation techniques

Reinnervation techniques, also termed nerve substitution techniques, are procedures that provide neural input to the distal facial nerve and facial musculature via motor nerves other than the native facial nerve. Nerve substitution should be achieved in patients with facial paralysis who lack the proximal nerve segment but still have an intact distal neuromuscular pathway, including an intact distal segment of nerve and facial musculature suitable for reinnervation. A motor donor nerve, other than the native facial nerve, is transferred and anastomized to the distal facial nerve stump and innervates the facial muscles in place of the injured proximal facial nerve.

In case of unilateral facial paralysis, the contralateral facial nerve represents the favorable choice as motor donor nerve, since its facial nucleus naturally provides inputs for a symmetrical and spontaneous mimetic function. A long cross-face jump graft is needed to connect the two sides of the face. In case of cross-face nerve grafting, facial muscle movement will emerge after at least 9-12 months after the procedure (i.e., the allotted time for axonal growth to cross the graft). Most surgeons feel the motor power provided by other cranial nerves is distinctly superior, and the use of the contralateral facial nerve strictly for reinnervation of native facial musculature has largely been replaced by cross face nerve grafting in conjunction with free muscle transfers.

Ipsilateral motor cranial nerves, like hypoglossal and trigeminal nerves, provide an alternative source of motor neurons, reinnervating the distal stump of the damaged facial nerve in a shorter period of time. ***Supplement C*** reports the Author's experience with masseteric-facial nerve anastomosis for early facial nerve repair. Facial muscles show signs of functional recovery within 2 to 9 months, mean 4.8 months from the surgery.

3.3. Muscle transposition

When a muscular reconstruction is needed, local and free muscle transfer can be performed to restore motor function. The recovery of movement is limited to the specific site of transplant.

Temporalis muscle transfers may be used to reestablish both the voluntary smile and the eyeblink. The vector of the *temporalis* muscle resembles that of the *zygomaticus major* and, thus, results in a lateral smile when the caudal tendon of the muscle is rerouted and attached to the corner of the mouth. The eyeblink reanimation with a *temporalis* flap will be described in the next paragraph. Transposition of *temporalis* muscle itself does not produce spontaneous mimetic function. Each movement necessitates a specific volitional action, in which the patient must consciously contract the transposed muscle in conjunction with the smiling and/or blinking activity.

With the advent of microvascular free tissue transfer, the opportunity to bring functional muscle from a distant site into the face became possible. In a number of clinical scenarios, this approach is preferred. First, if the proximal facial nerve stump is available but the facial musculature has been resected, a free muscle graft can be transferred and driven by the ipsilateral proximal facial nerve. This has the potential of

providing involuntary, mimetic movement in the face. Patients with long-standing facial paralysis in whom the temporalis transposition is not an option may achieve superior results from free muscle transfer powered by either the ipsilateral trigeminal nerve or a cross facial nerve graft rather than through an alternative regional muscle transfer.

Congenital facial palsy patients are also good candidates for the procedure because they lack adequate muscles of facial expression or facial nerve trunks for neurorrhaphy and may have other cranial neuropathies. The procedure is most commonly performed as a two-stage procedure for unilateral paralysis and a single-stage procedure for bilateral paralysis (i.e., Moebius syndrome). This is because for unilateral paralysis, the muscle is powered by a cross facial graft from a buccal branch of the healthy facial nerve, requiring a 9- to 12-month waiting period for axonal extension through the cable graft before muscle transplantation. For bilateral paralysis, the muscle is driven by the ipsilateral trigeminal or hypoglossal nerve, which eliminates the need for a regeneration phase and second operative procedure.

One-stage procedures are also possible. ***Supplements D*** *and* ***E*** report the Author's experience with one-stage *latissimus dorsi* free flap transfer and ancillary procedures for the reanimation of smile in patients with established unilateral palsy.

Supplement F explores the spontaneity of smile recovery after free flap facial reanimations, in light of their motor source (contralateral facial nerve vs. masseteric nerve).

3.4. Eyeblink reanimation

With special regards to the eyeblink reanimation techniques, they reinstate the cornea's protective mechanism and recover a more natural appearance and eye function. Surgical planning aims to restore coordinated eyelid function. Although achieving voluntary eye closure is one of the primary goals, it cannot guarantee return of involuntary blink. Restoration of the afferent pathway of the reflex is a prerequisite, but successful coordination of the reflex components and restoration of their time-related function are also required. Both static and dynamic procedures have been used to augment eye closure, but only dynamic procedures can lead to blink restoration. However, reanimation of the eyelids still remains controversial (*Boerner & Seiff, 1994; Vlastou, 2006*). The best functional results from the most current reanimations techniques restore only about 80% range-of-movement compared with the contralateral, healthy side. Moreover, even with the best anticipated range of movement, there is still an absence of synchronous, symmetrical movement across the face.

Static management techniques involve implantation of devices in the upper eyelid that mechanically aid eye closure. The most popular devices are the platinum weight and the palpebral spring implants. They're both effective in restoring motion to the paretic upper eyelid, but the palpebral spring is more so despite the frequent need for revisions (*Terzis, 2008*). One of the advantages of a weight implantation is that it is relatively inexpensive and the weight is relatively easy to remove, allowing it to be performed in the early stages of facial palsy and reversed in the event that reinnervation occurs (*Snyder, Johnson, Moore and Ogren, 2001*). While it can restore a substantial degree of lid closure and corneal wetting, however, its passive nature precludes it from preventing lower lid ectropion or restoring lachrymal pump function. Additionally, because it relies on gravity to lower the upper lid, it is ineffective in the prone position and is completely ineffective during sleep. As a result of these factors, the use of lid loading typically requires additional complimentary measures to effectively maintain eye health. Complications can include infection, implant migration, skin erosion, poor cosmetic appearance, and extrusion (*Jobe, 1993; Pickford, Scamp and Harrison, 1992; Rahman and Sadiq, 2007; Smellie, 1966; Tucker and Santos, 1999*).

Dynamic techniques involve nerve transfers and eye sphincter substitution procedures. Nerve transfer techniques include cross-facial nerve grafting and subsequent microcoaptations, masseteric-facial nerve anastomosis (see ***Supplement C***), mini-hypoglossal nerve transfers, and direct orbicularis oculi muscle

neurotization. Within the eye sphincter substitution procedures, the temporalis muscle transfer, first proposed by Gillies in 1934, has been used and modified by several authors (*Brusati, 1994*). This method is still in use because the principle of a facial reanimation with autologous tissue with low morbidity in the donor area is extremely valid. Although a masticatory muscle is unable to provide a spontaneous blinking reflex and a normal tear drainage, a good voluntary protection of the cornea and an aesthetic correction of the eyelids is obtained with this method. Other eye sphincter substitution techniques include pedicled frontalis or temporalis transfers, free platysma, occipitalis, gracilis subunits, extensor digitorum brevis, and a slip of adductor longus transfer (*Terzis, 2010*).

SUPPLEMENT A

Facial nerve reconstruction using a thoracodorsal nerve graft after radical parotidectomy.
Plastic and Reconstructive Surgery 2012; 129(5):852e-853e.

GUIDELINES

Viewpoints, pertaining to issues of general interest, are welcome, even if they are not related to items previously published. Viewpoints may present unique techniques, brief technology updates, technical notes, and so on. Viewpoints will be published on a space-available basis because they are typically less time-sensitive than Letters and other types of articles. Please note the following criteria:

- Text—maximum of 500 words (not including references)
- References—maximum of five
- Authors—no more than five
- Figures/Tables—no more than two figures and/or one table

Authors will be listed in the order in which they appear in the submission. Viewpoints should be submitted electronically via PRS' *e*nkwell, at www.editorialmanager.com/prs/. We strongly encourage authors to submit figures in color.

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Viewpoints

Facial Nerve Reconstruction Using a Thoracodorsal Nerve Graft after Radical Parotidectomy

Sir:

The deliberate sacrifice of the facial nerve may be necessary in oncologic surgery of the parotid gland when the tumor mass incorporates the facial nerve trunk and its branches.[1] In such cases, immediate repair of the severed facial nerve is mandatory to limit aesthetic and functional deficits. When direct anastomosis of the severed facial nerve is not possible, the best surgical option is immediate reconstruction of the nerve by interpositional nerve grafting, using a variety of possible nerve grafts.

Between October of 2003 and August of 2010, six patients affected by malignancies of the parotid gland, and one with multiple recurrences of pleomorphic adenoma (aged 34 to 78 years), underwent radical parotidectomy with sacrifice of the facial nerve. All patients had partial facial nerve deficit preoperatively according to the House-Brackman grading system[2]: two patients were classified as grade II, three as grade III, and two as grade IV. The facial nerve was immediately reconstructed by an interpositional thoracodorsal nerve graft (Fig. 1). The number of distal anastomoses between thoracodorsal nerve branches and distal facial nerve branches was three in one case, four in two cases, five in three cases, and seven in one case.

Facial nerve function recovered in all patients at a mean of 7.8 months after surgery. One year after the appearance of the first mimetic muscle contractions, patients underwent a detailed examination. Morphologic and functional results according to the House-Brackman system were grade I in two patients, grade II in two patients, and grade III for the last three patients (Fig. 2). Recovery of eyelid closure was good for all patients.

The thoracodorsal nerve is a favorable alternative to the most commonly used nerve grafts, such as the great auricular nerve, the sural nerve, the medial and lateral antebrachial cutaneous nerves, the cervical plexus branches, and the superficial radial nerve. Because of its appropriate branching pattern,[3] it can be used to reconstruct up to seven distal branches. Also, the appropriate matching of calibers between the facial nerve trunk and the thoracodorsal nerve trunk, and between facial nerve branches and thoracodorsal nerve branches, results in loss of fewer axons compared with

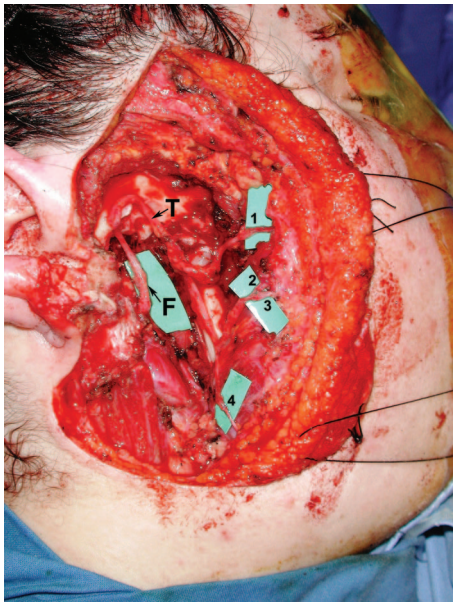

Fig. 1. Reconstruction of facial nerve branching after radical parotidectomy with an interpositional thoracodorsal nerve graft. The thoracodorsal trunk (*T*) is anastomosed proximally to the facial nerve trunk (*F*). Four distal branches of the thoracodorsal nerve are distally anastomosed to four main branches (*1*, *2*, *3*, and *4*) of the facial nerve.

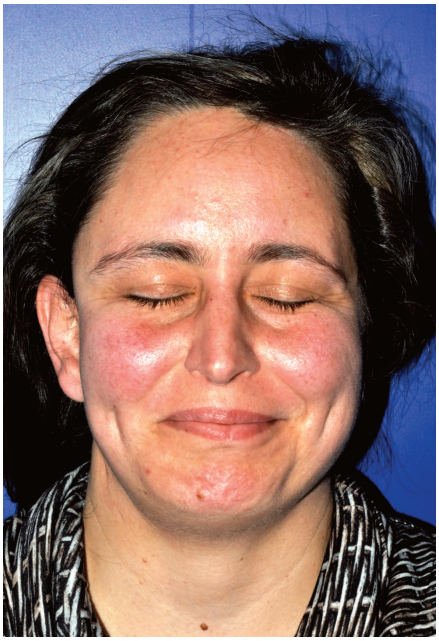

Fig. 2. Modest bulk deficit of the right parotid region is satisfactorily overwhelmed by complete recovery of facial nerve function.

multiple nerve grafts. Moreover, the thoracodorsal nerve is more favorable than most sensory nerves grafts used in terms of regeneration of the facial motor nerve.[4]

Finally, the possibility of harvesting a free deepithelialized flap based on perforators of the latissimus dorsi muscle and rib bone grafts for reconstructing the condyle and ramus of the mandible and overlying soft tissue after radical parotidectomy is an adjunctive advantage of the described technique.[5] Because of all of these advantages, the use of an interpositional thoracodorsal nerve graft represents a valid alternative to reconstructing the entire facial nerve branching system.

DOI: 10.1097/PRS.0b013e31824a62cd

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DISCLOSURE

The authors have no financial interests or personal relationships with other people or organizations that might inappropriately influence the work presented here.

PATIENT CONSENT

The patient provided written consent for the use of her image.

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Evidence-Based Analysis of Vein Graft Interposition in Head and Neck Free Flap Reconstruction

Sir:

Vein graft interposition is an accepted technique for microvascular reconstruction. However, in head and neck free flap reconstruction, vein grafting has rarely been addressed in the literature because of the relative infrequency of its use. In head and neck reconstruction, vein graft interposition was reportedly to be used in the following situations: (1) when the distance from the defect to the recipient vessels was greater than the length of the flap pedicle; (2) when vessel caliber mismatch existed between the recipient vessels and the flap pedicle; (3) when there were threatened or prior failed flaps; (4) when there were preirradiated graft beds; (5) for tumor recurrence; and (6) for trauma.[1–3] Whether vein graft interposition increases the risk of free flap loss in head and neck reconstruction remains controversial.[4] We decided to evaluate the existing literature, looking at the influence of vein graft interposition on free flap outcome in head and neck reconstruction through a systematic review.

We searched the PubMed database for articles published from January of 1990 to June of 2011. Our keywords included "free flap reconstruction" or "free tissue transfer," and "vein graft." This search was supplemented by a review of reference lists of potentially eligible studies. We excluded non-English articles, studies from the same institute with overlapping duration, and studies that also included free flap reconstruction in other body parts. Two

SUPPLEMENT B

Reconstruction of complex defects of the parotid region using a lateral thoracic wall donor site.
Journal of Cranio-Maxillofacial Surgery 2012 Dec (Epub ahead of print).

Journal of Cranio-Maxillo-Facial Surgery xxx (2012) 1–5

Contents lists available at SciVerse ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Reconstruction of complex defects of the parotid region using a lateral thoracic wall donor site

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ARTICLE INFO

Article history:
Paper received 27 March 2012
Accepted 16 October 2012

Keywords:
Parotid tumour
Lateral thoracic wall
Parotid complex defects
Facial nerve reconstruction
Thoracodorsal nerve

ABSTRACT

Radical treatment of parotid neoplasms may lead to complex parotid defects that present functional and aesthetic reconstructive challenges. We report our experience using the lateral thoracic wall as a single donor site.

Between 2003 and 2009, four patients with malignant tumours in the parotid gland underwent radical parotidectomy and simultaneous reconstruction using a perforator latissimus dorsi cutaneous free flap (de-epithelialized and entire skin paddle in two cases each). A thoracodorsal nerve graft was used in all cases to replace the intraglandular branches of the facial nerve. Costal grafts were used for mandibular reconstruction in two patients. All patients underwent postoperative physiotherapy. No donor-site complication occurred and all treatments achieved good aesthetic results. All patients recovered nearly complete symmetry at rest and partial facial mimetic function.

The lateral thoracic wall is a good donor site for the reconstruction of complex parotid defects.

1. Introduction

Radical treatment of parotid neoplasms may result in extensive resection of the parotid region and adjacent anatomical structures, which may include the mandibular ramus and condyle, overlying skin and may require sacrifice of the facial nerve. Failure to address these compound defects may lead to functional and aesthetic sequelae, such as a visible hollow in the parotid region, facial palsy, and loss of facial symmetry (Ioannides and Fossion, 1997). When resection involves the mandibular ramus, the chin deviates towards the affected side with loss of occlusion causing impaired chewing. In such cases, achieving a simultaneous high-quality reconstruction of both soft tissue and supporting skeletal structures is mandatory. Because local tissue is insufficient to produce a satisfying result, the compound use of free flaps and grafts may yield better outcomes (Ioannides et al., 1992; Ioannides and Fossion, 1997).

We present a series of four patients who underwent surgery for extensive parotid tumours and had reconstruction using the lateral thoracic wall.

2. Materials and methods

Four patients (two men and two women) underwent surgery for parotid malignancy in the Maxillofacial Surgery Department of S. Paolo Hospital, Milan, Italy, between October 2003 and December 2009 (Table 1). The histological diagnoses were carcinoma ex-pleomorphic adenoma ($n = 1$), high-grade mucoepidermoid carcinoma ($n = 1$) (Figs. 1 and 2), high-grade adenocarcinoma ($n = 1$), and leiomyosarcoma ($n = 1$) (Fig. 3). The patients age at the time of surgery ranged from 67 to 78years (mean 72.5 years), and the follow-up period ranged from 18 to 86 months (mean 28.2 months).

Tumour resection was accompanied by modified radical neck dissection in all patients. The patient with leiomyosarcoma underwent selective neck dissection due to the uncertainty of the preoperative histopathological diagnosis. Two patients had partial mandibulectomy and two underwent extensive skin resections. The intraglandular facial nerve was sacrificed in all cases, and was reconstructed using a thoracodorsal nerve graft anastomosed to the facial nerve trunk. Several distal branches of the thoracodorsal nerve were anastomosed to distal branches of the facial nerve, which had been sectioned within the parotid gland. In two patients, reconstruction of soft tissue bulk was achieved using a de-epithelialized latissimus dorsi free flap. In the other two patients, the

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http://dx.doi.org/10.1016/j.jcms.2012.10.006

Table 1
Patient characteristics, treatments, and outcomes.

Patient	Sex	Age (years)	Pathology	Operation	Reconstruction	Operation time	Preop HB	Postop HB	Time of initial postoperative mimetic muscle contraction (months)
B.F.	F	75	High-grade adenocarcinoma	Parotidectomy, facial nerve sacrifice, partial mandibulectomy	Latissimus dorsi perforator de-epithelialized cutaneous free flap, thoracodorsal nerve graft, rib graft	7 h	III	II	6
B.M.	F	67	High-grade mucoepidermoid carcinoma	Parotidectomy, facial nerve sacrifice, partial mandibulectomy, skin resection	Latissimus dorsi perforator cutaneous free flap, thoracodorsal nerve graft, rib graft	6 h	II	I	9
C.S.	M	70	Leiomyosarcoma	Parotidectomy, facial nerve sacrifice	Latissimus dorsi perforator de-epithelialized cutaneous free flap, thoracodorsal nerve graft	4 h 30 min	II	III	9
T.A.	M	78	Carcinoma ex adenoma	Parotidectomy, facial nerve sacrifice, skin resection	Latissimus dorsi perforator cutaneous free flap, thoracodorsal nerve graft	7 h 30 min	III	II	14

HB, House–Brackmann facial paralysis score.

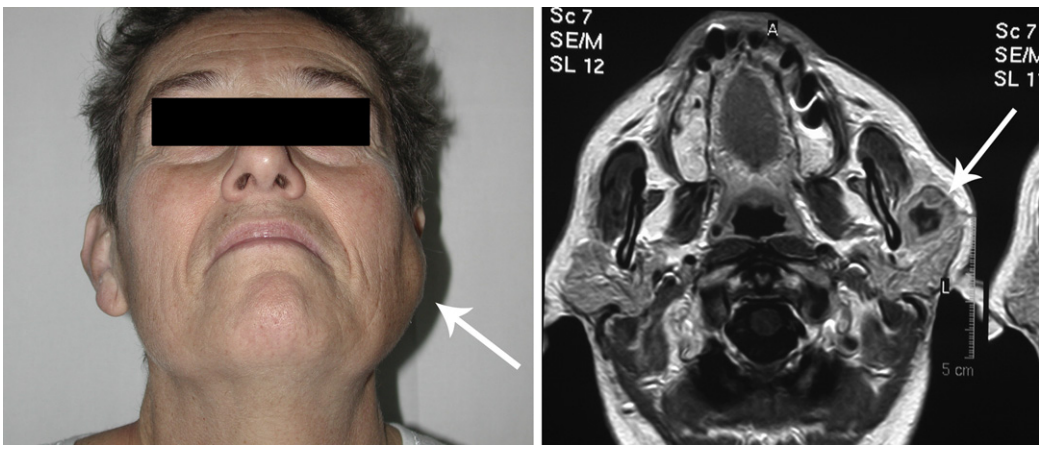

Fig. 1-2. Preoperative clinical (1) and radiological (2) images of patient BM, affected by high-grade mucoepidermoidal carcinoma (arrows) of the left parotid gland.

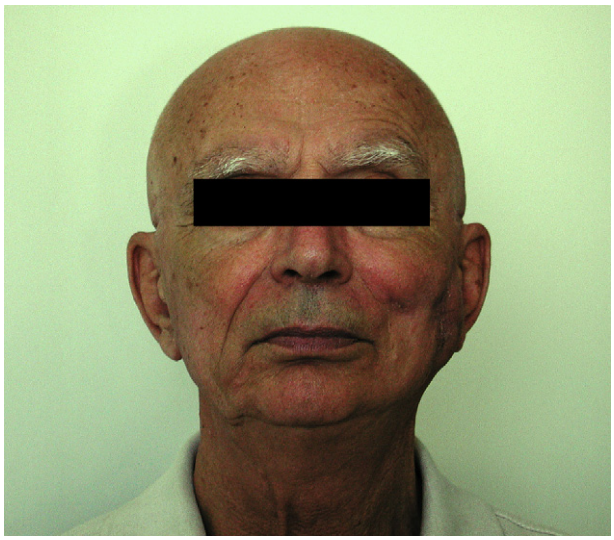

Fig. 3. Preoperative clinical image of the patient CS affected by a leiomyosarcoma of the left parotid gland.

entire skin paddle was used to cover the residual skin defect after surgical resection (Fig. 4).

In two patients, the tumour mass infiltrated the mandibular condyle and ramus medial to the parotid. Reconstruction was achieved with costal grafts harvested from the same donor site used to obtain the latissimus dorsi free flap and thoracodorsal

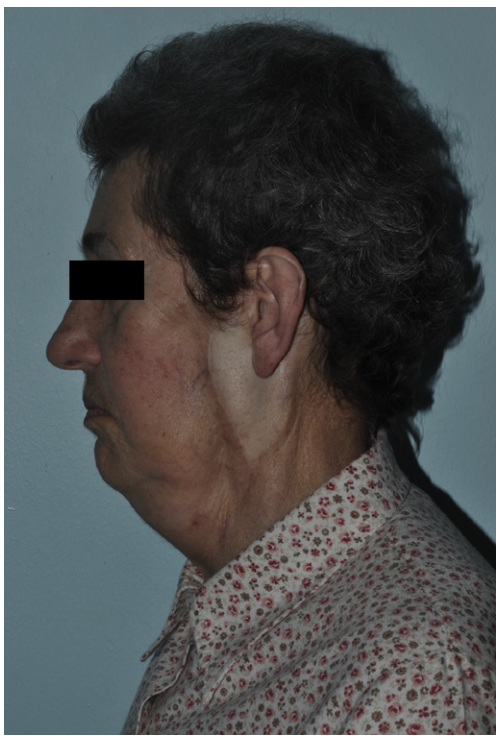

Fig. 4. Postoperative lateral view of the patient BM.

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Table 2
House–Brackmann facial paralysis scale.

Grade	Impairment
I	Normal
II	Mild dysfunction (slight weakness, normal symmetry at rest)
III	Moderate dysfunction (obvious but not disfiguring weakness with synkinesis, normal symmetry at rest). Complete eye closure with maximal effort, good forehead movement
IV	Moderately severe dysfunction (obvious and disfiguring asymmetry, significant synkinesis). Incomplete eye closure, moderate forehead movement
V	Severe dysfunction (barely perceptible motion)
VI	Total paralysis (no movement)

nerve. These two patients underwent 2 weeks of intermaxillary fixation and intense rehabilitation according to the Delaire technique (Delaire et al., 1975), followed by 4 weeks of therapy using active rubber bands and 4–6 weeks of therapy with a lateral plate that was progressively modified to gain additional contralateral mandibular movement.

The average total operating time was 6 h and 15 min.

All patients underwent full-dose postoperative radiotherapy. No complication or bone graft infection occurred during the follow-up period.

An independent panel of two physicians and one physiotherapist used the House–Brackmann scale to evaluate the symmetry of each patient's face at rest and the movements of the mimetic musculature at least 1 year after the first evidence of facial muscle contraction (Table 2) (House and Brackmann, 1985).

3. Results (Table 1)

The mean follow-up time was 4.8 years. All free flaps survived and no complication was observed at the recipient or donor sites. Good aesthetic results were achieved in all patients, with only slight asymmetry in two cases. Loss of free-flap bulk was minimal and all patients became stable within 6 months after surgery.

Both costal grafts survived, despite radiotherapy; with no gross resorption of the grafted bone evident on computed tomography (CT) scans taken 24 or 34 months after surgery. Individual occlusion was maintained with only partial functional impairment (28 and 32 mm maximal interincisal opening, 2 and 3 mm contralateral mandibular movement). These two patients showed good contouring of the lower third of the face with no chin deviation.

All patients recovered partial facial nerve function within 6–14 months (mean 9.5 months) after surgery, characterized by nearly complete symmetry at rest (Figs. 5 and 6) and some mimetic movements (primarily smiling and eyelid closure) (Figs. 7–9).

Facial reanimation results according to the House–Brackmann classification are reported in Table 1; one patient (25%) achieved a score of I, two patients (50%) obtained a score of II, and one patient (25%) had a score of III. All patients showed a one-level improvement in facial function between pre- and postoperative scores.

All patients showed consistent recovery of eyelid closure, with no need for tear-replacement eye drops. All patients showed mild synkinesia, characterized by good eyelid closure with the partial activation of the reconstructed nerve and eyelid closure accompanied by some degree of synkinetic smiling with maximal facial nerve activation (Mov 1).

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcms.2012.10.006.

To date, three patients are clinically and radiologically disease-free. The patient with high-grade mucoepidermoid carcinoma has both cervical and distal metastases.

4. Discussion

After total parotidectomy, loss of facial bulk frequently produces discomfort in the preauricular and retromandibular areas due to the evident impairment of the facial contour. Some tumours spread

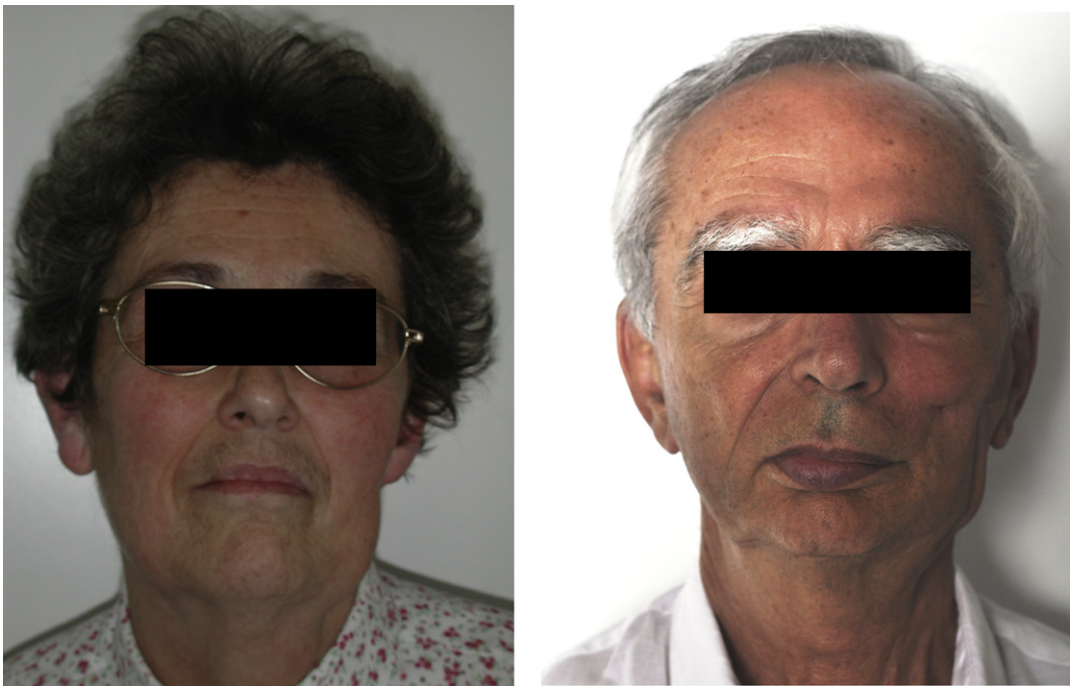

Fig. 5-6. Postoperative appearance of the patient BM (5) and CS (6) showing good symmetry of the face at rest.

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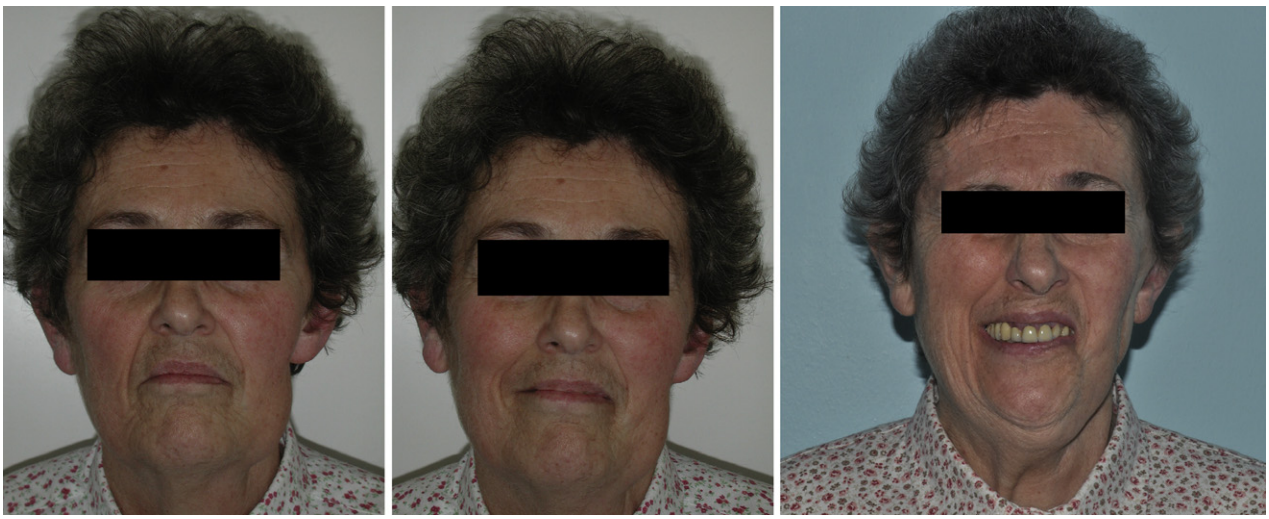

Fig. 7-9. Postoperative appearance of the patient BM 18 months after surgery: good symmetry of the face during eyelid closure (7) and smiling (8 and 9).

superficially and require skin resection, necessitating tissue transfer to close the surgical defect.

The radical treatment of tumours involving the deep lobe of the parotid may require partial mandibulectomy, potentially resulting in facial asymmetry characterized by the deviation of the mandible towards the affected side with loss of occlusion and impaired chewing. When facial nerve branches are resected together with the tumour, microsurgical reconstruction must be considered. Complex defects may remain after the surgical treatment of malignant parotid tumours, and any subsequent reconstruction must provide a large amount of soft and, sometimes hard tissue.

The hollowing left by total parotidectomy may be reconstructed using an abdominal fat graft transfer, as suggested by Conger (Conger and Gourin, 2008). They advocate this as a safe and effective means of achieving pleasant cosmetic results with a minimally invasive donor-site incision and no harvest-related morbidity. However, fat transfer does not provide sufficient coverage in cases of significant skin loss, and planned postoperative radiotherapy may cause significant resorption or devascularization. Therefore, more reliable flaps have been suggested (Davis et al., 1995; Chandarana et al., 2009).

The reconstruction of complex parotidectomy defects using the lateral arm free flap was described by Teknos (Teknos et al., 2003). This is a good reconstructive option as the posterior cutaneous nerve of the forearm can be simultaneously harvested for use as a cable graft for facial nerve reconstruction. However, the small bulk of this flap may not provide complete defect coverage, and the pedicle vessels may be of insufficient length to reach the recipient neck vessels. Although such flaps are fasciocutaneous, the authors report that some degree of postoperative atrophy may occur.

Ioannides and Fossion reported their experience with the use of the pectoralis major to reconstruct extensive parotid defects (Ioannides and Fossion, 1997). They argue that the pectoralis major flap has many advantages, including a long pedicle allowing the flap to readily reach the malar bone and external ear, the ease and speed of dissection, and its reliability. However, this flap provides a poor colour match in cases requiring a skin paddle, and the donor-site scar can be a drawback, especially in female patients. Consequently, these flaps are particularly indicated in elderly and medically compromised patients. In other patients, a latissimus dorsi free flap is suggested as first choice, due to its reliability, skin paddle and the possibility of harvesting a rib together with the flap when mandibular reconstruction is necessary, thereby avoiding the need to raise a second flap.

Kim et al. presented a large series of perforator flaps from the flank area, emphasizing the versatility of this donor site for skin reconstruction, since this area can provide different perforator flaps relying on musculocutaneous, septocutaneous and direct cutaneous perforators. These flaps provide a reliable, large skin paddle (up to 34 × 10 cm) with more versatile composition options if compared with other flaps (Kim, 2005).

Cannady et al. reported their experience with buried free flaps, including anterolateral thigh (ALT), fascial radial forearm, and lateral arm free flaps (Cannady et al., 2010). They suggest that the use of sternocleidomastoid or platysma flaps is avoided due to the risk of nerve injury, particularly the great auricular nerve, and the residual hollowed appearance of the donor site. They also advise against the use of superficial muscle aponeurotic system or temporoparietal fascia flap transposition. These flaps can be adequate for superficial parotidectomy defects but provide insufficient tissue for volume restoration following total parotidectomy. The authors argue that the ALT flap is ideally suited for this purpose due to the ease of two-team harvesting, the ability to sculpt and match tissue types, and the relatively low donor-site morbidity.

In 2007 Biglioli and Autelitano suggested the use of a parascapular flap to avoid the functional and aesthetic sequelae of total parotidectomy (Biglioli and Autelitano, 2007). This flap is reliable, but the donor site does not allow nerve harvest, in cases with facial nerve resection. Hyodo et al. proposed the management of total parotidectomy defects with a gastrocnemius muscle transfer and vascularized sural nerve grafting (Hyodo et al., 2007). The pedicle calibre is adequate for anastomosis to recipient vessels, but is somewhat short. Drawbacks associated with these flaps include donor-site morbidity and significant atrophy of the paralytic transferred muscle, leading to insufficient hollow coverage. The main advantage of this flap is the clinical superiority of nerve regeneration with vascularized (vs. non-vascularized) nerve grafts, however, the use of vascularized nerve grafts is controversial because reliable results may be achieved with traditional nerve grafts (Reddy et al., 1999).

In the standard treatment of benign parotid tumours or small-medium intermediate grade malignant tumours with no clinical or surgical sign of neurotrophic invasion, the preservation of all facial nerve branches is mandatory. In cases of preoperative facial paralysis or those in which dissecting the facial nerve trunk from

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the tumour mass during surgery is impossible, radical oncological treatment implies the sacrifice of the facial nerve.

The best results of functional facial nerve recovery are commonly accepted to be achieved when facial nerve repair is performed simultaneously (Seddon, 1943; White et al., 2006). This can be accomplished with direct epineural suturing of the two stumps if the length of the removed facial nerve allows for a tensionless suture. This almost never occurs in radical parotidectomy, in which the facial nerve is sectioned together with the tumour mass. Such cases require cable grafts. When the tumour mass shows wide facial nerve infiltration back to the stylomastoid foramen, the main trunk of the facial nerve as a source of motor regeneration is absent. In these instances, a different motor donor nerve should be considered, such as the hypoglossal or the masseteric nerve. Biglioli previously described the masseteric-facial nerve anastomosis for early facial reanimation as a reliable technique with low donor-site morbidity (Biglioli et al., 2012).

Since the main trunk of the facial nerve is more commonly available after parotid tumour resection, there are various options for the reconstruction of the interrupted facial nerve (Reddy et al., 1999).

The primary donor sites are the great auricular nerve or the sural nerve, although many other donor sites, such as the medial and lateral antebrachial nerves, the superficial radial nerve, branches of the cervical plexus, and the thoracodorsal nerve, have been considered.

The great auricular nerve, harvested as a traditional graft, or as suggested by Koshima, as a vascularized graft, seems to be the best choice because it is promptly available in the surgical field (Koshima et al., 2004; Biglioli et al., 2012); however, this practice is discouraged in oncological surgery due to concern about potential microscopic tumour involvement because the graft is at least partially resected together with the tumour.

The sural nerve is the most commonly used because it is long (up to 30 cm) and has abundant nervous fascicle (Reddy et al., 1999). It is associated with reduced donor-site morbidity and is easy to harvest. However, this nerve reconstruction option has an intrinsic defect. When several peripheral stumps must be connected to the main trunk following total parotidectomy, no more than one sural nerve stump may fit the trunk of the severed facial nerve, leading to incomplete reconstruction of the facial nerve branches.

We advise the use of the thoracodorsal nerve graft because this motor nerve is long and has an appropriate branching pattern. One such graft can be used to reconstruct up to seven distal branches of the facial nerve (Iwasawa et al., 2002). The trunk of the thoracodorsal nerve can be grafted to the facial nerve by a single anastomosis. The same is true for the distal branches of the thoracodorsal and facial nerves. Moreover, the same lateral thoracic wall donor site can be used to simultaneously harvest the latissimus dorsi cutaneous perforator flap, the thoracodorsal nerve graft, and a rib graft which can be used reconstruct the mandibular condyle and ramus (Ioannides and Fossion, 1997). In our opinion, this unique versatility makes this region the ideal choice for the reconstruction of complex parotid region defects.

5. Conclusions

The treatment of parotid neoplasms may result in extensive anatomical resection with functional and aesthetic sequelae. Surgical reconstruction is challenging, requiring the replacement of extensive tissue loss, reconstruction of the facial nerve and its branches, and the correction of mandibular ramus deficits. The lateral thoracic wall is an ideal donor site providing tissue addressing all of these requirements with minimal morbidity.

Role of funding source

No sources of support/grant.

Conflicts of interest

None declared.

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Please cite this article in press as: Biglioli F, et al., Reconstruction of complex defects of the parotid region using a lateral thoracic wall donor site, Journal of Cranio-Maxillo-Facial Surgery (2012), http://dx.doi.org/10.1016/j.jcms.2012.10.006

SUPPLEMENT C

Masseteric-facial nerve anastomosis for early facial reanimation.
Journal of Cranio-Maxillofacial Surgery 2012; 40(2): 149-155.

Journal of Cranio-Maxillo-Facial Surgery 40 (2012) 149–155

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Masseteric–facial nerve anastomosis for early facial reanimation

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ARTICLE INFO

Article history:
Paper received 22 August 2010
Accepted 1 March 2011

Keywords:
Masseter–facial anastomosis
Facial paralysis
Early facial reanimation
Masseter nerve

ABSTRACT

Objective: Early repair of facial nerve paralysis when cortical neural input cannot be provided by the facial nerve nucleus, is generally accomplished anastomozing the extracranial stump of the facial nerve to a motor donor nerve. That is generally the hypoglossus, which carries a variable degree of morbidity. The present work aims to demonstrate the effectiveness of the masseteric nerve as donor for early facial reanimation, with the advantage that harvesting is associated with negligible morbidity.
Methods: Between October 2007 and August 2009, 7 patients (2 males, 5 women) with unilateral facial paralysis underwent a masseter–facial nerves anastomosis with an interpositional nerve graft of the great auricular nerve. The interval between the onset of paralysis and surgery ranged from 8 to 48 months (mean 19.2 months). All patients included in the study had signs of facial mimetic muscle fibrillations on electromyography. The degree of preoperative facial nerve dysfunction was grade VI following the House-Brackmann scale for all patients.
Results: At the time of the study, all the patients with a minimum follow-up time of 12 months after the onset of mimetic function had recovered facial animation. Facial muscles showed signs of recovery within 2–9 months, mean 4.8 months, with the restoration of facial symmetry at rest. Facial movements appeared while the patients activated their chewing musculature. Morbidity related to this intervention is only the loss of sensitivity of earlobe and preauricular region.
Conclusion: The present technique seems to be a valid alternative to classical hypoglossal–facial nerve anastomosis because of similar facial nerve recovery and lower morbidity.

1. Introduction

Facial paralysis are distinguished into two main groups according to the presence or absence of facial fibrillations at needle electromyography. Recent paralysis, mainly lasting less than two years (but some of them are older), generally show these signs and are eligible for reactivation of facial nerve anastomosing it to a donor one (early facial reanimation) (Terzis and Tzafetta, 2009). Indeed, when the proximal stump of the seventh cranial nerve cannot be used for anastomosing, the motor stimulus must be accomplished by utilizing another cranial motor nerve.

The contralateral facial nerve, using the technique of cross-face nerve grafting (Smith, 1971; Scaramella and Tobias, 1973), allows recovery of facial nerve mimetic function both under voluntary and emotional stimulus, thus providing the preferred innervation. This technique should be performed when the denervation time is less than 5 months in order to obtain fair results (Frey et al., 2006). A longer waiting time lead to a high percentage of unsuccessful operations. Donor-site sensory deficit in the lower extremity is an additional disadvantage of this procedure. The "babysitter" procedure – a cross-face nerve grafting associated with a partial hypoglossal/accessory spinal–facial nerve anastomosis, was introduced in 1984 by Terzis (1990), to restore facial nerve function when denervation time is more than 6 months (up to 27 months). This procedure allows quick recovery of facial nerve function while cross-face sural nerve grafting is undergoing axonal nerve ingrowth. By the time the distal end of the grafted sural nerve is to be anastomosed to the facial nerve, the facial muscles and neuromuscular junctions have not fallen into irreversible atrophy.

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1010-5182/$ – see front matter © 2011 European Association for Cranio-Maxillo-Facial Surgery.
doi:10.1016/j.jcms.2011.03.005

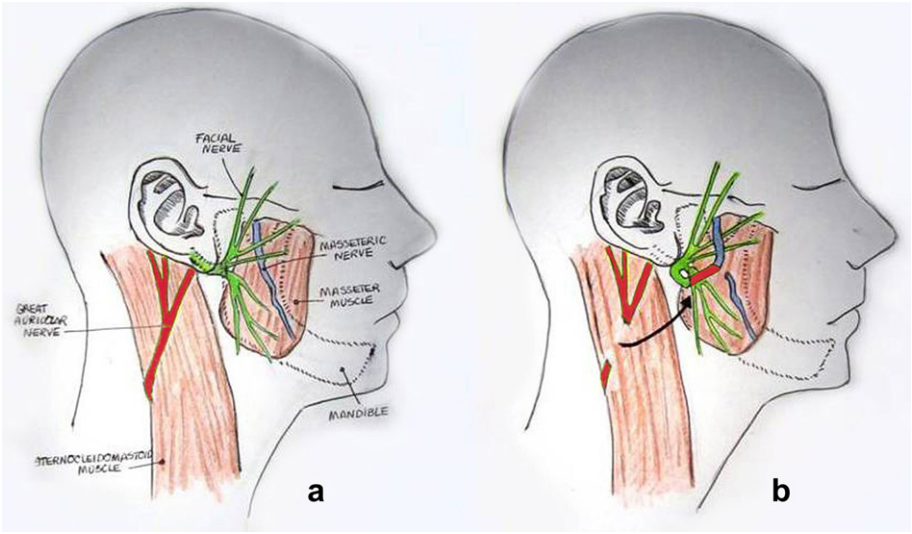

Fig. 1. Drawing of masseter to facial nerve anastomosis. (a) Facial nerve, masseteric nerve and great auricular nerve are identified. (b) 5–6 cm of great auricular nerve is grafted between the proximal end of the masseteric nerve and the main trunk of the extracranial facial nerve.

When neither the contralateral facial nerve or the ipsilateral one are available, because of multiple cranial nerve involvement, Moebius syndrome or the time since the onset of facial paralysis is too long to consider a cross-face nerve graft procedure, an alternative donor motor nerve is needed.

Spinal accessory–facial nerve anastomosis, first performed by Ballance in 1895 (Van der Graf et al., 2008), was the first to be described in literature. Functional downgrading of the sternocleidomastoid and trapezius muscle functions is a major drawback of this technique. Currently this technique is mainly utilized when the hypoglossal nerve is completely or partially damaged as well as when swallowing is already problematic.

The motor roots of the cervical plexus are an alternative but less favourable motor source, indicated only when complex multiple cranial nerve involvement is present (Terzis and Konofaos, 2008).

Currently the most frequently used donor nerve is the hypoglossus, first attempted by Korte (1903) in 1901. Hypoglossal–facial nerve end-to-end anastomosis is considered an effective and reliable technique that gives satisfactory results. Unilateral denervation of the tongue is the most common consequence, leading to tongue atrophy in 50–70% of cases and worsening eating and swallowing ability in 20–45% of cases (Yetiser and Karapinar, 2007). Functional results are typically mass movements of the face and synkinesis associated with extreme tongue movement that are frequently observed. Modification of the anastomosis technique from end-to-end to end-to-side seems to reduce tongue dysfunction, but the success of this modified technique on facial reanimation is still unclear.

In order to reduce the morbidity associated with early facial reanimation while maintaining a high rate of success, the masseteric nerve, branching from the trigeminal nerve, has already been shown to be a reliable alternative. A few reports describe its use for selective facial nerve branch reanimation (Escat and Viela, 1925; Spira, 1978; Bermudez and Nieto, 2004) or for chronic facial reanimation (Zuker et al., 2000).

The new technique describes early reanimation accomplished by anastomosing the masseteric nerve to the entire facial nerve trunk with a great auricular nerve interpositional graft. (Fig. 1).

2. Surgical technique

1:200.000 epinephrine is injected 5 min before surgery subcutaneously into the parotid region along the intended line of the skin incision, which has been marked. This is a face-lift type incision, beginning in the temporal region, passing hidden behind the tragus, under the earlobe and extending into the mastoid region. An antero-inferior skin flap is elevated in order to access the parotid-masseter region.

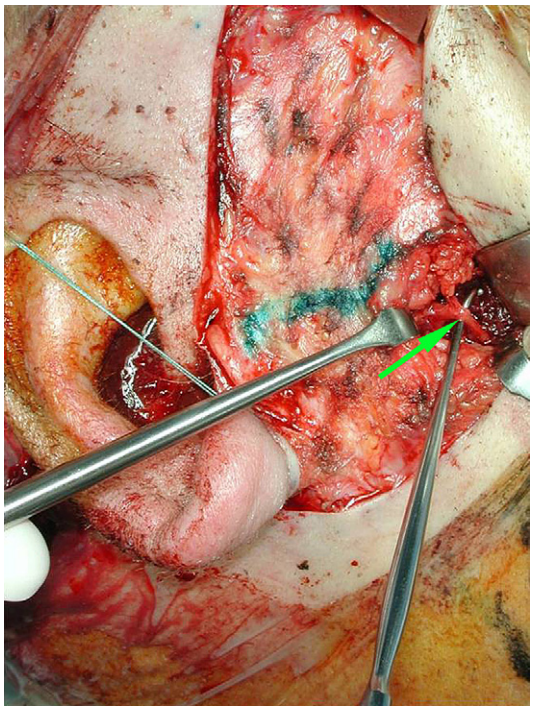

Fig. 2. The masseteric nerve identified into the muscular parenchyma (arrow).

The first nerve to be identified is the great auricular nerve. This is immediately deep to the superficial cervical fascia, 4–5 cm inferior to the earlobe, over the anterior border of the sternocleidomastoid muscle. The nerve is traced inferiorly for few centimetres and superiorly until it enters the parotid gland. 5–6 cm of the main trunk are taken to be used as an interposition nerve graft.

Now the VII nerve is identified at its exit from the styloid foramen by the standard extracranial antegrade technique. All the nerve trunk and first 2 cm of the main branches after the

bifurcation are traced. Finally, the masseter motor nerve is identified in the muscle parenchyma (Fig. 2). Surgical landmarks are the zygomatic arch and the posterior border of the masseter muscle. Detaching the muscle insertion to the zygomatic arch is not necessary as the masseteric nerve is really deep at this level. It is best to enter into the muscle 1 cm above the arch and 1 cm medial to the posterior border. The upper and middle branches of the facial nerve may be seen over the masseter surface. These must be spared when dissecting between them. The nerve lies 1.5–2 cm deep to the muscle surface and is made visible by gently dissecting the muscle fibres along their axis (almost vertical). These part easily and the nerve shows up spontaneously.

One or two small collateral branches of the masseteric nerve may be cut when proceeding supero-inferiorly to allow harvesting 2.5/3 cm of nerve trunk.

The facial nerve trunk is now cut at its exit from the styloid foramen and the masseteric nerve is cut distally. Both nerves are rotated to match each other. The few centimetres between their extremities are filled by the interposition graft of the great auricular nerve. This is set backwards in order to lose as few axonal fibres as possible while new fibres are growing through the graft.

Both proximal (masseteric nerve/great auricular nerve) and distal anastomoses (great auricular nerve/facial nerve) are accomplished end-to-end with a few 10-0 epineural stitches surrounded by fibrin glue (Fig. 3).

The parotid fascia is sutured over the anastomoses to provide good vascularity for the graft, and to protect the whole nerve route. Meticulous haemostasis and positioning of suction drainage is important. Finally, a well hidden aesthetic suture ends surgery.

3. Materials and methods

Between October 2007 and August 2009, 7 patients (2 men, 5 women) affected by unilateral complete facial paralysis underwent a masseter–facial nerve anastomosis with a great auricular interpositional nerve graft. The ages of the patients ranged between 23 and 48 years (mean 35.1 years). The time from the onset of the paralysis ranged between 8 and 48 months (mean 19.2 months). Patients operated within 12 months from the onset of paralysis were documented to have the VII nerve transected intraoperatively during previous cranial base surgery. The aetiology was a complication of skull base surgery in 6 cases and a Bell's palsy lasting 18 months in 1 case. All palsies were grade VI on the House-Brackmann scale. Clinical evaluation was complemented by preoperative needle electromyography (EMG) that assessed complete facial nerve and muscle injury in all patients. At the EMG and needle EMG study all patients presented with severe (complete) denervation in the facial nerve territory with lack of motor unit action potential (MUAP) recruitment and nerve trunk inexcitability (direct stimulation at tragus and evaluation of blink reflex responses).

All patients had fibrillations demonstrating mimetic musculature presence despite the length of time since denervation (Terzis and Tzafetta, 2009). Those patients who did not show fibrillations underwent free-flap transposition for facial reanimation because of the extremely low possibility of masseter–facial nerve anastomosis to achieve success. The trigeminal motor component was tested clinically by palpating the temporal region when chewing and by needle EMG in the ipsilateral masseter muscle in order to use it as donor motor nerve.

After surgery, all patients were instructed to call a member of the team at first movements of the face. As soon as the patients called, a clinical evaluation was carried out and the first postoperative EMG was performed.

All patients received postoperative physiotherapy from the time recovery began for one year. Patients were asked to watch themselves on a mirror (bio-feedback) while achieving symmetry at rest, biting and without biting, and while smiling or making grimaces. All movements had to be slow, allowing selective muscle control; patients were taught to gradually reduce the strength of bite necessary to achieve mimetic muscle activation during the rehabilitation period.

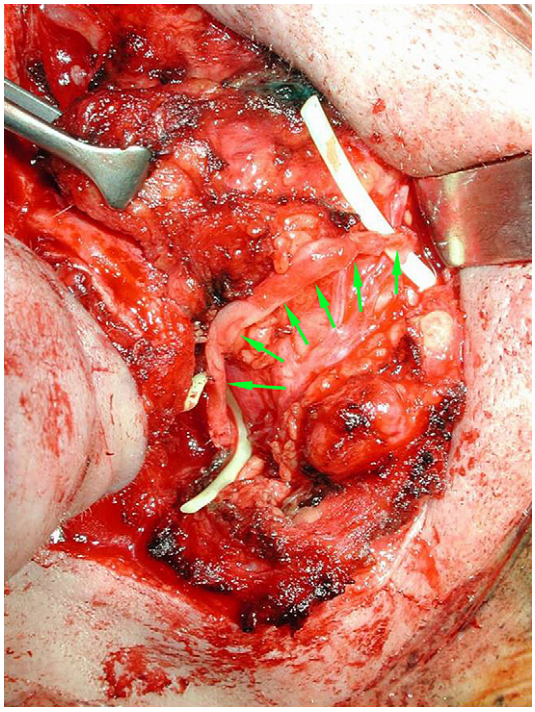

Fig. 3. A tract of great auricular nerve (arrows) grafted between masseteric and facial nerves.

Table 1
Results classification (Terzis and Noah, 1997).

5	EXCELLENT	Symmetrical smile with teeth showing, full contraction
4	GOOD	Symmetry, nearly full contraction
3	MODERATE	Moderate symmetry, moderate contraction
2	FAIR	No symmetry, minimal contraction
1	POOR	Deformity, no contraction

Evaluation of facial reanimation was done 12 months after the first clinical signs of mimetic recovery after surgery. All the patients who underwent the surgical operation have this minimum follow-up time at the time of the study. From then on, patients underwent a routine clinical evaluation every three months. At the time of the study, patients underwent clinical examination to assess the symmetry of the face at rest and the quality and quantity of the dynamic recovery. Patients were asked to smile and close their eyes while activating their chewing musculature. The quality of eye closure and mouth corner movement and any synkinesis or mass movement were recorded and studied by one physician and a physiotherapist. Results were classified according to the J. Terzis scale (Terzis and Noah, 1997) (Table 1). Finally, patients were recorded on a video-camera while left in a room alone (to avoid any external influence) watching a funny video, looking for any spontaneous activation of the reanimated hemi-face.

4. Results

The average duration of surgery was 2 h and 15 min. Wound healing and postoperative recovery were uneventful in all patients.

At the time of the study, all the patients operated on had recovered facial mimetic function. Recovery time ranged from 2 to 9 months after surgery, mean 4.8 months.

If we consider orbicularis muscle contraction while activating the chewing muscles complete eyelid closure was achieved in 4 patients and partial closure, with 1–2 mm scleral show, was seen in 3 patients. Before surgery, the mean scleral show was 5.7 mm and the mean eyelid closure improvement was 5 mm. Data related to each patient are shown in the table below (Table 2).

Clinical evaluation showed that the final result of symmetry at rest and dynamic restoration of smile while activating the chewing musculature was excellent in two cases (Figs. 4a–b, 5a–b, 6a–b, 7a–b), good in three cases and adequate in two cases. The only patient with long-lasting paralysis (48 months) was among those two with adequate result at smiling and partial lid closure.

Among all patients light/medium strength activation of the masticatory muscles leads to the movement of the lower two-thirds of the face. This leads to a pleasant full dental smile on observation.

All patients showed synkinesis between the upper and the lower parts of the face on maximal chewing effort.

Partial discrimination of facial movement of the lower two-thirds of the face towards the upper third was possible in all patients by concentrating and modulating the strength of chewing signal.

Table 2
The table explains the data relative to scleral show in 7 patients before and after surgery.

Cases	Scleral show		Improvement (mm)
	Before surgery (mm)	After surgery (mm)	
PZ 1	7	2	5
PZ 2	6	0	6
PZ 3	5	0	5
PZ 4	6	0	6
PZ 5	7	2	5
PZ 6	3	1	2
PZ 7	6	0	6
Mean	**5.7**	**0.7**	**5**

Three patients showed partial activation of the *frontalis* branch of the facial nerve; these patients had the best discriminatory skill within the different branches.

Observing the video of patients watching the funny movie, none of the patients recovered a spontaneous smile. All of them activated only the non-operated side mimetic musculature while laughing spontaneously. So the operated side could be activated only by voluntary stimulus.

One patient reported limited mouth opening during the first 8 postoperative weeks, due to masseter scar formation. Recovery of full opening of the mouth was reached by 3 weeks of physiotherapy. None reported limited strength in chewing. One patient showed thinning of the cheek postoperatively, probably due to masseter muscle atrophy because of denervation. He refused a lipofilling procedure because he felt asymmetry was not significant.

5. Discussion

The first attempts at the use of the masseteric nerve as a donor motor nerve in facial reanimation were done in 1925 by Escat and Viela (1925). There were a few preliminary reports by Spira (1978) and anatomical studies by Brenner and Scholler (Fournier et al., 1997; Brenner and Schoeller, 1998) followed, but no wide clinical series have been published yet.

In 2000 Zuker et al. (2000) popularized the use of the masseter motor nerve as donor source to reinnervate free gracilis flaps in patients affected by Moebius syndrome. Six years later the same authors published a series of 45 gracilis muscle transfers innervated by the masseteric motor nerve in 27 patients affected by Moebius syndrome with excellent morpho-functional results (Manktelow et al., 2006).

In 2004 Bermudez and Nieto (2004) published a case report of masseteric–facial nerve transfer, with anastomosis between the branch of the masseteric nerve to a zygomatic branch of the injured facial nerve. This procedure was suggested as a good alternative for facial reanimation in patients with partial palsies. Initial movement appeared 4 months after surgery and complete recovery was seen 6 months postoperatively.

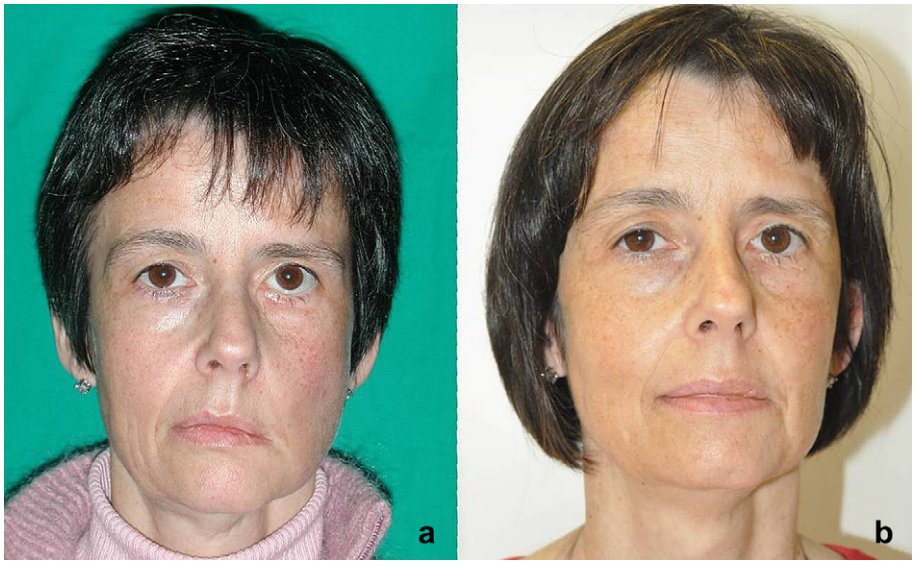

Fig. 4. (a) Preoperative image of a 48 years old female patient, affected by facial paralysis after acoustic neuroma surgery. Masseteric to facial nerves anastomosis was accomplished 8 months after insetting of paralysis. (b) Appearance of patient at rest 9 months postoperatively (first contraction 4 months after masseteric to facial nerves anastomosis).

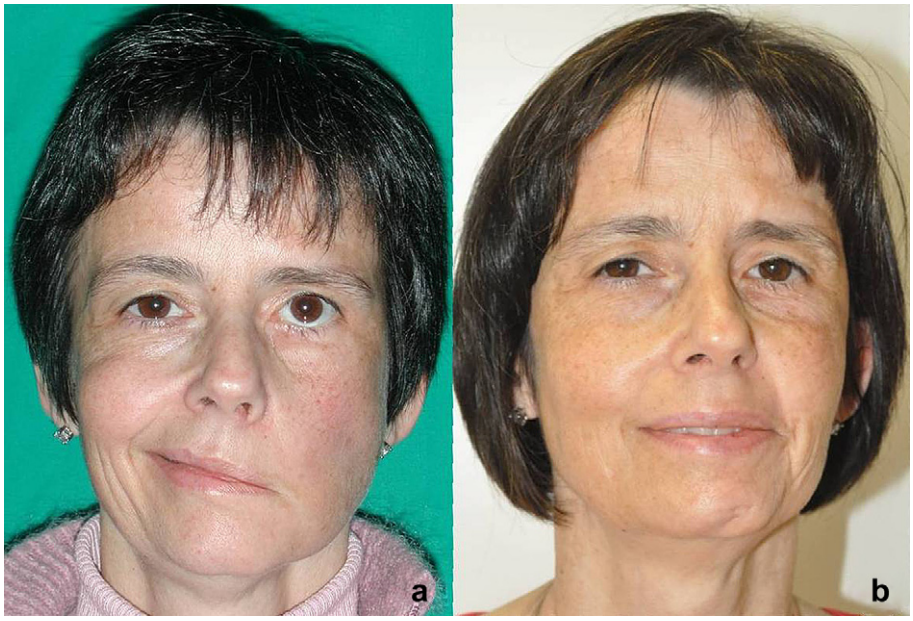

Fig. 5. (a) The attempt to use mimetic musculature preoperatively disfigure the patient. (b) Restoration of smiling is symmetrical 9 months postoperatively.

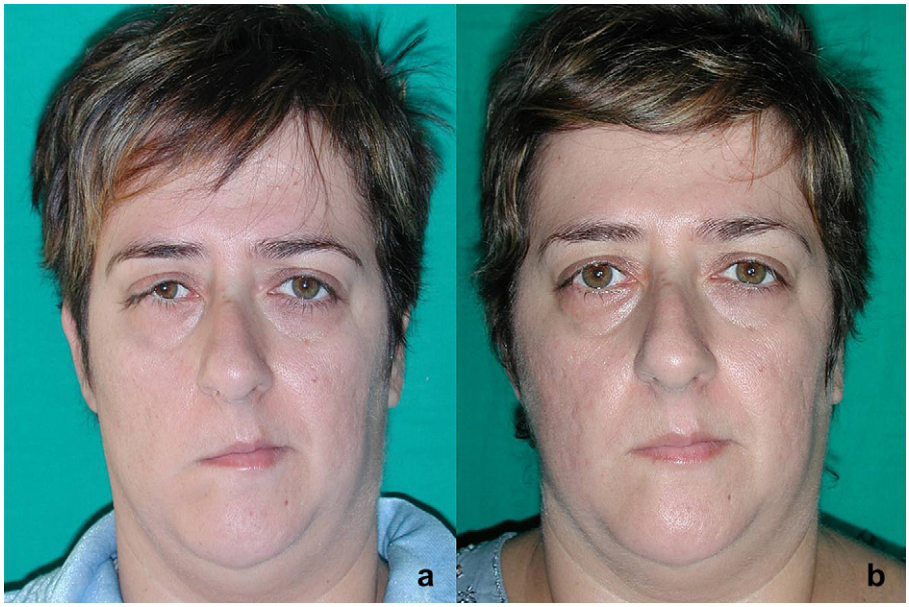

Fig. 6. (a) Preoperative image of a 40 years old female patient, affected by facial paralysis after acoustic neuroma surgery. Masseteric to facial nerves anastomosis was accomplished 19 months after insetting of paralysis. (b) Partial symmetry of the face at rest 12 months after surgery (first contraction 5 months after masseteric to facial nerves anastomosis).

In the case of complete facial palsy, the distance between the main trunk of the facial nerve and the masseteric nerve might be filled by tracing all facial nerve and its branches running into the parotid gland parenchyma as in case of superficial parotidectomy and aligning it to reach the masseteric nerve stump, but, we feel that this is too traumatic for the nerve itself and we prefer to use a segment of interpositional nerve graft.

The authors believe that the great auricular nerve represents the best choice for grafting as it is available in the same operative field and the subsequent earlobe sensory deficit may be considered a low donor-site morbidity (Biglioli et al., 2002).

The lack of spontaneity of smiling using trigeminal source has been widely reported. Because of this, techniques for reanimation in chronic palsy shifted from a trigeminal motor source, such as the deep temporalis nerve (Harii et al., 1976), to the contralateral facial nerve (Biglioli et al., 2009). Recently Manktelow et al. (2006), studying Moebius patients using masseter donor source, assessed the recovery of spontaneous smile in 89% of patients, at a mean follow up of 4.7 years. Other authors have shown that cortical adaptation to restoration of smiling after free muscle transfer innervated by the masseteric nerve is possible (Lifchez et al., 2005). Faria et al. (2007) suggested that an automatic smiling-like movement may be possible since smiling and chewing are similar functions, even if they have not observed any spontaneity in smiling within the masseter nerve as donor source. A distinction must be made between spontaneous and automatic movement, as

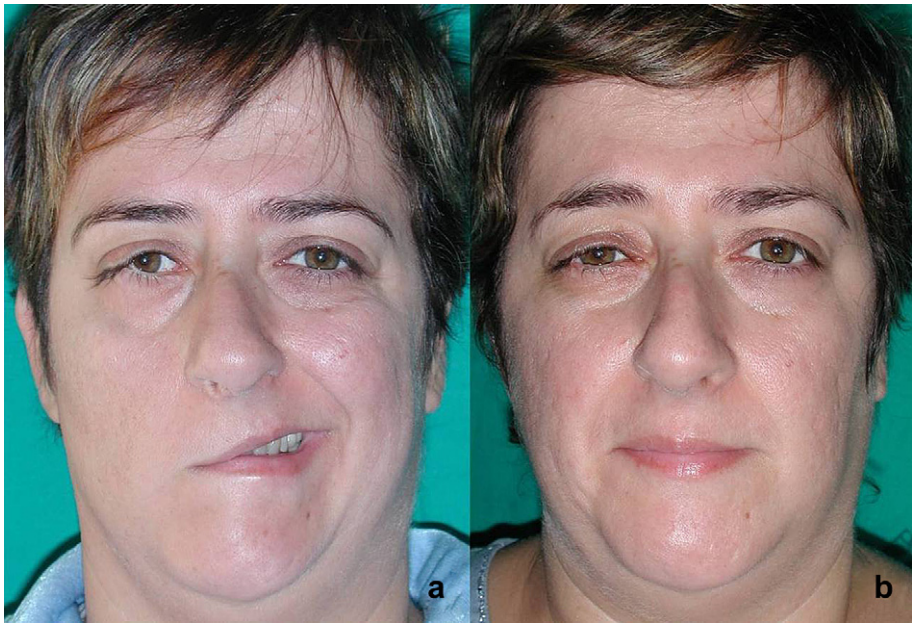

Fig. 7. (a) The attempt to use mimetic musculature preoperatively disfigure the patient. (b) Restoration of smiling is symmetrical 9 months postoperatively.

the latter is accomplished by the patients almost not thinking about "when he wants" to smile. A spontaneous smile is absolutely not voluntary when the persons laugh without "wanting" to. From our video investigation this does not happen when having a trigeminal motor source such as the masseter muscle. Again Manktelow et al. (2006) believe that the ability to smile spontaneously depends on the intensity of early practice. That might be possible in Moebius patients, but it is not seen in our series despite physiotherapy.

All our patients underwent an intensive physiotherapy program. Visual feedback in front of the mirror allows awareness to be gained of the newly acquired motor pathways of the facial muscles, now innervated by trigeminal nerve (masseteric nerve). Patients were taught to achieved symmetry at rest and then to activate their mimetic muscles under masticatory stimulus and finally without it. They learned to moderate their biting strength in order to achieve desired symmetry and movement. Voluntary smile were easily learned by the patients, while the possibility to smile under emotional stimulus has not been confirmed yet.

Evaluation of results requires the analysis of soft tissue corrections and their pre- and postoperative symmetry compared to the contralateral side. Some authors have concentrated their efforts on devising the most scientific way to quantitatively analyze cutaneous landmarks (Okada, 2001; Proff et al., 2006). Sforza et al. (2010) enhanced those analyses, introducing a very accurate scientific method to detect facial movements. Others authors consider an easy subjective clinical measurement more practical, giving anyone the ability to use it and to share data (Terzis and Noah, 1997). This is the classification method we chose.

No donor-site morbidity related to loss of masseter muscle function was observed in the study, except a transient limited mouth opening due to masseter muscle scar formation. This result is consistent with Brenner and Schoeller (1998) anatomical studies showing that both the presence of two or more nerve branches in 75% of cases and the closure of the temporalis muscle should avoid any postoperative dysfunction.

Masseter muscle atrophy has not been reported in the literature yet, though we observed it in one patient. Despite this the patient denied having any difficulty chewing. Aesthetic deficits could be addressed by a lipofilling procedure.

6. Conclusion

Masseteric–facial nerve anastomosis with an interpositional great auricular nerve graft is a valid alternative to hypoglossal–facial nerve anastomosis in early facial reanimation for complete facial paralysis, allowing the recovery of complete facial nerve function with low donor-site morbidity.

Conflict of interest

All authors disclose any financial and personal relationship with other people or organizations that could inappropriately influence their work.

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SUPPLEMENT D

Single-stage facial reanimation in the surgical treatment of unilateral established facial paralysis.
Plastic and Reconstructive Surgery 2009; 124(1): 124-133.

Single-Stage Facial Reanimation in the Surgical Treatment of Unilateral Established Facial Paralysis

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Background: Surgical treatment of unilateral long-standing facial paralysis requires transposition of new musculature to restore the function of the atrophied mimetic musculature. Facial reanimation with free neuromuscular flaps is actually the accepted standard treatment. Two-stage procedures have been used for years, with a total flap recovery time of 18 to 24 months. In 1998, Harii proposed single-stage facial reanimation using the latissimus dorsi flap, showing a faster recovery compared with two-stage procedures. The present study evaluated the results of the authors' center applying the single-stage facial reanimation.

Methods: From April of 1999 to April of 2006, 33 patients with unilateral established facial paralysis underwent single-stage facial reanimation via latissimus dorsi free flap transplantation. Time from the onset of paralysis ranged from 20 months to 64 years (mean, 11.6 years). Patients were followed postoperatively for at least 24 months. Results were studied and compared using Terzis and Noah's 1997 classification.

Results: Among the 33 patients included in the study, there was an average reinnervation time of 8.9 months. According to Terzis and Noah's classification system, 12 patients (36.3 percent) were considered grade V, 12 (36.3 percent) were grade IV, four (12.2 percent) were grade III, two (6.1 percent) were grade II, and three (9.1 percent) were grade I.

Conclusions: Single-stage facial reanimation with a latissimus dorsi flap achieved morphofunctional results similar to those obtained with the classic two-stage technique. In addition, the authors were able to reduce the morbidity associated with treatment and the time required for recovery. (*Plast. Reconstr. Surg.* 124: 124, 2009.)

Unilateral facial paralysis results in the inability to contract the mimetic musculature and, in long-term cases, the coarse distortion of facial morphology, especially during activation of the contralateral musculature. The treatment of unilateral established facial paralysis has two goals: to reach symmetry of the face at rest and to partially restore facial movement. Facial reanimation is a surgical technique used to restore the facial mimetic musculature (i.e., the spontaneous smile) in the inferior two-thirds of the face and eyelid closing in the superior third. A series of ancillary procedures is used to optimize the morphofunctional improvements.[1]

When a long-standing facial paralysis is present, transposition of new musculature is re-

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Received for publication May 16, 2008; accepted April 14, 2009.

DOI: 10.1097/PRS.0b013e3181aa0e2b

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

Supplemental digital content is available for this article. A direct URL citation appears in the printed text; simply type the URL address into any web browser to access this content. A clickable link to the material is provided in the HTML text of this article on the *Journal*'s Web site (www.PRSJournal.com).

quired to restore the function of the atrophied musculature. Today, transplantation of a muscular free flap is the accepted standard treatment, as this leads to the best morphological results.[2–6] This is accomplished by most surgeons using a two-stage technique, as suggested in 1980 by O'Brien et al.[7] The recovery time associated with this procedure is approximately 18 to 24 months. To reduce the length of treatment and recovery, Harii et al. proposed single-stage facial reanimation using muscular transplantation of the latissimus dorsi.[8] The present study evaluated the results of our center applying this technique.

PATIENTS AND METHODS

Briefly, the single-stage facial reanimation technique involves the harvest of a muscular free flap in the thoracodorsal region and the contemporary surgical preparation of the paralyzed facial region in which the flap will be positioned (Fig. 1).

The cutaneous pocket in the face must be prepared at the subcutaneous level. Otherwise, unaesthetic cutaneous folds may occur during contraction of the flap due to strict adhesion between the skin and the transplanted muscle.

A cheek pocket is created with a preauricular incision and extended inferiorly and posteriorly to the earlobe to avoid scars into cervical region; vascular anastomoses are easily performed using facial vessels as recipients via a short incision approximately 2 cm long.

For correct formation of the nasolabial fold during contraction of the flap, the cutaneous pocket must be extended approximately 1.5 cm medially to the ideal position of the fold itself. When the flap subsequently contracts, the natural skin crease will form a new nasolabial fold symmetrical to the contralateral side. Four or five 3-0 polyethylene stitches are positioned across the residual fibers of the orbicularis oris muscle. If this is not visible, the stitches are passed through the deep subcutaneous tissue. No additional incision on the nasolabial fold or intraorally is added to insert the stitches.

A 1.5- to 2-cm incision is made on the nonparalyzed side along the lines of the cutaneous tension that correspond to the posterior edge of the musculus zygomaticus major, at which facial nerve branches are present. Activation of the levator labii superioris and zygomaticus major muscles can be evaluated using an electrostimulator. This technical step is facilitated when the profile of the musculus zygomaticus major has previously been sketched. This branch is then sectioned and subsequently anastomosed to the thoracodorsal nerve to provide motor stimulation.

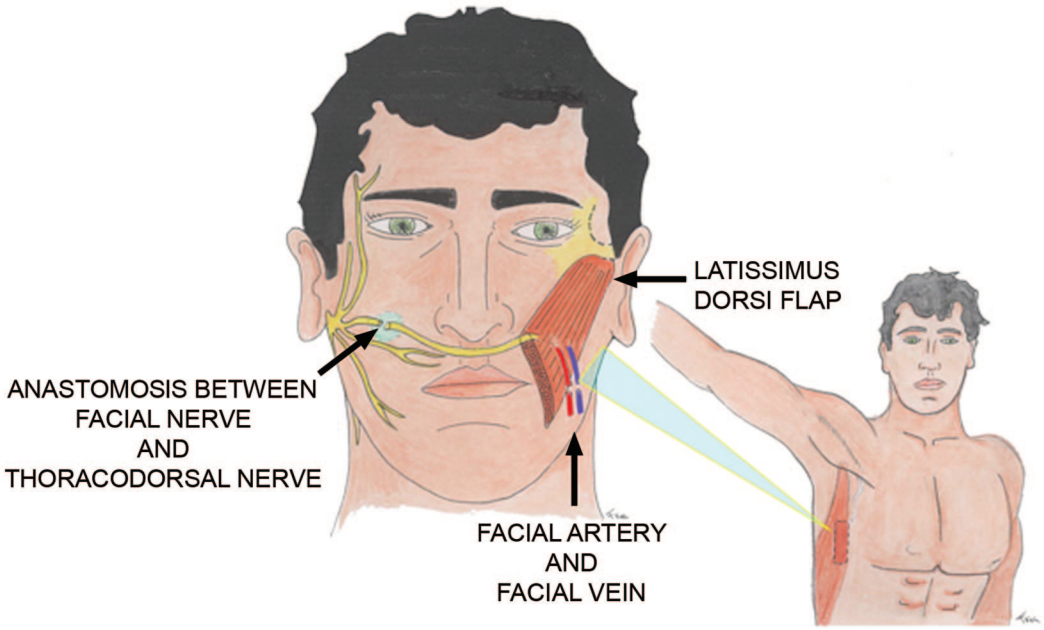

Fig. 1. Scheme of the single-stage facial reanimation procedure according to Harii et al. (One-stage transfer of the latissimus dorsi muscle for reanimation of a paralyzed face: A new alternative. *Plast Reconstr Surg.* 1998;102:941–951). A small portion (approximately 10 × 6 cm) of the latissimus dorsi muscle is harvested from the anterior side of it. The flap is set subcutaneously into the previously prepared cheek pocket while the nerve is anastomosed to a branch of the contralateral facial nerve.

Simultaneously, the thoracodorsal nerve is traced in the axillary region until the posterior chorda of the brachial plexus is reached. The tracing is continued for 0.5 to 1 cm, to obtain an 11- to 12-cm segment; another 3 to 4 cm may be obtained via a thin intraparenchymal dissection of the muscle, for a total segment length of 15 to 16 cm (Fig. 2).

This is the most delicate stage of the facial animation procedure, as it requires the separation of the arterial and venous thoracodorsal branches from the nerve branches; in addition, branches of the thoracodorsal nerve not destined for the muscular segment that will be transplanted must be simultaneously sacrificed. The decision regarding which section of the nerve to utilize for obtaining optimal thoracodorsal nerve length is generally based on the surgeon's experience.

After dissection of the neurovascular pedicle, a rectangular portion of the latissimus dorsi is harvested, centered on the pedicle and its bifurcations, and placed in a subfascial position on the deep surface of the muscle. Flap size is determined in accordance with the patient's facial dimensions, but generally the flap is 4 to 6 cm wide and 8 to 12 cm long. The thickness of the flap will be different in different people, ranging between 1 and 2.5 cm cranially (proximal to the modiolus once transposed) and 0.5 and 1.5 distally (at the zygomatic arch later on). The cranial margin of the flap is sectioned with a gastrointestinal stapler, as described by Asato et al.[9] This step creates an attachment medially to the nasolabial fold without having to strip the stitches. Then, the muscular free flap is settled into the cheek pocket in its final position by parachuting it on the stitches. The hilum of the pedunculus is set medially in the face to take advantage of the entire length of the thoracodorsal nerve. The thoracodorsal nerve is then transposed subcutaneously onto the contralateral hemiface to execute the nerve anastomosis. The distal edge of the muscle is fixed to the zygomatic arch; light pressure must be kept on the muscle to contrast the contracture that occurs when it is detached from the chest. The tension of the flap must be sufficient to overcorrect the operated area. If the muscle is thin and does not lead to evident bulk, it may be anchored to the deep temporalis fascia. By doing so, it is possible to use a larger contractile mass.

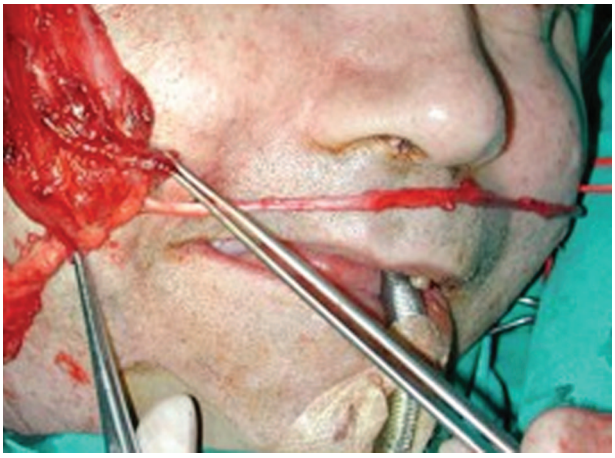

Fig. 2. A 15- to 16-cm segment of thoracodorsal nerve is required to reach a branch of the contralateral facial nerve.

Patients

Thirty-three patients were operated on from April of 1999 to April of 2006 for established facial paralysis and underwent a latissimus dorsi free flap transposition. Follow-up time was 24 months. Causes of paralysis are listed in Table 1.

All patients underwent electromyographic evaluation of their mimetic musculature preoperatively to confirm established facial paralysis.[10] Patients were also interviewed regarding their personal identities, problems experienced in everyday life that were related to their pathological condition, and their ability to close their eyes, breathe through the nose, chew, and speak.

Postoperative periodical medical examinations were performed every 3 to 4 months. During each office visit, facial objectivity was evaluated at rest and during activation of the mimetic musculature.

As soon as muscle functioning began, patients were referred to the physiotherapist of our team, who taught each patient the physical training to be performed in front of a mirror and, later on, without a mirror.

Table 1. Causes of Paralysis

Causes of Paralysis	No. of Patients
Sequelae of surgery for eighth nerve neurinoma	17 (51.5)
Congenital paralysis	4 (12.2)
Cranial base trauma	3 (9.1)
Sequelae of surgery for seventh nerve neurinoma	2 (6.1)
Sequelae of Bell's palsy	2 (6.1)
Sequelae of excision of facial nerve hemangioma	1 (3)
Sequelae of meningitis	1 (3)
Sequelae of radiotherapy	1 (3)
Complications of brain aneurysm	1 (3)
Sequelae of the exerecis pontino hemangioma	1 (3)
Total	33 (100)

Twenty-four months postoperatively, patients underwent a specific assessment of facial reanimation according to Terzis and Noah's classification[11] (Table 2). Results were based on photographic evaluation of facial symmetry at rest and during contraction and rated on a scale from I to V, with I considered "poor" and V considered "excellent." A panel consisting of a physiotherapist, a maxillofacial surgeon, and a maxillofacial surgery resident not involved in the operations graded the patients.

Spontaneity of flap contraction according to emotional stimulus was assessed by leaving the patient alone in a room to watch a comic movie for 10 minutes. No one was present during this time to embarrass the patient or to inhibit his or her spontaneity.

Electromyographic tests were included in a protocol of serial controls (every 2 months) to evaluate flap recovery. These controls were interrupted 6 months after the beginning of muscle contraction.

To maintain the patency of the vascular anastomoses for at least 30 days postoperatively, patients were given acetylsalicylic acid (100 mg/day). During the 5 days immediately after surgery, flap viability was evaluated via external eco-Doppler monitoring, with the probe positioned in proximity to the vascular pedicle.

Statistical Analysis

Data were summarized by generating mean and standard deviations. Statistical analyses were conducted by using SYSTAT12 (SPSS, Inc., Cary, N.C.). A one-way analysis of variance test was performed to investigate whether the satisfaction results were distinguishable when the corresponding Terzis and Noah scale for each patient was used as a factor. Spearman rank order correlation coefficients were computed to investigate the correlation between the satisfaction results and the Terzis and Noah scale rank for each patient. Results of analyses were considered significant for p values less than 0.05.

Table 2. Final Results*

Grade	Description	No. of Patients (%)
V: Excellent	Symmetry with good tone at rest; full contraction; symmetrical smile with teeth showing	12 (36.3)
IV: Good	Symmetry at rest; nearly full contraction	12 (36.3)
III: Moderate	Moderate symmetry at rest; moderate contraction	4 (12.2)
II: Fair	No symmetry at rest; minimal contraction	2 (6.1)
I: Poor	Deformity; no contraction	3 (9.1)

*Results were rated according to the classification of Terzis and Noah (from Terzis JK, Noah ME. Analysis of 100 cases of free-muscle transplantation for facial paralysis. *Plast Reconstr Surg.* 1997;99:1905–1921).

RESULTS

Age at the time of operation ranged from 5 to 73 years (mean, 47.8 years; SD, 15.2 years). A total of 70 percent of patients had left facial paralysis. Time from the onset of paralysis ranged from 20 months to 64 years (mean, 5.3 years; SD, 128.4 months).

Among the 33 patients included in the study, we observed a large variability in times of onset of contraction, with an average time to reinnervation of 8.9 months (range, 50 days to 22 months; SD, 3.7 months). According to the classification system by Terzis and Noah, 12 patients (36.3 percent) were considered grade V, 12 (36.3 percent) were grade IV, four (12.2 percent) were grade III, two (6.1 percent) were grade II, and three (9.1 percent) were grade I (Table 2 and Figs. 3 through 8).

In 20 patients (60.6 percent), contraction resulted in the activation of the collateral mimetic musculature involved in the smiling movement. In two patients (6.1 percent), activation of the mimetic musculature required simultaneous closing of the contralateral eye, at least partially. In two patients (6.1 percent), activation of the transplanted muscle was more effective during the kissing movement instead of during smiling.

Two patients (6.1 percent) who had difficulty coordinating flap function with the contralateral mimetic musculature improved as they repeated exercises in front of a mirror, utilizing visual control of the movements as suggested by physiotherapist.

In one patient (3.0 percent), flap infection occurred, which is why treatment with daily washings and antibiotic therapy were necessary. The infection resolved within 1 week. The patient was rated as grade II 24 months later. In six patients (18.2 percent), prolonged muscle contraction or pseudospasm of the flap occurred, causing visible discomfort (Table 3).

If muscle tension appeared excessive or insufficient at 6 months after the onset of contraction, the flap was revised. In three patients (9.1 percent), muscular tension was slackened by disconnecting and unstacking the superior two-thirds of the flap from the superficial and deep planes and by repositioning the flap more caudally; however, this was effective in only one patient (grade III

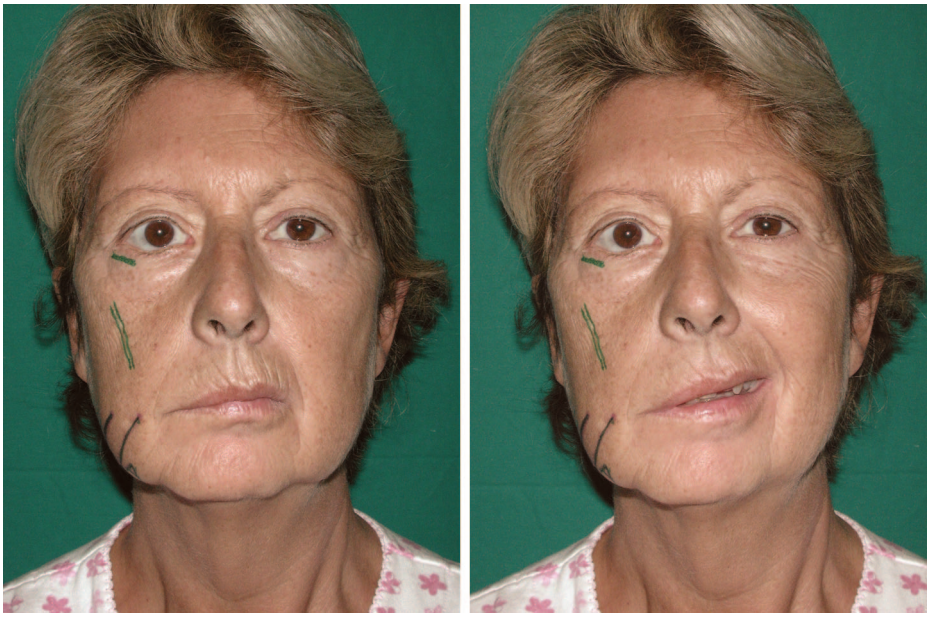

Fig. 3. Case 1. (*Left*) Preoperative appearance of the face at rest. The ptosis of the midface and the deviation of the oral rim are evident. (*Right*) Preoperative appearance of the face during activation of facial mimetic musculature. The patient's face is grossly distorted.

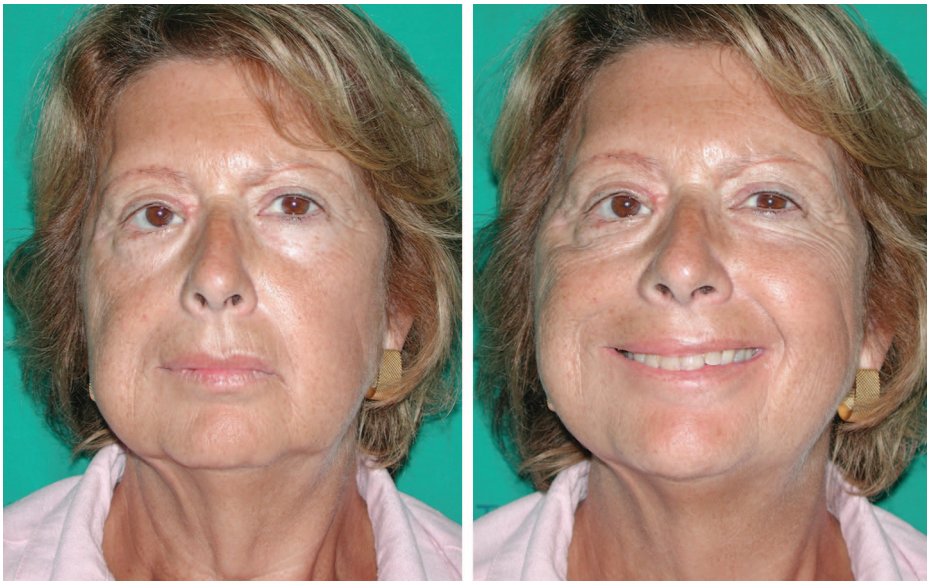

Fig. 4. Case 1. (*Left*) Good recovery of the symmetry of the middle third of patient's face at rest and (*right*) during smiling due to activation of the flap.

preoperatively to grade V postoperatively, according to the classification of Terzis and Noah[11]). In the other two patients, we had to assist after renewal of the pseudospasm within a few months. These patients who underwent secondary surgery together with another two patients who had spasm of the flap were treated with local injections of botulinum toxin, which temporarily solved the pseudospasm and is still administered every 4 months. Three patients needed cranial repositioning of the muscle; one patient's score did not improve (grade III), while the other two patients moved from grade III to IV and from grade III to V. The mean improvement of the six patients who underwent secondary surgery was 0.83; from a preoperative grade of III, one patient improved to

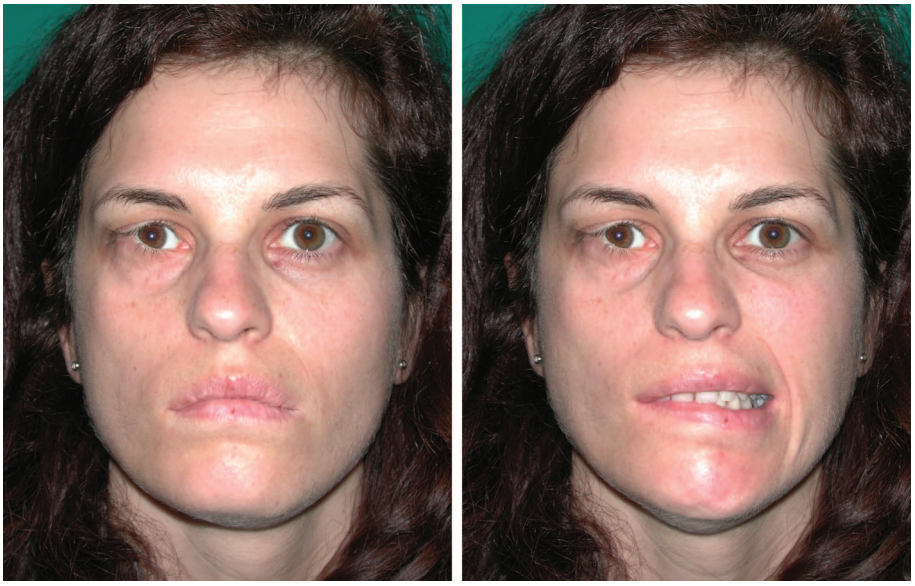

Fig. 5. Case 2. Preoperatively, there is slight asymmetry of the face at rest (*left*) and during activation of the facial mimetic musculature (*right*).

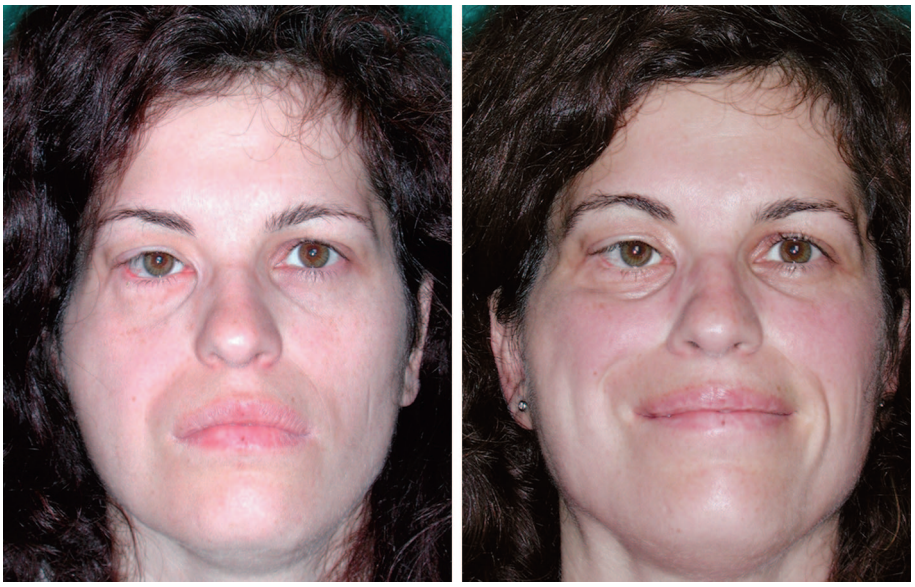

Fig. 6. Case 2. Postoperatively, there is enhanced symmetry of the soft tissue of the lower two-thirds of the face at rest (*left*). The nasolabial fold is enhanced in comparison to the patient's preoperative appearance. (*Right*) There is good symmetry of the middle third of the face during smiling due to activation of the flap.

grade IV, two patients improved to grade V, and three patients were unchanged.

Results of electromyographic analysis did not correspond with clinical results. In most patients in whom objective functional recovery was noted, no voluntary flap activity was registered on electromyography and results of the nerve conduction test were negative. From this point of view, our study data were not reliable, and therefore are not described in this report.

In five patients (15.2 percent), we observed an excessive bulk of moderate size. In one case of more evident bulk, we reduced the thickness of the superior two-thirds of the flap during the revision and simultaneous cranial replacement of the flap. In the other cases, this procedure seemed too invasive rel-

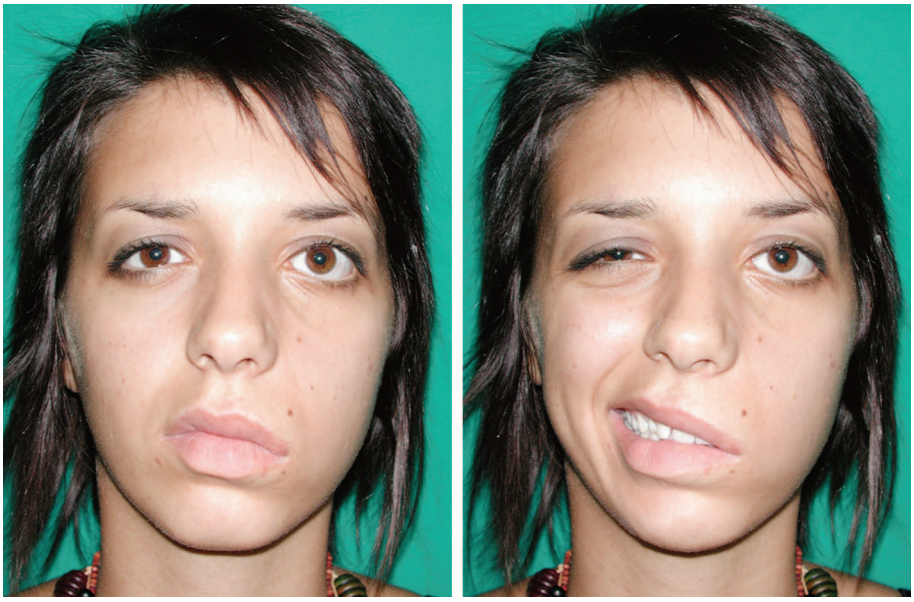

Fig. 7. Case 3. Congenital facial paralysis. (*Left*) Preoperatively, ptosis of the soft tissues is enhanced, despite the patient's young age. (*Right*) There is gross distortion of the face during activation of facial mimetic musculature.

Fig. 8. Case 3. There is good recovery of the symmetry of the middle third of the face at rest 12 months after surgery (*left*) and during smiling due to spontaneous activation of the flap (*right*).

ative to the size of the bulk, especially when one considers that there were few complaints regarding the issue. The facial and thoracic surgical wounds healed normally in all patients.

Results of the study of audiovisual registration (while the patients were watching a comical movie) showed the spontaneity of muscle activation during smiling in all patients, when this type of observation was possible (25 patients). See **video**, **Supplemental Digital Content 1,** which demonstrates the patient laughing while watching a funny video. The spontaneity of smiling gives a more pleasant aspect to facial mimetic movements, ***http://links.lww.com/A1412***.

Table 3. Complications*

Complication	No. of Patients (%)
Pseudospasm	6 (18.18)
Infection	1 (3.0)
Synkinesis	2 (6.1)
Flap loss	0* (0.0)

*The viability of buried flaps is not guaranteed by the use of an external Doppler probe.

Video 1. See **Video, Supplemental Digital Content 1,** which demonstrates the patient laughing while watching a funny video. The spontaneity of smiling gives a more pleasant aspect to face mimetic movements, ***http://links.lww.com/A1412*** .

All three patients with a grade of I were excluded from this evaluation because flap activity was null. Five patients were excluded because they did not enjoy the movies, so they did not smile or laugh at all.

All patients interviewed before surgery reported embarrassment about their appearance (most of them talked with a hand covering the paralyzed cheek) and cited this as the reason for undergoing surgery. All patients complained about same difficulties on the pathological side during nasal inspiration and reported involuntarily biting of the cheek while chewing. Most of them also reported worsening in their speech after the onset of paralysis.

Interviews accomplished 24 months after surgery provided the following results: two patients (6.1 percent) were enthusiastic about the procedure, 10 patients (30.3 percent) were satisfied, 15 patients (45.4 percent) were mildly satisfied, and six patients (18.2 percent) were unsatisfied. Only five patients (15.2 percent) reported improvement during nasal inspiration. Twenty-six patients (78.8 percent) reported improvement in involuntarily cheek biting while chewing. Sixteen patients (48.9 percent) felt their speech ability had improved.

One-way analysis of variance was performed to investigate whether the final subjective satisfaction was different depending on the results observed on the Terzis and Noah scale. Results showed that subjective satisfaction differed depending on the final result, according to the Terzis scale (analysis of variance, $p < 0.05$). Specifically, satisfaction was correlated with the final results on the Terzis and Noah scale, as confirmed by the Spearman rank order correlation coefficient ($r = 0.757$).

The Doppler signal was recorded during the 5 days immediately after the operation for all patients but one, in whom the signal during the fifth day was lost. This patient had the lowest final grade in the series (grade I). No flaps were removed, although flap viability cannot be guaranteed due to the low reliability of external Doppler flow in detecting venous signals (Table 3).

DISCUSSION

In 1998, Harii et al. proposed a new surgical technique to harvest the latissimus dorsi flap.[8] In adult patients, 15 to 16 cm of the dorsal nerve are harvested via a proximal dissection of the thoracodorsal nerve until its origin from the posterior chorda of the brachial plexus and the distal dissection of the muscle parenchyma. This length is suitable to anastomose the nerve to one or more branches of the contralateral facial nerve for the musculus zygomaticus major. This surgical step is essential to ensure that the correct stimulus is used, as the nerve branches for that muscle are invariably involved in smiling. During the surgical procedure, the selected branch of the facial nerve is evaluated by electrostimulation and on an anatomical basis. Nevertheless, in two cases, we observed the need for the patient to partially contract the contralateral eye to activate the flap, most likely because a part of the donor nerve fibers destined to the orbicularis oculi.[12] In two other cases, the patients contracted the transplanted muscle more effectively during the kissing movement than during smiling; however, a more convincing interpretation is that part of the donor fibers was delegated to the innervation of the orbicularis oris. The best way to try to avoid that problem is to proceed medially with the dissection. On the other hand, that maneuver may lead to branches that are too thin to be anastomosed successfully. The solution to the problem, therefore, may be difficult.

After analyzing the patient videos, we continued to consider a spontaneous smile more aes-

thetically pleasing than a voluntary one, as it generally happens in the normal population. This suggests that the activation of the transplanted muscle occurs both via an emotional stimulus and via a voluntary action.

Interviews showed differences between the grading system score and the patient's perception of results. In most cases, patients were less enthusiastic than the panel.

Single-stage facial reanimation has been proposed to reduce the time required for treatment and recovery.[13–20] The single-stage procedure involves one nerve anastomosis instead of two, as required by the two-stage technique with nerve cross-face grafting. Theoretically, this would guarantee the passage of a larger number of nerve fibers, though results are no better than those of most two-stage techniques.[21]

The scientific literature reports excessive bulk in 24.4 percent of patients who undergo facial reanimation with microvascular flaps.[1] In this study, only five of 33 patients (15.2 percent) complained of excessive bulk. To avoid excessive bulk, it is critical to obtain a thoracodorsal nerve graft that is at least 15 cm long and to harvest a very distal portion of the latissimus dorsi where it is particularly thin.

Revision of flap tension was necessary in 18.2 percent of cases in our study. This incidence may have been reduced by a surgeon better skilled at finding the "correct" tension positioning for the transplanted muscle. The necessity of resetting the flap position was demonstrated in a series of ancillary procedures, including eyebrow suspension, revision of the nasal groove, and correction of residual eyelid insufficiency, which were required to optimize the surgical results.[1]

For the two children in the series, we avoided making even the smallest incision into the facial vessels by isolating and sectioning them from the nasolabial fold via a preauricular incision prolonged inferiorly and posteriorly to the earlobe.[22] In this fashion, we were able to rotate the vessels laterally and to anastomose them to the thoracodorsal vessels.

Although the House-Brackmann scale is universally utilized to classify facial paralysis, most authors find it unsuitable for facial reanimation patients.[23] In our opinion, the best classification system is the one proposed by Terzis and Noah,[11] because of its ease of use and its utility in evaluating the two most important endpoints of facial reanimation: symmetry at rest and quality of smiling.

Patients do not experience any particular deficit associated with the donor site, according to data present in the scientific literature about latissimus dorsi flap harvesting.[24] That has to be compared with a similar absence of deficit associated with the harvesting of the most utilized free flaps in facial reanimation, such as the gracilis and pectoralis minor.[25] Among two-stage procedures, the deficit of sural nerve grafting may not be neglected.[26]

CONCLUSIONS

In the present study, single-stage facial reanimation with a microsurgical latissimus dorsi flap achieved morphofunctional results similar to those obtained with classic two-stage techniques. In addition, the procedure spared our patients the deficit associated with sural nerve grafting and reduced the time to recovery.

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SUPPLEMENT E

Deep-planes lift associated with free flap surgery for facial reanimation.
Journal of Cranio-Maxillofacial Surgery 2011; 39(7): 475-481.

Journal of Cranio-Maxillo-Facial Surgery 39 (2011) 475–481

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Deep-planes lift associated with free flap surgery for facial reanimation☆

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ARTICLE INFO

Article history:
Paper received 10 December 2008
Accepted 14 September 2010

Keywords:
Facial reanimation
Deep-planes lift
Free flap

ABSTRACT

Between April 1999 and April 2008, 37 patients with long-standing facial paralysis underwent a one-stage facial reanimation with neuromuscular free flaps: 28 patients (group A) underwent flap transposition only; 9 patients (group B) underwent a deep-planes lift (DPL) composed of the superficial muscoloaponeurotic system + parotid fascia at the time of facial reanimation. The postoperative and final results were compared between groups A and B, following the classification of Terzis and Noah (1997). Before the onset of contraction, only group B patients (100%) showed good or moderate symmetry at rest, while none of the patients of group A had a symmetric face.

The respective final results for patients in groups A and B who already showed the onset of flap contraction were excellent in 28.6% and 44.5%, good in 42.9% and 33.3%, moderate in 10.7% and 22.2%, and fair or poor and fair in 17.8% and 0% of patients, respectively. The DPL allows immediate symmetry of the face at rest and contributes to upgrading the final static and dynamic results in facial reanimation with free muscular flaps.

1. Introduction

Surgical treatment of established paralysis of the middle third of the face may be performed using static or dynamic techniques. Static methods include soft tissue suspensions, usually performed to correct cheek ptosis and facial asymmetry (Liu and Sherris, 2008), while dynamic processes, or *facial reanimations*, are used to restore facial movement with the transposition of new musculature (Harii et al., 1976).

Static techniques may be performed at any time from the onset of paralysis, but do not lead to facial movement recovery. During time soft tissue ptosis generally worsens, impairing surgical results. So those techniques are currently mainly utilized for older patients or as ancillary procedures. Facial reanimation with free flaps has the aim to partially restore facial movement, especially lid closure and smiling. These are performed after 18–24 months, when muscle atrophy is considered irreversible and when no signs of mimetic musculature fibrillation are present on an electromyogram (EMG). The transplantation of free flaps is now the mainstay of facial reanimation, as this leads to the best morpho-functional results. There are two main options described in literature to apply those flaps. The classical one is a two-stage procedure: during the first operation a cross-face nerve graft with sural nerve is performed. Eight to 12 months later a muscle free flap is set into the paralyzed hemiface and anastomized to the nerve transfer (Vedung et al., 1984). The second option is a one-stage transfer with immediate anastomosis of the muscle nerve to the contralateral facial nerve branch (Harii et al., 1998) or to the homolateral masseter motor nerve (Zuker et al., 2000). In the last case recovery of contraction is quicker (3–4 months instead of 7–9 needed for Harii's procedure) and "quantity" of smiling seems to be more guaranteed. Controversies remain around spontaneity of smiling using this trigeminal motor source (Manktelow et al., 2006; Faria et al., 2007). For this reason, surgeons who consider it important to obtain an emotional contraction prefer the use of the contralateral facial nerve as the motor source (Biglioli et al., 2009).

In 1998, Harii et al. (1998) proposed a single-stage reanimation technique to transplant the latissimus dorsi flap into a paralyzed hemiface and to anastamose the thoracodorsal nerve to one or more branches of the musculus zygomaticus major branch of the contralateral facial nerve. This technique allows the recovery of facial movement 7–9 months after surgery (Biglioli et al., 2009). The final results are analyzed by observing both the facial symmetry at rest and the flap contraction while smiling (Terzis and Noah, 1997).

☆ The authors had full freedom of investigation and there were no potential conflicts of interest. There was no grant support for this study.

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1010-5182/$ – see front matter © 2010 European Association for Cranio-Maxillo-Facial Surgery.
doi:10.1016/j.jcms.2010.09.003

Ancillary procedures such as cranial repositioning of the flap or static soft tissue suspension are often required to correct residual facial ptosis after free flap reanimations (O'Brien et al., 1990; Terzis and Noah, 1997; Takushima et al., 2005). From this experience, it was hypothesized that static suspension of the midface may be performed at the same time as facial reanimation, to obtain immediate postoperative symmetry at rest and the best final result.

We performed a deep-planes lift (DPL) composed of the superficial muscoloaponeurotic system + parotid fascia (Gosain et al., 1993) in association with facial reanimation with a free latissimus dorsi flap in a group of patients with established unilateral facial paralysis. The results were compared to those of a group of patients who underwent flap transposition only.

2. Materials and methods

Between April 1999 and April 2008, 44 patients with long-standing (24 months to 57 years, mean 47.7 years) unilateral facial paralysis underwent a one-stage facial reanimation with neuromuscular latissimus dorsi free flaps (Harii et al., 1998). Among those the first 29 formed a group of patients who received only free flap transposition. Since February 2005, all patients have been operated on with a simultaneous DPL and free flap transposition. A second group of 16 patients receiving both procedures contemporaneously was added into the study. DPL consisted of harvesting a flap compound by a superficial muscoloaponeurotic system antero-inferiorly and parotid fascia flap postero-superiorly (Fig. 2). The flap is lifted superiorly, and fixed to the periosteum of the zygomatic arch with 3/0 prolene stitches, with sufficient tension to obtain symmetry of the midface with a slight overcorrection (Figs. 1 and 2). Incisions define a flap 4–5 cm wide and are designed in a curvilinear form, following the main axis of smiling. Inferior extension of the incisions stops (generally 2–3 cm from lip structures) when pulling of the flap allows a significant superior lift of cheek tissues and definition of the nasolabial fold. A small area above the posterior part of parotid gland is left without fascia.

Only the 37 patients who had a postoperative follow-up of 24 months were included in this study, because their results were considered stable. The 37 (20 males, 17 females) patients included in the study were divided into two groups: group A consisted of 28 patients who underwent the flap transposition only and group B consisted of 9 patients who underwent a DPL at the same time as the facial reanimation. Age of the patients ranged from 6 to 71 years, mean 51.3 years. The cause of paralysis was sequelae of surgery for eighth and seventh nerve neurinoma in 27 cases (72.9%), congenital paralysis in four cases (10.8%), cranial base trauma in three cases (8.1%), sequelae of meningitis in one case (2.7%), sequelae of Bell's Palsy in two cases (5.5%).

Three weeks after the surgery, when most of the postoperative oedema had regressed, all 37 patients underwent a clinical examination of the facial symmetry at rest (Table 1), following the classification of Terzis and Noah (1997).

Postoperative examinations were performed every 3 months. After the onset of flap contraction, the facial symmetry at rest and during activation of the mimetic musculature was evaluated (Terzis and Noah, 1997), paying attention to the contribution of the DPL to the final static and dynamic results. The results were based on photographic evaluation and rated on a scale from I to V, with I considered "poor" and V "excellent" (Table 1).

Six patients in group A underwent a secondary revision of the flap tension: in these cases, follow-up started after the second procedure (Figs. 3 and 4).

After the onset of contraction all patients received bio-feedback physiotherapy, watching in front of a mirror the effect of activation of the flap and learning the quantity of stimulus that would allow

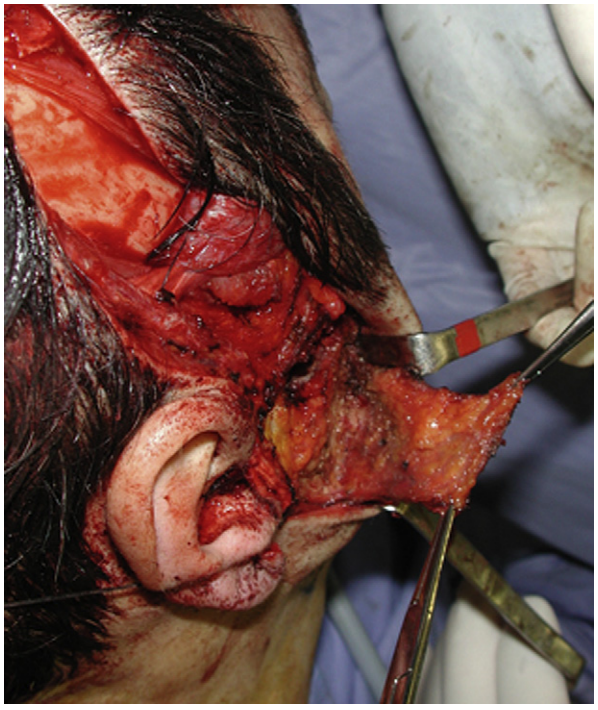


Fig. 1. The deep-planes flap elevated before its lift upward and backward.

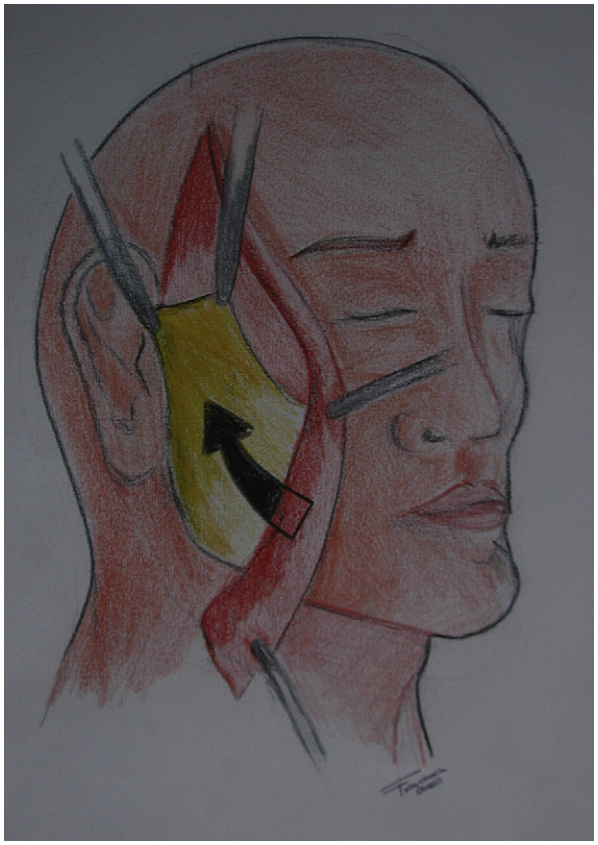


Fig. 2. Drawing of the DPL: a SMAS and parotid fascia flap with inferior pedicle is lifted cranially in order to contrast soft tissues ptosis.

Table 1
Results classification (Terzis and Noah, 1997).

5	Excellent	Symmetrical smile with teeth showing, full contraction
4	Good	Symmetry, nearly full contraction
3	Moderate	Moderate symmetry, moderate contraction
2	Fair	No symmetry, minimal contraction
1	Poor	Deformity, no contraction

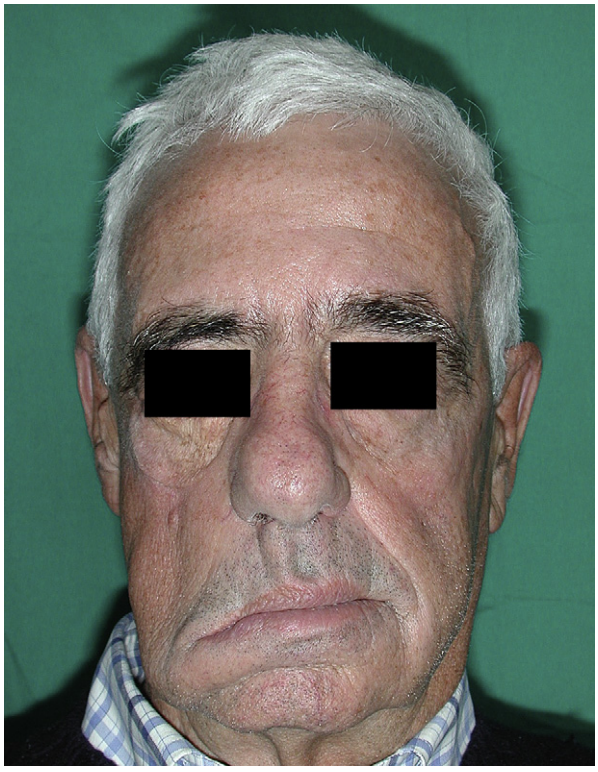


Fig. 3. Case 1: preoperative view of a patient with complete right facial paralysis and evident ptosis of soft tissues.

the most pleasant and symmetric smile. As the patient became confident with his new smile, exercises with the mirror were progressively stopped. No physiotherapy was given to obtain a spontaneous smile (Fig. 5).

3. Results

None of the 28 patients of group A showed a symmetric midface at the postoperative evaluation performed 3 weeks after surgery (100% grade 1 following Terzis and Noah).

In contrast, all nine patients in group B showed partial recovery of symmetry at rest, owing to the restoration of the nasolabial fold and the correction of soft tissues ptosis and labial philtrum deviation. The quality of the static result was good (grade 4) in seven (77.8%) and moderate (grade 3) in two (22.2%) patients. No dynamic result was yet present. The four patients in group B who had the worst preoperative lagophthalmos showed an improvement in their symptoms related to corneal exposure and a reduced use of lubricant eye drops and sunglasses.

The median recovery time of the flap contraction was 8.9 months (50 days to 22 months).

The evaluation of the dynamic results, performed after 24 months, showed that eight patients (28.6%) in group A had an excellent result, i.e., good symmetry of the middle third of the face

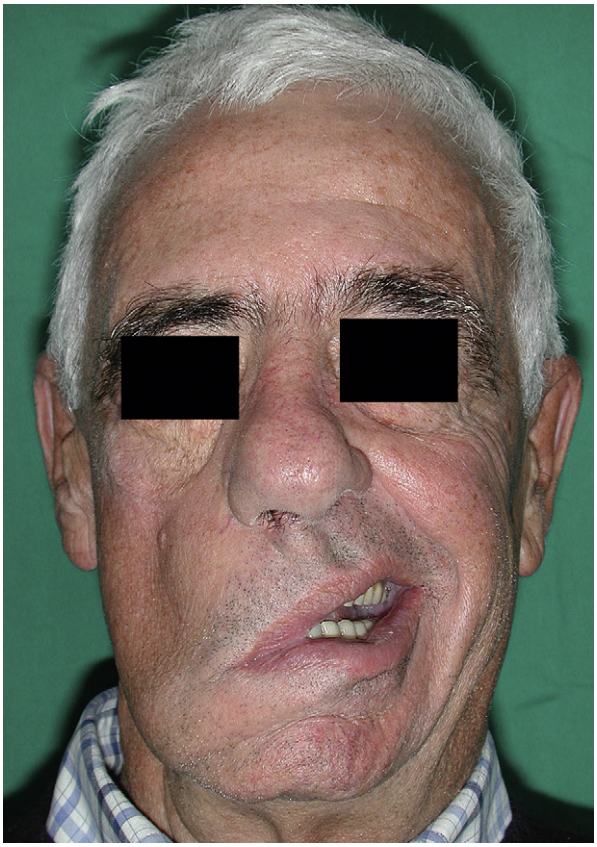


Fig. 4. Case 1: preoperative view of the patient while activating facial musculature. It is evident the disfigurement of facial mime.

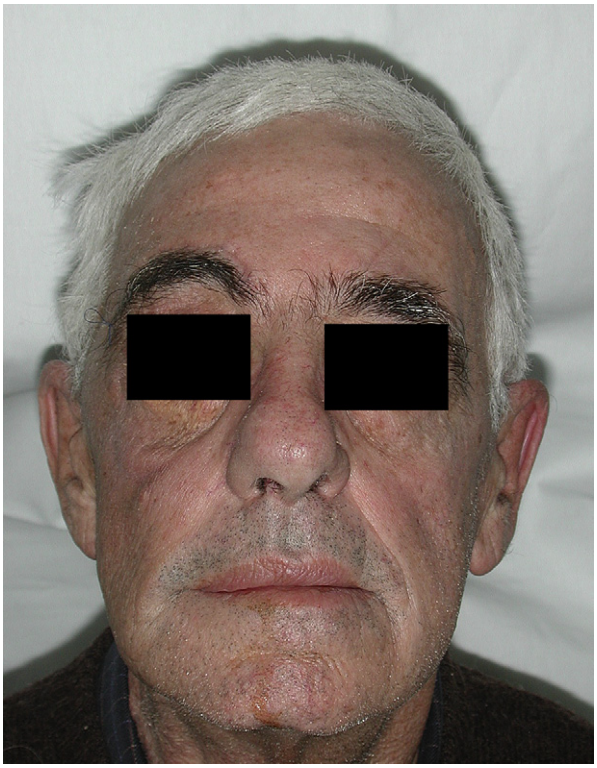


Fig. 5. Case 1: 1 month postoperatively: the patient appears almost symmetric at rest. The right eyebrow is slightly overcorrected to prevent subsequent ptosis.

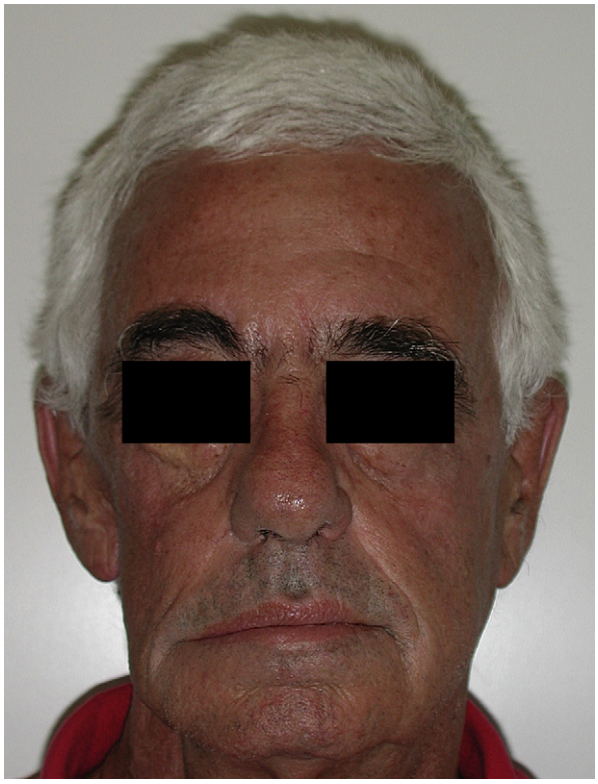


Fig. 6. Case 1: the patient 2 years after surgery, with good symmetry at rest.

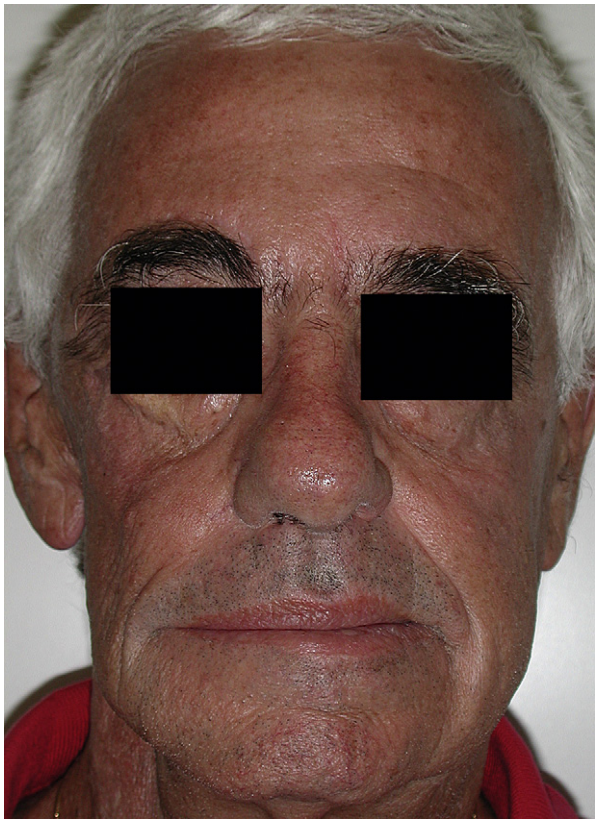
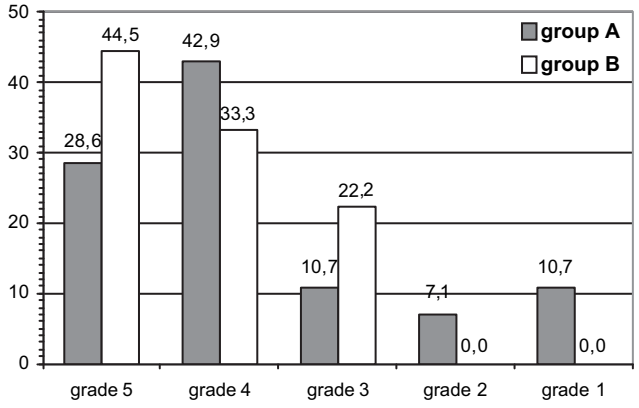


Fig. 7. Case 1: the patient 2 years after surgery: the symmetry of the face is maintained during smiling.

Table 2
Immediate static and final static-dynamic results, according to Terzis and Noah grading scale, with grade 1 considered poor and grade 5 considered excellent result (Terzis and Noah, 1997).

Grade	Three weeks after surgery		Twenty-four months after surgery	
	Only static result		Static–dynamic result	
	Group A	Group B	Group A	Group B
	28 pt (%)	9 pt (%)	28 pt (%)	9 pt (%)
5	/	/	8 (28.6%)	4 (44.5%)
4	/	7 (77.8%)	12 (42.9%)	3 (33.3%)
3	/	2 (22.2%)	3 (10.7%)	2 (22.2%)
2	/	/	2 (7.1%)	/
1	28 (100%)	/	3 (10.7%)	/

Table 3
Final results according to Terzis and Noah grading scale, with grade 1 considered poor and grade 5 considered excellent result (Terzis and Noah, 1997). Results are expressed in percentage (%).



at rest and full flap contraction while smiling, with teeth showing bilaterally (grade 5) (Figs. 6 and 7). In 12 patients (42.9%), the final result was good (grade 4), with good symmetry at rest and a symmetric, nearly full flap contraction. Three patients (10.7%) had a moderate result (grade 3), with slight asymmetry at rest and moderate flap contraction while smiling; two cases (7.1%) had a fair final result (grade 2), and facial reanimation failed (grade 1) in three cases (10.7%). In group B, the results were excellent (grade 5) in four (44.5%), good (grade 4) in three (33.3%), and moderate (grade 3) in two (22.2%) patients. The final results are summarized in Tables 2 and 3.

No age-related differences were observed between the two groups. There was no correlation between time of the paralysis onset and time of recovery.

Six patients in group A (21.4%) underwent a flap tension revision: in three cases, the muscle tension was reduced by disconnecting and releasing the superior two-thirds of the flap from the superficial and deep planes and repositioning the flap more inferiorly; however, this was effective in only one patient, who improved from grade 3 preoperatively to grade 5 postoperatively, as evaluated according to Terzis and Noah (1997). The other two patients had renewed pseudospasm within a few months, which we treated with local injections of botulinum toxin, which resolves the pseudospasm temporarily and is administered every 4 months. Another three patients needed superior repositioning of the muscle. The score remained at 3 in one patient, while it improved from 3 to 4 and from 3 to 5 in the other two. The mean improvement of the six patients who underwent secondary surgery was 0.83. The results are shown in Table 4.

Table 4
Revision of muscular tension (grading following Terzis and Noah classification).

Scale of pre-operation (No. of patients)	Scale of postoperation	No. of patients	
		Unchanged	Improved
Grade 3 (6)	Grade 3	3	
	Grade 4		1
	Grade 5		2

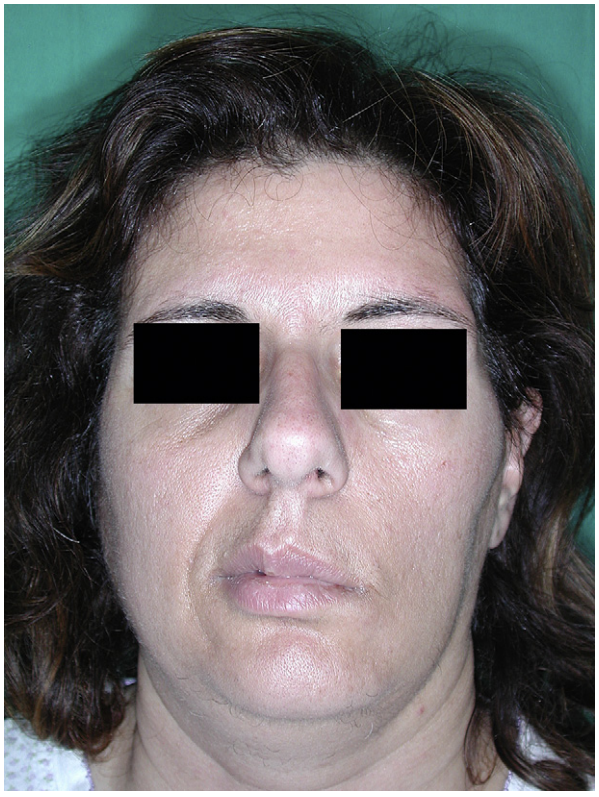


Fig. 8. Case 2: preoperative image of a 44-year-old patient with complete long-standing facial palsy. Note filter contralateral deviation and ptosis of the homolateral modiolus.

None of the 15 patients in group B underwent secondary surgery for flap tension correction.

In two cases sialoceles occurred and healed spontaneously in 15 days.

4. Discussion

Static soft tissue suspensions are traditionally used to improve aging faces (Senechal et al., 1982; Calderón et al., 2004, 2008). Use of a deep-plane facial lift in association with other static suspension techniques may achieve symmetry of the midface (Rubin and Simpson, 1996; Sasaki and Cohen, 2002; Sasaki et al., 2003). The SMAS flap is also known as a technique used in primary post-parotidectomy reconstruction for benign parotid tumours (Giannone et al., 2008), although a total conservative parotidectomy should be considered carefully in case of superficial adenomas because of the increased risk of facial nerve injury despite the same recurrence risk as superficial approaches (Zernial et al., 2007).

Facial reanimation with neuromuscular free flaps is actually the gold standard treatment of chronic facial palsy (Biglioli et al., 2009) (Fig. 8). Single-stage facial reanimation has been proposed to

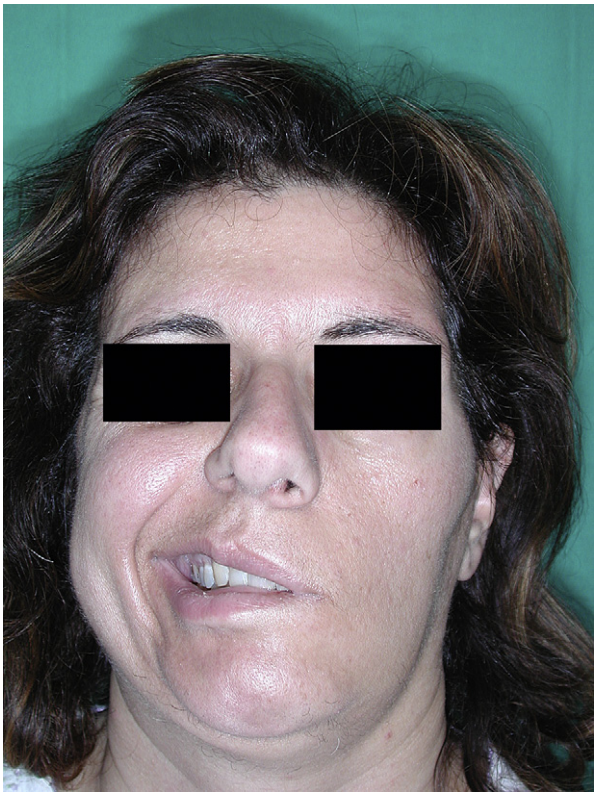


Fig. 9. Case 2: gross distortion of the face while activating mimetic musculature preoperatively.

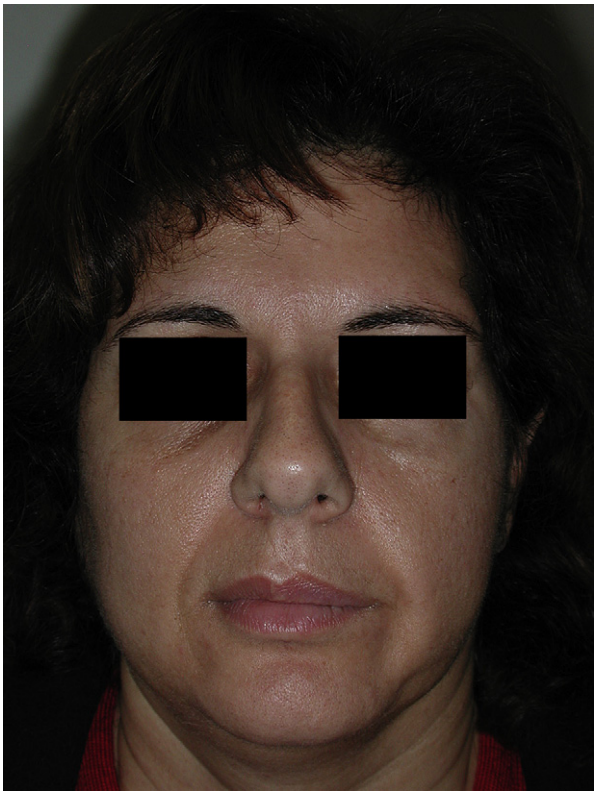


Fig. 10. Case 2: substantial symmetrization of the face 2 months after surgery. Static result is achieved mainly by DPL as flap function began 6 months postoperatively.

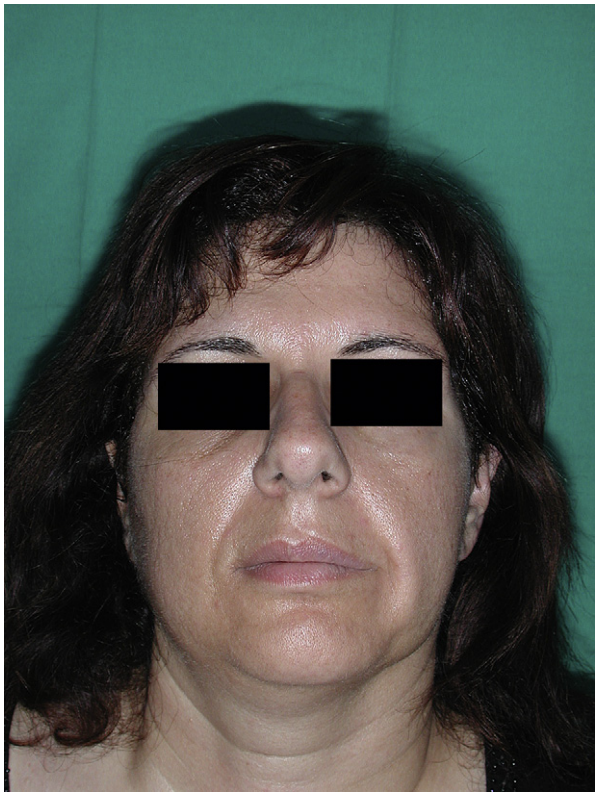


Fig. 11. Case 2: maintenance of static result achieved soon after surgery at 2 years postoperatively.

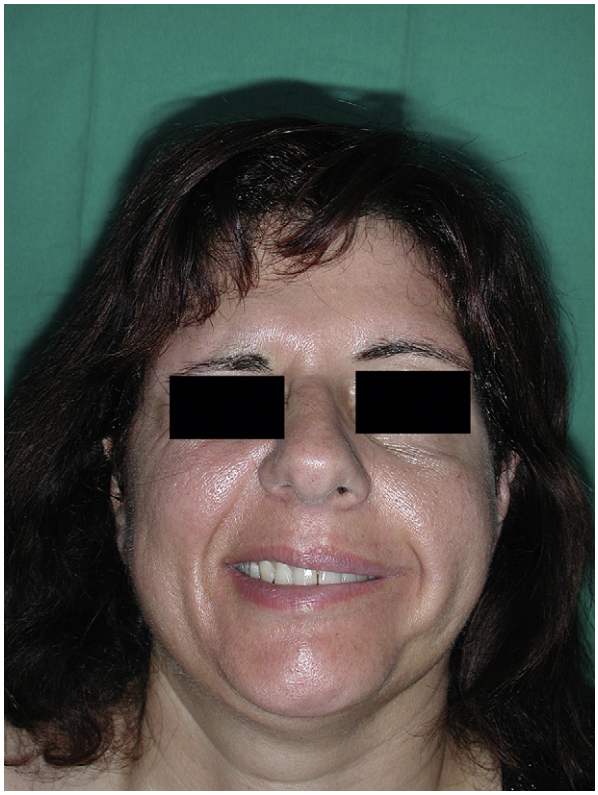


Fig. 12. Case 2: good contraction of the flap with little asymmetry of smiling graded 4 according to Terzis and Noah.

reduce the time required for treatment and recovery (Wang et al., 1989). The single-stage procedure involves one nerve anastomosis instead of two, as required by the two-stage technique with nerve cross-face grafting (Kumar, 1995; Kumar and Hassan, 2002). This would allow the passage of a higher number of fibres, though results are not better than those of most two-stage techniques (Harii, 1987; Kumar and Hassan, 2002).

Takushima et al. (2005) considered static suspensions as ancillary procedures after facial reanimation with free neuromuscular flaps, when a correct flap tension was not obtained and residual cheek ptosis was observed.

Analysis of our results showed that patients who underwent a DPL at the time of facial reanimation with free flaps had better immediate and final results than patients who underwent the flap transposition only (Tables 2 and 3). In patients with poor free flap postoperative contraction, the DPL allowed an improvement of the final static result (Figs. 9 and 10).

The DPL allows the surgeon to obtain intraoperative symmetry of the midface leading to an immediate postoperative result much superior to that of a flap transposition without static suspension (Harii et al., 1976; Harrison, 1985; Frey, 1999; Takushima et al., 2005). This has a positive psychological impact on patients waiting for the onset of flap contraction; for the same reason, some authors suggest performing temporary suspensions, even in acute palsies, before normal facial movement recovers (Ozaki et al., 2008). For those who fail to reach adequate contraction of the flap, at least symmetry of the face at rest is obtained. This is the case of three patients of group A graded 1. Cause of failures could have been thrombosis of pedicle vessels leading to a switch of transposed tissues from flap to graft, without significant contractile potential. Otherwise too little ingrowth of axons into the flap may be the cause of failure. If a DPL had been accomplished simultaneously to the free flap transposition, static symmetry would have been improved.

The group A patients who had the most severe preoperative asymmetry were treated with an overcorrection of the flap tension: this led to a painful contraction of the flap in five cases (21.3%), requiring a reduction in flap tension with superior repositioning of the flap in three cases and botulinum toxin injection in the other two cases. This complication was avoided in the group B patients, because the deep-planes lift resulted in immediate symmetry of the face and led to a more accurate tension of the muscular flap.

The improvement of symptoms related to corneal exposure in the group B patients who had the worst preoperative lagophthalmos may be due to reduced downwards traction on the lower lid by the lifted midface tissues. This constitutes a further advantage of the DPL. The DPL does not substitute for dynamic lagophthalmos surgical corrections, such as temporal fascia and muscle flap rotation (Brusati et al., 1998), but can improve the results of lid surgery. In borderline or asymptomatic cases, for which an eventual surgical correction of the lid incompetence is debatable, this decision may be postponed until after midface surgery.

Comparing the results of groups A and B (Tables 3 and 4), 44.5% of the patients in group B obtained an excellent final result versus 28.6% in group A. Moreover, no group B patients had poor results (grades 1 and 2). These data suggest that the improved final results in group B patients were attributable to the contribution of the DPL in combination with facial reanimation with free flaps (Figs. 11 and 12).

5. Conclusion

A deep-planes lift combined with facial reanimation with free flaps is a useful technique for the surgical correction of long-term facial paralysis. It facilitates the correct setting of the flap tension in the paralyzed hemiface, and gives an immediate postoperative

result, which is important for patient satisfaction, thereby improving patient compliance. The technique also improves the final static and dynamic results of facial reanimation.

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Conflict of interest

The authors had full freedom of investigation and there were no potential conflicts of interest. There was no grant support for this study.

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SUPPLEMENT F

Recovery of emotional smiling function in free-flap facial reanimation.
Journal of Oral Maxillofacial Surgery 2012; 70(10): 2413-2418.

Recovery of Emotional Smiling Function in Free-Flap Facial Reanimation

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Purpose: Long-standing unilateral facial palsy is treated primarily with free-flap surgery using the masseteric or contralateral facial nerve as a motor source. The use of a gracilis muscle flap innervated by the masseteric nerve restores the smiling function, without obtaining spontaneity. Because emotional smiling is an important factor in facial reanimation, the facial nerve must serve as the motor source to achieve this fundamental target.

Materials and Methods: From October 1998 to October 2009, 50 patients affected by long-standing unilateral facial paralysis underwent single-stage free-flap reanimation procedures to recover smiling function. A latissimus dorsi flap innervated by the contralateral facial nerve was transplanted in 40 patients, and a gracilis muscle flap innervated by the masseteric nerve in 10 patients. All patients underwent a clinical examination that analyzed voluntary and spontaneous smiling.

Results: All patients who received a latissimus dorsi flap innervated by the contralateral facial nerve and recovered muscle function (92.5%) showed voluntary and spontaneous smiling abilities. All patients who received a gracilis free flap innervated by the masseteric nerve recovered function, but only 1 (10%) showed occasional spontaneous flap activation. During those rare activations, much less movement was visible on the operated side than when the patient was asked to smile voluntarily.

Conclusions: The masseteric nerve is a powerful motor source that guarantees free voluntary gracilis muscle activation; however, it does not guarantee any spontaneous smiling. Single-stage procedures that use a latissimus dorsi flap innervated by the contralateral facial nerve have a lower success rate and obtain less movement; however, spontaneous smiling is always observed.

J Oral Maxillofac Surg 70:2413-2418, 2012

Current facial reanimation procedures to correct long-standing facial paralysis aim to restore facial symmetry at rest while activating the mimetic musculature.[1-3] Surgeons have concentrated their reconstructive efforts on the recovery of 2 main movements: eyelid closure and smiling. Eyelid closure is functionally most important, because without it, the eye globe is insufficiently protected and lubricated, and keratitis and corneal ulcers can develop, leading to partial or total loss of visual function.

Smiling is the most important facial movement for communication, the demonstration of a positive attitude toward others, and the sharing of positive emotions. One can smile voluntarily to communicate

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0278-2391/12/7010-0$36.00/0
doi:10.1016/j.joms.2011.11.031

friendship and a positive attitude or spontaneously from an emotional stimulus. Spontaneous smiling is perceived as more pleasant and natural; indeed, most people dislike their appearance in photographs with a forced and unnatural smile.

The first experience of Harii et al[4] with gracilis muscle transplantation innervated by a trigeminal branch, the deep temporal nerve, as a motor source provided good smiling function, but failed to produce spontaneity. To achieve more natural smiling function, the procedure was refined using a contralateral facial nerve branch as the motor source.[5,6] The use of this technique has produced satisfactory smiling quality and spontaneity. However, the proportion of recovered muscle function and quantity of contractions has varied.[7,8] Similar results, with a shorter recovery time, can be obtained with single-stage facial reanimation procedures. The most common is based on transplantation of a latissimus dorsi free flap.[9]

Manktelow et al[10] recently applied the facial reanimation technique proposed by Zuker et al[11] in patients with Möbius disease and long-standing acquired facial paralysis. They reported the recovery of 100% of transplanted muscle function and high percentages of spontaneous smiling function. The ability to shift from voluntary to spontaneous smile production was noted in a consistent number of patients and attributed to brain plasticity. Faria et al[12] used the same technique, but observed no recovery of spontaneous smiling function.

The transplantation of a gracilis muscle flap innervated by the masseteric nerve seems to achieve better functional outcomes than the use of free flaps innervated by the contralateral facial nerve.[11,12] However, the failure to achieve the goal of recovering emotional smiling function is unacceptable.

The present study examined the recovery of smiling function in response to an emotional stimulus in patients who had undergone facial reanimation procedures using free flaps.

Materials and Methods

In accordance with the ethical principles stated by local institutional review board, from October 1998 to October 2009, 50 patients affected by long-standing unilateral facial paralysis underwent single-stage free-flap reanimation procedures to recover smiling function. A latissimus dorsi flap neurotized by a contralateral branch of the facial nerve was used in 40 patients (group 1), and a gracilis muscle free flap anastomised to the homolateral masseteric nerve was used in 10 patients (group 2). Group 1 contained 28 males and 12 females, ranging in age from 6 to 77 years (mean 47.4). Group 2 contained 8 males and 2 females, ranging in age from 16 to 63 years (mean 42.3).

All patients had complete homolateral facial paralysis (House–Brackman stage VI), confirmed by preoperative electromyographic evaluation of the mimetic musculature. The contralateral facial nerve branches and homolateral masseteric nerve were also tested to ascertain their suitability as donor nerves.

The etiology of paralysis in group 1 was previous cranial base surgery in 22 (55%), trauma in 4 (10%), parotid surgery in 4 (10%), congenital in 4 (10%), Bell's palsy in 2 (5%), brain surgery in 2 (5%), sequelae of meningitis in 1 (2.5%), and radiotherapy in 1 (2.5%). The etiology of paralysis in group 2 was previous cranial base surgery in 8 (80%) and congenital in 2 (20%).

Postoperative clinical examinations were performed at 3, 6, 9, and 12 months after surgery. At each office visit, facial objectivity was evaluated at rest and during the activation of the mimetic musculature.

The patients were asked to contact the surgical team to schedule an immediate examination when they or those close to them observed the first voluntary movement of the commissure. On the initiation of muscle function, the patients were referred to our team's physiotherapist, who instructed each patient to perform physical training in front of a mirror and, later, without a mirror.

At 12 months after the initial transplanted muscle contraction, all patients underwent a prolonged clinical examination to analyze the voluntary and spontaneous smiling functions. Standardized photographs were taken at rest and during standardized facial movements. The results were classified according to the 5-stage system developed by Terzis and Noah.[13] Needle electromyography was also performed to test flap contraction during the activation of the masseteric or contralateral facial nerve.

To evaluate spontaneous smiling function, the patients underwent a prolonged clinical examination during which they were given time to become comfortable. Videos of the patients watching a comedic movie were also recorded and analyzed. Each patient was left alone in the viewing room to avoid embarrassment or the inhibition of spontaneity. To ensure the success of the test, each patient was asked to select a preferred movie from a series of available movies. The videos were analyzed later by a team consisting of 2 surgeons and 1 physiotherapist.

Results

The initial recovery of muscle function was achieved within an average of 7.4 months (range 2 to 22) in the 40 patients who underwent latissimus dorsi transplantation innervated by the contralateral facial nerve. The standardized photographs were analyzed according to the Terzis and Noah system; the recov-

ery of muscle function was classified as excellent in 14 patients (35%), good in 15 (37.5%), average in 5 (12.5%), poor in 3 (7.5%), and failed in 3 patients (7.5%).

The 10 patients who underwent gracilis muscle transplantation innervated by the masseteric nerve recovered initial muscle function within an average of 4.2 months (range 3 to 13). The results were classified as excellent in 3 patients (30%; Figs 1-5), good in 5 (50%), and average in 2 (20%). No patient in this group was classified as having poor or failed functional recovery.

All patients who underwent latissimus dorsi transplantation and recovered muscle function were able to smile voluntarily and spontaneously. Slightly less muscle function was detected between spontaneous and voluntary activation in a few cases.

Only 1 patient (10%) who underwent gracilis muscle transplantation innervated by the masseteric nerve recovered spontaneous smiling function. Rare spontaneous flap activation was observed in this patient; while watching a comedic movie, the patient activated the flap once in every 9 spontaneous smiles. The contraction was barely visible during spontaneous activation and was much less pronounced than the contractions obtained during voluntary activation.

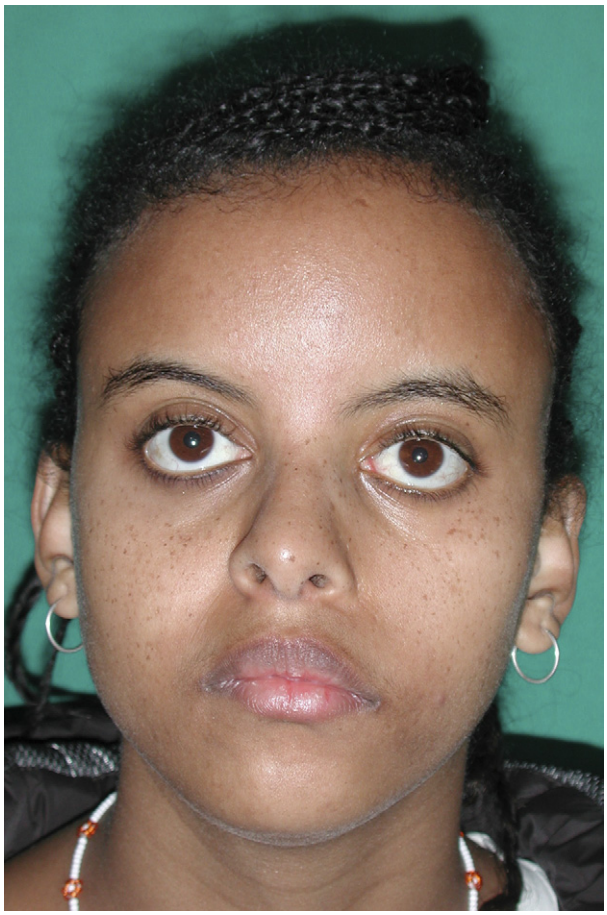

FIGURE 1. Preoperative view showing patient with congenital facial paralysis at rest: slight asymmetry of facial features.

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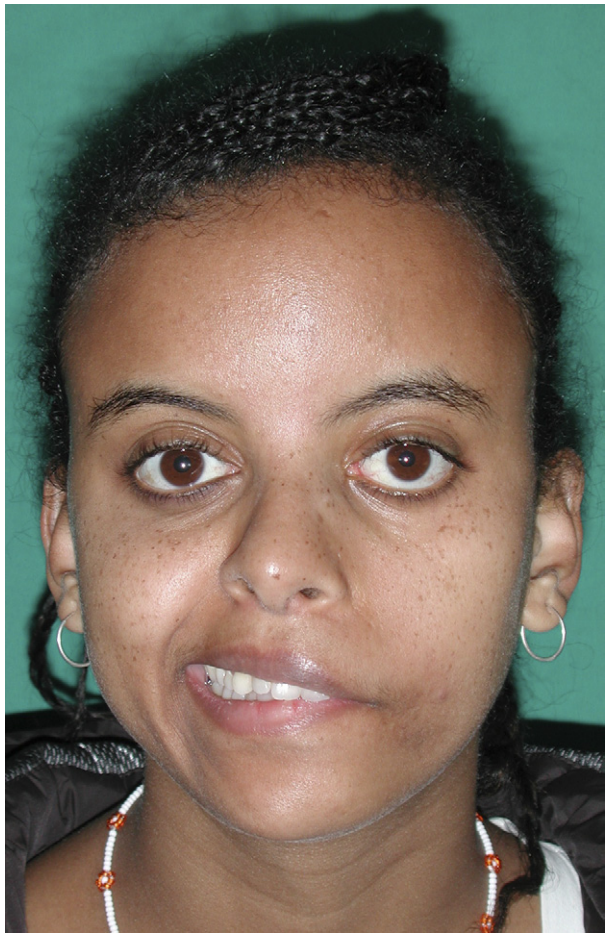

FIGURE 2. Preoperative view showing worsening of facial asymmetry during smiling.

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Discussion

Zuker et al[11] proposed the use of a gracilis muscle flap anastomised to the masseteric nerve for facial reanimation in patients with Möbius disease who were affected by bilateral facial paralysis. This procedure consistently achieved the rapid reinnervation of the flap (within 2.5 to 4 months) and a high quantity of contractions.[14] The investigators reported no flap failure in their series of 10 patients. From these positive results, the procedure gained great popularity and was also used in adults and for unilateral paralysis.[15] In an effort to improve facial reanimation outcomes, we changed from a single-stage latissimus dorsi procedure to the use of a gracilis flap neurotized by the masseteric nerve in response to these outstand-

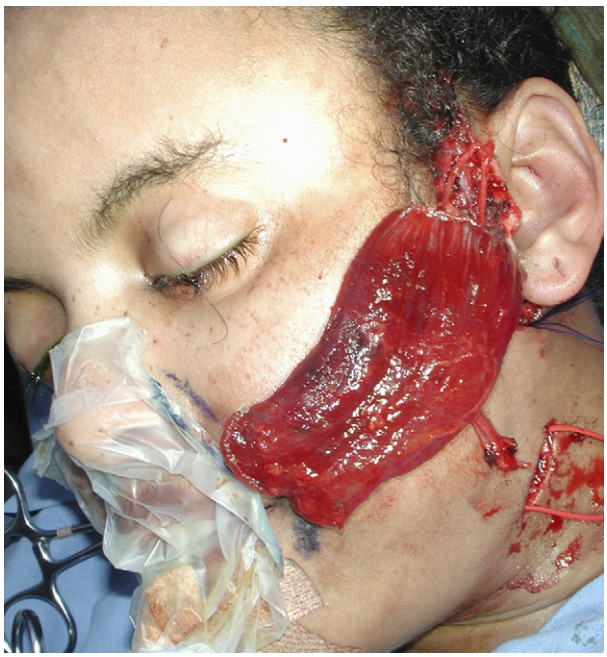

FIGURE 3. Intraoperative view showing facial reanimation by gracilis free-flap transplantation.

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ing reports. The new procedure resulted in satisfactory static symmetry and smiling function outcomes. However, the spontaneous smiling function results were disappointing, as noted when talking to the patients during the examinations and observing them when spontaneously smiling. The patients never used the flap during spontaneous smiling and appeared to remain paralyzed. Thus, some goals of facial reanimation were attained, such as the restoration of symmetry at rest, voluntary smiling function, and the improvement of eating, drinking, and speech functions; however, the paralysis remained evident when the patients spontaneously expressed themselves.

Relatives and friends provided a range of responses when asked whether the patients generally used the flap when smiling voluntarily. Although the patients were generally able to smile without clenching their teeth after a few months of physiotherapy, flap activation requires a voluntary effort in some instances. Although the stimulus becomes automatic over time,[10,15] this process is not consistent, and activation does not become spontaneous. One does not need to think about the performance of an automatic movement, such as taking a spoon from the table to eat cereal at breakfast. Spontaneity is related to emotional expression, such as crying in response to sad news. Patients who underwent gracilis transplantation innervated by the masseter nerve could often activate the flap automatically when smiling at someone they met, but they did not use the flap when laughing at a joke.

Although some investigators[10,16-18] have hypothesized that brain plasticity is responsible for the conversion to spontaneous masticatory nerve stimulus, this might be true only for patients with Möbius disease, who have made up the largest proportion of analyzed patients. Faria et al[12] and Gousheh and Arasteh[19] observed no spontaneous smiling function in large series of patients without Möbius disease who were affected by long-standing facial paralysis.

The recovery of emotional smiling function is not optional in facial reanimation. The intentional neglect of this function leads to failure in the most pleasant aspect of outcomes. People frequently dislike their smiling appearance in photographs because the voluntary smile is perceived as unnatural and slightly false. We can only imagine the extent to which this psychological situation is amplified in a patient with long-standing facial paralysis. Thus, the ability to smile in a pleasant way is extremely important.

Initial experiences with free-flap facial reanimation made it clear that the use of the facial nerve was the

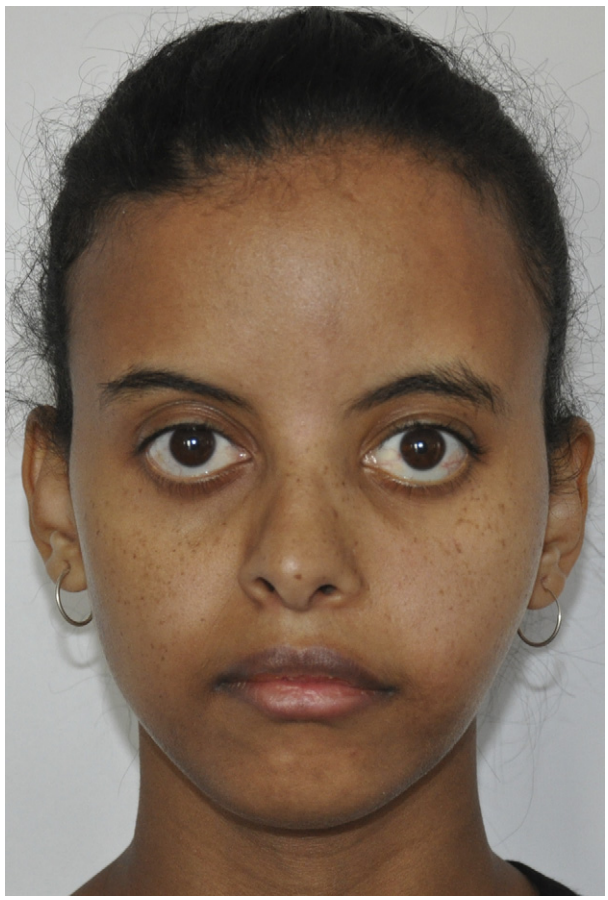

FIGURE 4. View at 18 months postoperatively showing increased facial symmetry at rest.

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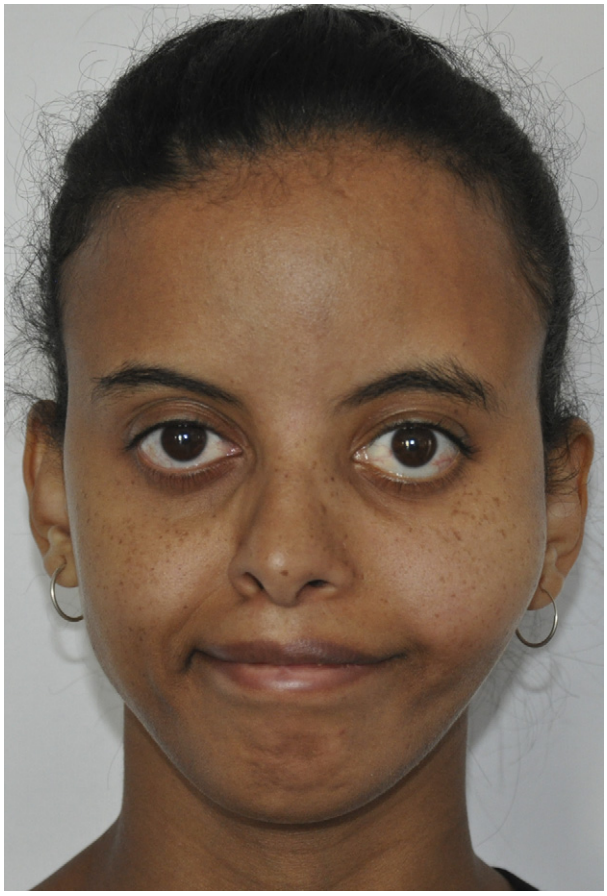

FIGURE 5. View at 18 months postoperatively showing good quality of voluntary smiling but results were spoiled by no visible movement during spontaneous smiling.

Biglioli et al. Free-Flap Facial Reanimation. J Oral Maxillofac Surg 2012.

only method to consistently achieve spontaneous smiling function. The initial procedure of Harii et al,[4] who neurotized the transferred gracilis muscle using the deep temporal nerve, was refined by Vedung et al[6] and O'Brien et al[7] to improve the natural response to stimuli. However, the results obtained in our series of patients have indicated that the use of the masseteric nerve does not achieve spontaneous smiling function. Numerous studies have confirmed that the use of the facial nerve is the only method to guarantee the ability to produce spontaneous facial expressions.[20-22]

In an effort to achieve a satisfactory quantity of contraction and appropriate activation of the contralateral facial nerve, Watanabe et al[23] used a latissimus dorsi flap innervated directly by the contralateral facial nerve, according to the technique developed by Harii et al,[4] and then created a second neurotization through close contact with an area of the masseter muscle. The results of this combined procedure were convincing, and our team is working to develop a similar technique. From the observation that gracilis transplantation innervated by the masseter muscle achieves better contraction than transplantation using a latissimus flap, we devised a new single-stage reanimation technique with dual innervation: a gracilis muscle flap innervated by the masseteric nerve received a second nerve input with a cross-facial sural nerve graft anastomised to a contralateral facial nerve branch. The preliminary results seem to be encouraging.

In conclusion, the use of the masseteric nerve in facial reanimation procedures does not achieve spontaneous smiling function. The use of the facial nerve is the only method to ensure correct stimulus production for facial mimicry, although the outcomes could vary quantitatively.

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4. ELECTRICAL STIMULATION IN NEURAL INTERFACES

4.1. General principles

Neural prostheses are devices that interface with the nervous system or other electrically excitable tissues in order to restore function. Examples of such systems include: pacemakers to restore cardiac rhythm; cochlear implants to restore hearing; retinal implants to restore vision; neuromuscular implants to restore movement. Electrical stimulation of the *orbicularis oculi* (*OO*) muscle, or its motor nerve branch, may have potential for restoring eyelid movement. This section provides a brief review of the biophysical principles on which the concept of neuromuscular stimulation is based, as well as a brief history that includes previous studies of its application to the *OO*.

For most, if not all practical neural prostheses, muscle activation is achieved by—electrical depolarization of the motor nerve and not by direct depolarization of muscle membrane. In fact, the stimulus amplitude required to activate a muscle directly is much greater than that required to activate it through its nervous stump. Alpha motoneurones synapse with a group of muscle fibers at neuromuscular junctions. An α-motoneuron and the muscle fibers it innervates is called motor unit. When an action potential reaches the presynaptic terminal of a neuromuscular junction it triggers release of the neurotransmitter acetylcholine, which in turn causes a muscle action potential leading to muscle contraction.

In neuroprosthetics, action potentials are generated by currents injected into the extracellular space. These currents produce voltage gradients in the vicinity of the axon that induce capacitive membrane currents and transmembrane potential changes. When the membrane potential change reaches threshold, an action potential is generated that is identical to a naturally elicited action potential. The distally propagating action potential will cause neurotransmitter release at the axon' s presynaptic terminal generating the same effect as a naturally evoked action potential.

The injection of current requires the use of two electrodes, an anode and a cathode. These can be placed in a monopolar configuration where the cathode is far away and the current spreads over a wider area, or in a bipolar configuration where the electrodes are relatively close and current is steered toward the cathode. Because currents that run parallel to the axon are most effective at stimulating neurons, the use of properly oriented bipolar stimulation (i.e. along the direction of the nerve, with the cathode closer to the muscle) can result in more selective target activation.

Electrodes pass current into the extracellular fluid by charging and discharging the capacitance between the metal surface and fluid. This converts the electronic current in the electrode to ionic current. Different tissues tend to contain different concentrations of ions and have different physical structures that result in tissue-specific conductance. In general, however, it can be assumed that the body acts as a large volume conductor. The capacitive flow of current between the electrode surface and surrounding fluid is a fully reversible process and can continue as long as the electrode surface potential remains below the value at which electrolysis can occur. Once this potential has been exceeded, irreversible reactions will take place that will actually strip molecules from the electrode surface and cause gas formation that results in pH changes. The amount of charge that can be injected without exceeding this voltage depends on the electrode

material and surface area. From the cellular point of view, membrane properties are very important in determining neuron's reactivity, particularly the diameter and degree of myelinisation. The ability for a cell to depolarize depends on the ability to discharge its capacitive membrane. Thus, neurons with shorter membrane time constants can be activated with shorter pulses. Additionally, larger myelinated axons have greater spacing between their nodes of Ranvier, resulting in greater transmembrane voltages due to extracellular currents. As a general rule the largest, most myelinated structures tend to be activated first (inverse recruitment).

Stimulation pulses can be either voltage controlled or current controlled. The local potential gradient, which determines whether a neuron is depolarized, is a direct result of the current injected. The problem with voltage controlled pulses is that the current delivered to the tissue depends in part on the impedance of the electrode itself, which can fluctuate over time. Thus, injected currents can vary within the same stimulation system. Regulating the current, instead, ensures that the voltage gradients produced within the tissue will be more consistent, and gives a direct measure of the charge density delivered across the electrode-electrolyte interface. For these reasons current-controlled pulses are more commonly used for neural prosthesis applications.

The field of functional electrical stimulation more commonly uses biphasic square wave pulses to provide balanced charge injection. Thus, the first phase of the pulse charges the electrode surface and the opposite phase discharges it back to its resting state. This is particularly important for implanted neural prosthetic systems. Safe charge density limits for commonly used electrode materials are listed in *Table 4.1*. In order for an action potential to occur, the local cell membrane must be depolarized above threshold, which requires the use of cathodic (negative) current. A cathodic extracellular current will cause an outward current which depolarizes the cell membrane.

Tab. 4.1
Charge Density Limits for Electrode Materials

Material	Charge Density Limit (mC/cm^2)
Au	0.490
TiN	0.687
Pt	4.134
Ir	17.078
IrO_x	28.450
IrO_x (after activation)	95.100

Adapted from (Slavcheva, Ewe, Schnakenberg, & Mokwa, 2004).

Biphasic electrical stimulation pulses have three basic parameters: pulse width, pulse amplitude, and pulse frequency. The combination of pulse width and pulse amplitude determines the charge injected, while the passive electrical properties of the surrounding tissue determine its distribution and resulting potential gradients. The current density will be the greatest in the vicinity of the electrode and decrease with distance as it spreads through the volume conductor comprised of the body fluid, exposing neurons closer to the electrode to larger voltage gradients.

The minimum stimulus intensity necessary to activate a neuron depends on the duration of the stimulation pulse, and is defined by LaPicque's Equation

$$I = b(1 + c/d)$$

where I is the stimulus intensity, b is the rheobase value, c is the chronaxie, and d is the pulse duration. The rheobase value is the minimum stimulus intensity required to elicit a response with an infinitely long pulse and is defined by the membrane properties of the neuron and the coupling between the neuron and the stimulating electrode. Thus, increasing the distance from the stimulating electrode will increase the rheobase value and therefore increase the necessary stimulus intensity for eliciting a response at all pulse durations proportionately. The chronaxie value is the minimal pulse duration at which a stimulus at intensity twice the rheobase may elicit a response. The chronaxie is directly related to the time constant of the neuron and is therefore purely a property of the cell itself.

Most neuromuscular prosthesis applications rely on stimulation of the motor axons that innervate the target muscles, rather than direct activation of the muscle fibers (*Peckham & Knutson, 2005; Ranck, 1975*). There are two primary reasons why stimulation of motor axons is more efficient than stimulation of denervated muscle fibers: the chronaxie values of myelinated motor axons are orders of magnitude shorter than those of bare muscle fibers (*Geddes, 1999*), and activation of a single motor axon will cause activation of all the muscle fibers within the motor unit it innervates while denervated muscle fibers must be activated individually. The difference in chronaxie values between motor axons and muscle fibers is due to the differences in their anatomical structures and can be explained by the underlying biophysics. As mentioned above, the chronaxie of a cell is proportional to its membrane time constant. Motor axons are smaller than muscle fibers and are myelinated. This may give motor axons a greater membrane resistance; however, it also gives them a substantially lower membrane capacitance. This difference in membrane capacitance translates to motor axons having a much shorter membrane time constant, and therefore chronaxie value, than muscle fibers.

As a result of their longer membrane time constants, activation of denervated muscle fibers requires the use of relatively long duration pulses, which have a greater potential to simultaneously activate unmyelinated pain fibers in the vicinity. This also results in a high amount of charge injection with each stimulation pulse, placing greater constraints on power supply and electrode design. Additionally each individual denervated muscle fiber must be activated directly, meaning that sufficient charge to induce activation must reach every fiber that is to be recruited (as opposed to indirect activation through motor axons, which only requires activating currents to reach the motor nerve in order to recruit all innervated muscle fibers). Given the rapid fall off of current density with distance from the electrode, very high amplitude stimulation pulses are generally required to activate large regions of denervated muscle. These factors combine to make it very electrically expensive to activate denervated muscle and increase the probability of discomfort associated with the stimulation.

In skeletal muscle, as opposed to cardiac muscle, muscle cells are activated directly by the applied stimulus or through their nerve supply rather than by propagation from adjacent muscle cells. Therefore, for direct muscle activation the stimulus level must be sufficient to activate all muscles fibers of interest, which is usually all of the myocytes in the muscle. Because the electric potential decreases inversely to the separation between the electrode and target cell, very large stimulus amplitudes are required to activate directly muscle cells only a few millimeters away from the electrode. These amplitudes can easily be in excess of values considered to be non-injurious for all but the smallest muscles. For this reason, motor prostheses are considered practical only for muscles that retain their motor innervations (*Mortimer and Bhadra, 2004*).

4.2. Clinical applications

Applications involving neuromuscular stimulation can be divided into three separate categories: therapeutic electrical stimulation (TES), neuromodulatory stimulation (NMS), and functional electrical stimulation

(FES) (*Loeb and Lan, 2001*).

TES is essentially electrically induced exercise, in which the desired effect is achieved not by the movement itself but rather by the trophic changes it induces in the stimulated muscle. TES applications include stimulation of the paralyzed shoulder muscles in stroke patients to prevent or reverse shoulder subluxation caused by disuse atrophy (*Faghri et al., 1994*) and electrical stimulation to reduce spasticity following spinal cord injury (*Stefanovska, Vodovnik, Gros, et al., 1989*).

NMS involves the use of preprogrammed stimulation patterns to pace or modulate some neural function without the use of any control signals. Examples of NMS applications include pacing of the phrenic nerves to achieve respiration in patients with central hypoventilation (*Glenn and Phelps, 1985*) and sacral nerve stimulation for bladder voiding (*Brindley and Rushton, 1990*).

FES involves the use of neuromuscular stimulation in combination with command signals and control feedback to reanimate muscles for functional tasks. Examples of FES applications include gait-triggered peroneal nerve stimulation to correct foot-drop in stroke patients (*Wieler et al., 1999*) and electrical stimulation of the finger muscles based on the residual activity in the proximal or contralateral limb to provide assisted grasp function in quadriplegics (*Prochazka, Gauthier, Wieler, and Kenwell, 1997*).

The origins of neuromuscular prostheses are derived from the early cardiac pacemakers of the 1950s, which used single channel stimulation to modulate cardiac function (*Loeb, 2001*). This technology was originally extended to neuromuscular applications in both the upper and lower extremity in the 1960s and has led to additional developments in the areas of bowel and bladder function and respiration (*Peckham and Knutson, 2005*). Despite its early promise and the decades of research that have followed, neuromuscular stimulation has historically enjoyed modest clinical and limited commercial success. One reason for this was the choice of early applications. The field began rather ambitiously, and subsequently much effort has been directed at the goal of making paraplegics walk, a high-risk activity that requires very sophisticated control of the muscles involved (*Loeb and Lan, 2001*).

Past FES systems have generally used open loop configurations developed for specific applications. Additionally, they have favored either surface stimulation, which has issues with high power dissipation, poor muscle selectivity, and system donning requirements, or leaded implantable systems, which have extensive surgical requirements and potential for lead breakage. A great deal of current FES research is being directed at the development of platform technologies suitable for multiple applications, minimally invasive implantable systems, and the acquisition and incorporation of command and feedback signals for closed loop control.

5. THE BIONIC EYEBLINK

5.1. Historic overview

Many studies upon the feasibility of an implantable device restoring a bionic eyeblink have been performed so far. This section will review the methods and outcomes of these studies.

5.1.1. First attempts on rabbits and dogs

First attempts were published in the late 70' s, when Tobey and Sutton investigated the effects of contralateral triggered stimulation of the paralyzed *orbicularis oculi* muscle (*OO*) in the rabbit (*Tobey and Sutton, 1978*). Contralateral healthy *OO* EMG activity was used as a trigger for eliciting electrical stimulation in one of three modes: single stimulus of fixed intensity, single stimulus of variable intensity, and trains of stimuli with variable duration and intensity. Stimulation was monopolar and varied from 3 to 5V at 200ms. Authors reported the ability to generate blink and to produce a reasonably symmetric response to contraction on the normal side. Limiting factors were reported as controlling the location of the response and the synkinesis due to activation of adjacent muscles; however duration and intensity matching were good.

Otto and coworkers first demonstrated the feasibility of electrically stimulating the paralyzed *OO* also in dogs (*Otto et al., 1986*). Bipolar cardiac pacing electrodes were implanted in the superior portions of both the normal and paralyzed *OO*s, near the medial canthus. Approximately three months after the onset of paralysis, EMG activity from reflex induced blinks in the normal side was recorded under mild sedation and used to trigger stimulation pulses in the paralyzed *OO,* by using a single square-wave pulse. The values for stimulus pulse width and pulse amplitude are unknown. The authors reported the restoration of "*functional symmetry*" achieved by stimulating a blink that "*appeared normal*" and very good tolerance of the system.

Eleven years later, Otto published a second manuscript on electrical stimulation to restore function in the paralyzed *OO* in the rabbit (*Otto et al., 1997*). This study included an acute pilot phase to determine anatomy for facial nerve dissection and stimulus parameters capable of achieving complete eyelid closure, a chronic pilot phase in which one test animal was stimulated, and an investigational phase in which six rabbits were chronically stimulated for a duration of 30 days. During the investigational phase, the facial nerve was sectioned and ligated and rabbits were implanted with exposed stainless steel wire electrodes that spanned the upper and lower eyelids. Beginning on the 11th day following nerve dissection, a battery powered backpack stimulator was used to deliver single biphasic voltage controlled stimulation pulses between the electrode in the upper lid and the electrode in the lower lid. Stimulation pulses were delivered every 10 seconds for 24 hours, each day. Stimulus amplitude was generally fixed around 4.8V and pulse duration generally ranged from approximately 20 to 90 ms with a mean of 37.18 ms but was reported to require little adjustment. The author concluded that the reported research demonstrates that "*functional restoration of the rabbit OO can be accomplished with direct electrical stimulation of peripherally denervated muscle for a short period of time without evidence of injury to muscle and without obvious*

undue discomfort".

A functional nerve stimulation of the injured facial nerve in dogs was also attempted with a wireless nerve stimulation (*Cao et al., 2008, 2009*). A cuff electrode was placed around the zygomatic branch of the injured facial nerve while recording the contralateral healthy orbicular oculi. The range of stimulus amplitude was 100-500mA, pulse width 200ms and frequency of 100Hz.

5.1.2. Electro-mechanical properties of innervated and denervated facial muscles.

In 1986 Rothstein and Berlinger published a feasibility study of electronic reanimation of facial palsy in the rabbit (*Rothstein and Berlinger, 1986*). They collected strength-duration data for innervated muscles (*OO* and *zygomaticus major*) and denervated muscles two weeks following facial nerve section, however it was not specified that these were for twitch movement. They used voltage controlled stimulation pulses delivered at 2 and 33 pulses/second with pulse widths that varied from 0.1 to 2.0 ms. Stimulation was bipolar with stainless steel electrodes that were "*implanted percutaneously at opposite ends of each of the denervated muscle groups*". Additionally, EMG activity was recorded from healthy *OO*s at different degrees of closure. The results section stated that "*in most cases there was a significant increase in minimum stimulation threshold for the respective muscles after denervation*". There seemed to be very little difference, however, in the rheobase and chronaxie values for innervated versus denervated muscles listed in their tables, and these rheobase values seem to be substantially greater than the minimum voltages in the actual strength-duration curves, so it is unclear how these values were reached.

Big effort was made in the 80's by Broniatowski, who placed miniature strain gauges on rabbits mimetic muscles (of the healthy side), with a central modulating unit triggering the stimulation of a contralateral facial musculature previously denervated and reinnervated via cross-over nerve-muscle pedicles (*Broniatowski et al., 1987*). The central modulating unit was linked to the nerve-muscle pedicle via a monopolar electrode. Facial wiggle resulting from direct electrical facial nerve stimulation caused synchronous contraction of all reinnervated strap muscles under study.

In a second step, the distal limb of the system was modified and the electronic stimulator was upgraded, demonstrating perfect synchrony between intact and reinnervated sides, thus fine tuning of reinnervated facial musculature was possible (*Broniatowski et al., 1989 Sep*),. In order to upgrade the control of the reinnervated muscles, their tension was adjusted by varying the pulse width (0.1-10 msec) of a constant 0.5 mA current applied to the nerve pedicles. Contraction (strain-gauge compression) of the intact face was followed by reciprocal graded relaxation of the reinnervated straps. Conversely, facial relaxation (elongation) induced graded strap contraction.

An agonist-antagonist relationship was thus created between the two effectors (*Grundfest-Broniatowski et al., 1989*). This approach may allow the paralyzed face to be electrically reanimated from the intact side in a symmetrical fashion closer to the physiologic state. In a pilot study in the rabbit, proprioceptive information originating in facial muscles (considered as agonists) was artificially channeled to nerve pedicles, reinnervating straps to produce antagonist action in order to lead to finer control of reinnervated muscles of the face or elsewhere (*Broniatowski et al., 1989 Jun*).

Another study involved bi-level cross-facial innervations in dogs and showed a balanced coupling of oral and ocular muscles from the intact side (*Broniatowski et al., 1991*). After severing the facial innervation unilaterally, a nerve pedicle from a cervical motor nerve was implanted into the orbicularis oris and from the deep temporal nerve into the orbicularis oculi. Graded contraction on the intact side was induced by stimulating the ipsilateral facial nerve with currents of various pulse widths. The resulting compression of a strain gauge on the intact face triggered a two-channel, opto-isolated, pulse width-modulated stimulator to produce agonistic graded contraction at one level of the reinnervated side (*oral*) and reciprocal relaxation in its reinnervated counterpart (*ocular*).

Salerno et al. studied the electrophysiological properties of the denervated *OO* in dogs (*Salerno et al., 1990*). They unilaterally ligated and transected the facial nerve in 10 dogs and performed acute percutaneous

stimulation with EMG needle electrodes under general anesthesia an average of 54 days later. For *OO* stimulation, two electrodes were inserted into the upper lid area; however the exact locations were not reported. For palpebral nerve stimulation, two monopolar electrodes were inserted into the perineurium of branches of the facial nerve innervating the upper and lower lids, respectively, with a ground electrode placed in the ear. Single square wave current controlled galvanic stimulation pulses were used to elicit first a muscle twitch and then a blink for each configuration over a range of pulse widths and the minimum threshold values were recorded for each. The most noteworthy findings were that the denervated *OO* had significantly lower twitch rheobase values and higher twitch and blink chronaxie values than either the normal *OO* or *palpebral* nerve. Mean denervated *OO* chronaxie values ranged from 30 to 48 ms, while normal *OO* ranged from 0.08 to 0.14 ms and *palpebral* nerve was approximately 0.06 milliseconds. There were no significant differences between twitch or blink parameters for normal *OO* and *palpebral* nerve. The majority of twitch and blink threshold data were reported for pulse widths ranging from 0.03 to 2.0 ms. Amplitudes for producing a twitch in denervated *OO* within this range were greater than those required to produce a full blink in normal *OO* and *palpebral* nerve. A separate denervated twitch curve was presented for pulse widths ranging from 5 to 400 ms, however the graphical and tabular data for this curve do not correspond and there is a distinct discontinuity between the denervated twitch curves for 0.03 to 2.0 ms and 5 to 400 ms. Denervated blinks were only reported for pulse widths ranging from 5 to 400 ms, and the graphical and tabular data for this curve do not correspond either. In a follow up publication, the authors demonstrated that *functional electrical stimulation* (FES) may have a therapeutic effect in speeding recovery of the blink reflex resulting from reinnervation after seventh nerve damage (*Salerno, Bleicher, & Stromberg, 1990*). A third study investigated the effects of electrical exercise on the electrophysiological properties of denervated *OO* in four dogs compared to four no stimulated controls (*Salerno et al., 1991*). It reported a possible temporary decrease in the electrical threshold to achieve complete blink that reversed over time, as well as probable muscle fiber type conversion leading to greater percentages of type II fibers in denervated *OO* muscles that had undergone chronic stimulation.

Somia et al. stressed the advantages of FES in order to keep the normal sarcomere pattern, prevent muscle degeneration, enhance its recovery after surgical reinnervation, up-regulate the production of neurotrophic factors by the muscle itself (*Somia et al., 2001*). Moreover they compared single and multi-channel electrical stimulation of canine paralyzed *OO.* Fourteen days after bilateral facial nerve resection, percutaneous wire electrodes were inserted into the *OO* on both sides through a needle. One side received single channel bipolar stimulation between contacts in the upper lid superior to the medial and lateral canthi. The other side received multi-channel stimulation consisting of two bipolar stimulation channels in the upper lid and two in the lower lid. The stimulation protocol involved the use of trains of monophasic pulses lasting a total of 300 ms and delivered at 60 Hz. The pulse widths investigated ranged from 0.3 to 1.0 ms and the amplitudes ranged from 0.1 to 4.9 mA. The parameters recorded to study the eyelid movement were the *twitch* (threshold contraction, minimal noticeable change in the palpebral fissure) and *blink* (complete eyelid closure). They concluded that only the multi-channel stimulation may lead to a complete eyelid closure at lower electrical stimulation thresholds, stimulating specific areas of the muscles and thus miming normal eyelid function. The authors discussed the ability of multiple channels to contain stimulation currents and focus them in the pretarsal region of the *OO*, where they reported achieving the most effect in producing electrically elicited eyelid closure.

A few years later Sachs and colleagues investigated the kinematics of eyelid movement after electrical stimulation of *OO* in the rabbit (*Sachs et al., 2007*). Normal, denervated and reinnervated muscles were stimulated by biphasic square wave pulses, while a high speed video camera recorded the eyelid behavioral response. Normal and reinnervated muscled showed similar kinematics. Moreover, increasing pulse width and number of pulses had a significant effect on the duration of the eyelid closure. They found out that trains of 10ms biphasic pulses delivered at 50Hz were the most effective stimuli to elicit lid closure. The qualitative assessment of the eyelid twitch elicited by threshold level stimulation revealed that the

contraction was generally limited to a small area focused adjacent to one of the stimulating electrodes, especially after long duration pulses stimulation. This problem would be bypassed by a nerve stimulation leading to a full contraction of the orbicularis oculi muscle. Assessment of eyelid movement elicited by single biphasic pulses suggested a twitch more rapid than the natural one. A complete lid closure could not be consistently achieved with single pulse stimulation.

5.1.3. Restoring the eyeblink in humans.

In 2009 Chen et al. designed a closed-loop eyelid reanimation system in humans and analyzed its design challenges: pain threshold barrier, patient-to-patient differences (blink detection and stimulation patterns), synchrony of the eyeblink (*Chen et al., 2009*). They proposed an electro-chemical stimulation in order to produce a fully controlled and painless blink. By injecting 100uL ACh into the *OO*, the required amplitude to produce an artificial blink was reduced from 9V to 3V. Moreover, pulse train simulation allowed to reduce the current required to eyeblink of about 40%, reproducing the motor control in human body. In 2010 Kurita performed a feasibility study of electrical stimulation of the frontalis muscle (chemically paralyzed) with square pulses triggered by the contralateral healthy hemi-forehead movements (*Kurita et al., 2010)*. Each pulse had a width proportional to the maximal amplitude of the healthy side EMG signal.

5.1.4. The first implantable prototype.

An implantable medical device to restore spontaneous blink for patients with long-term, unilateral facial nerve paralysis is being developed by Ripple LLC (Salt Lake City, USA). The system is designed to electrically stimulate the paretic eyelid when EMG electrodes detect normal blink from the contralateral eye to produce a synchronous blink. A conductive polymer stimulation array will be implanted along the length of the palpebral component of the paretic OO. Multiple stimulation sites will allow clinicians to selectively activate muscle tissue to evoke spontaneous blink via a diffuse injection of low levels of charge across the array. The device is powered by a small, external module worn behind the ear similar to a cochlear prosthesis, which activates the implant with a wireless reflected impedance signal and provides a user interface to control stimulation intensity. To date Ripple has developed a prototype device that has been tested in *in vitro* verification trials and validated in preliminary animal & human subject studies (*McDonnall, 2012*). This device has not yet received regulatory approval for clinical use (*McDonnall D, personal communication, May 2012).*

5.2. Kinematics of the bionic eyeblink

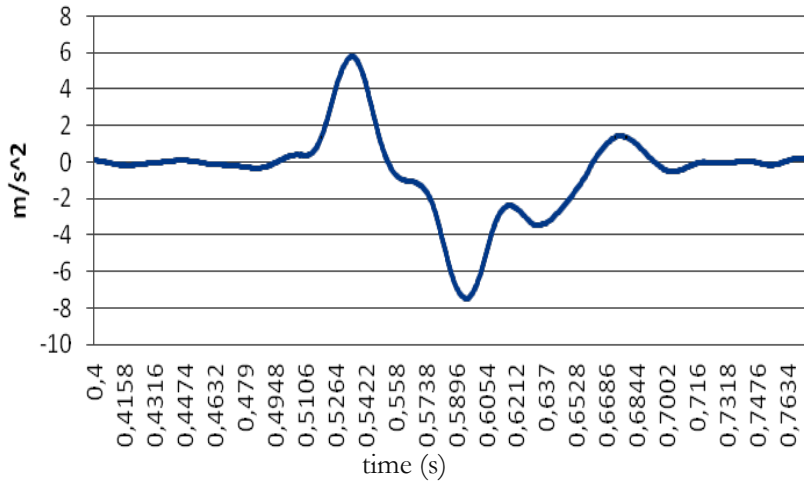
Studying the kinematics of prosthetically evoked eyeblinks allows tracking the eyelids motor response to the FES of the facial nerve. It represents a crucial point in the evaluation of results. In the course of the experimental simulation of a closed-loop facial pacing device, eyelid movements must be quantified bilaterally and compared. Questions to be answered are: *are eyeblinks speed and duration similar between the two sides? which is the delay between the trigger signal and the bionic eyeblink? does the overall motor response look natural and cosmetically acceptable?* Some of the answers will be discussed further in the next chapter. A few alternative methods have been tested by the Author in the course of the research and will be briefly described as follows.

5.2.1. Micro accelerometer.

An accelerometer is an electromechanical device built to measure acceleration through certain directions. Dynamic accelerometers sense the amount of dynamic acceleration and allow to analyze the way the device is moving. In the experiments described in *Supplement K* an analog single-axis micro accelerometer (EGAX-T-10 Y, Entran Sarl), weight 0.5g, was taped onto the upper eyelids of both sides of the face. First,

the kinematics of normal eye blinks was studied. Participants were asked to look ahead for 1 minute. Their blink frequency, speed, and duration were recorded and analyzed offline and average peak acceleration was calculated. The sensor allows computing both the eyelid vertical acceleration and also the duration of eyelid closure during blinking, which is extract from the time-variant acceleration profile at known initial and final conditions (see Fig. 5.2.1.).

Fig. 5.2.1.
Acceleration signal of spontaneous blinking activity



The kinematics of the FES-elicited eyeblinks - on the contralateral side - was also recorded, and compared to the one of the natural eyeblinks. Finally, average-peak acceleration was plotted against stimulus intensity in recruitment curves, describing the motor response of the *OO* to different patterns of stimulation. The performance of the EGAX micro accelerometer was adequate for the requirements of that specific protocol, although a lighter device would allow more accurate or multiple measurements in further studies.

5.2.2. Gyroscope.

An alternative method for the quantitative assessment of eyelid movements is based on the use of a gyroscope. In the experiments described in *Supplement G*, an ultra-small (4x8x2mm) and ultra-lightweight (0.2 g) gyro (ENC03-R, Murata Manufacturing Co., Kyoto, Japan) was taped to the upper eyelid, whose angular velocity was directly measured during prosthetically assisted eyeblinks. The sensor allows computing both the eyelid angular displacement and the duration of eyelid closure during blinking, by processing the eyelid angular velocity signal which is directly measured.

The gyro-based method represents an innovative system for the study of the bionic eyeblink kinematics.

5.2.3. High speed videocamera.

Within available eye tracking technologies, high speed camera analysis is a validated system to track the video footage of the eyelids movements. Its application can be extended to the study of bionic eyeblinks kinematics. Video-based systems consist in videotaping the eyelid and computing by image processing the differences in brightness on images of the palpebral fissure during the closing and opening phases of the blink. Eyelid movements can be quantified in relation to the timing of delivered pulse trains using video recordings of the eye.

In the ongoing trial of nerve FES of individuals with acute facial palsy, we are performing high speed video recording to study the kinematic of the bionic blinks. A stimulation hardware illuminates an LED

(placed within the recorded video frame) with each delivered pulse, and our high-speed video system records the eye at 1000 frames/s (240x256 pixel CCD camera model 25105100; KayPentax B/W System, Montvale, NJ). Individual video frames are then analyzed using ImageJ software (available at http://rsbweb.nih.gov/ij/download.html) to track palpebral fissure in relation to iris diameter over time (temporal resolution of 10 ms/image). The data acquisition system receives a TTL pulse signal from the high-speed video system which allows off-line analysis of eyelid movement characteristics with electrode location and stimulation parameters (amplitude, frequency, and train duration).

Finally, blink characteristic such as threshold to initial twitch (movement), complete eye closure, maximal closure velocity, and relative upper versus lower lid contributions are measured in relation to stimulation parameters.

5.2.4. Optoelectronics.

Three-dimensional motion analyzers allow an objective, non-invasive assessment of soft tissue facial movements. The three-dimensional assessment of facial movements using an optoelectronic motion analyzer was found to be a minimally disturbing, reliable method, accurately detecting total and local motion during the performance of standardized facial animations (*Sforza et al., 2010a,b*). The displacement of passive markers is used to investigate facial motion without

interfering with the movement, and custom algorithms allow compensation for head motion, without the need for head holding (*Mehta et al., 2008*).

In order to track the eyeblinks, optoelectronic motion analyzers detects the three-dimensional position of a small, weightless, passive marker glued on the upper eyelid rim in correspondence of a selected anatomical landmark. The kinematics of the eyeblinks is gathered after the three-dimensional movements are computed and the modulus (intensity) of the three-dimensional vector of maximum displacement from rest s calculated.

In the clinical setting, the optoelectronic analysis is a useful method to assess and follow up surgical results. It also allows a comparison of results obtained with different procedures. *Supplement H* reports a pilot optoelectronic analysis of the outcomes of masseteric-facial nerve anastomosis technique for early facial nerve repair and discusses this method in light of the current three-dimensional motion analyzers.

Facial movements were recorded using an optoelectronic three-dimensional motion analyzer with a 120 Hz sampling rate (SMART System, BTS, Milano, Italy). The instrument uses nine high-resolution infrared sensitive charge-coupled device video cameras coupled with a video processor that defines a working volume of 60 (width) x 60 (height) x 60 (depth) cm3; metric calibration and correction of optical and electronic distortions are performed before each acquisition session using a 20-cm wand, with a resulting mean dynamic accuracy of 0.121 mm (SD 0.086), corresponding to 0.0158% (*Sforza et al., 2010b*). The patient sat inside the working volume on a stool, and was asked to perform a series of standardized facial movements.

During the execution of the movement, for any camera special software identified the two-dimensional coordinates of 16 passive markers positioned on facial landmarks. Subsequently, all the coordinates were converted to metric data, and a set of three-dimensional coordinates for each landmark in each frame that constituted each movement was obtained.

The three-dimensional assessment of eyelid movements using an optoelectronic motion analyzer represents an alternative eye tracking system to study the kinematics of bionic eyeblinks.

5.3. Blink detecting glasses for facial pacing

Patients with recent acute onset of unilateral peripheral facial paralysis, with either an intact facial nerve or an injured but intact or grafted facial nerve (see groups 1-3 in Introduction) may benefit from a biomimetic

device to facilitate eye closure during waking hours, until the recovery process is complete. These patients may benefit from a temporary external electrical device that restores coordinated blinking without causing significant discomfort. Patients needing an implantable neuroprosthesis can still wear an external eyeblink detection system that communicates wirelessly with the implanted stimulation apparatus.

The design of the device involves an attachment of the sensors to the frame of a pair of eyeglasses. The box containing the integrated circuit and the battery would hang behind the neck or by the belt, and the wires and electrodes would run along the glasses to the locations on the face where they would be attached as depicted in Fig. 5.3.3.

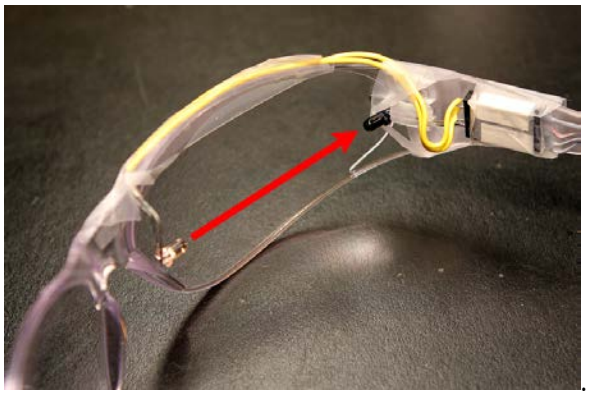
5.3.1. Eyeblink detection systems.

A half of our investigation has been dedicated to recording spontaneous human eyeblinks with a system that could be harmless, real-time detecting, with proper signal strength, accurate and eventually implantable. Neural and muscular recordings represent the basis of most biomimetic devices that record signals and provide motor functions to patients with paralysis. Electromyography (EMG) recording can reveal the electrical activity of facial muscles 10 to 12ms prior to the onset of movements; this makes it a very desirable tool for a successful real-time pacing. We explored the application of EMG to the detection of spontaneous eyeblinks.

A multichannel surface EMG recording system detected the activity of the right *orbicularis oculi*, masseter and zygomatic muscles in 15 healthy volunteers. Custom software filtered each independent EMG channel and registered a blink when suprathreshold activity was detected from the *orbicularis oculi* without simultaneous activity from the masseter or zygomatic recording locations. Experiments were carried out while the participants were relaxed and produced particular oro-facial movements. When participants were relaxed, sensitivity and specificity of eyeblink detection was 100%. Smiling and chewing activities affected the computer output in 23.9%±6.7% and 55.8%±8.8% of trials, respectively. A software filter coupled with multi-channel EMG recording eliminated spurious outputs during smiling or chewing. In the process the filter also eliminated 14-20% of valid blink signals. Results are discussed in ***Supplement J.***

In collaboration with the Facial Nerve Team of the Harvard Medial School in Boston, we are also working at an innovative external eyeblink detection system, based on infrared (IR) sensors that can be attached on a pair of eyeglasses. Glasses are equipped with an IR emitter/detector pair oriented horizontally across the palpebral fissure, creating a monitored IR beam that is interrupted when the eyelids close (Fig. 5.3.1.).

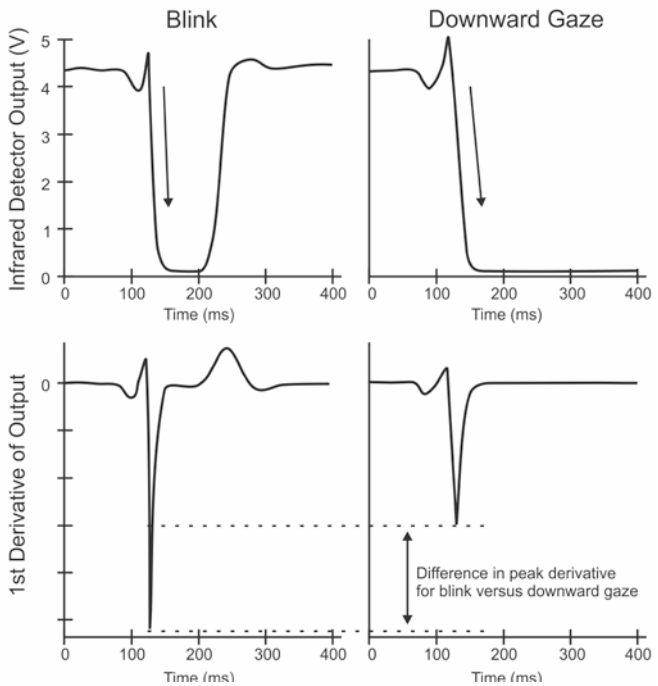
Fig. 5.3.1.
IR-based eyeblink detection system



A prototypal system has been built and tested in 24 healthy volunteers. Video-quantified blinking has been compared with IR sensor signal magnitude and rate of change in 24 participants while they were relaxed, shifted gaze from central to far peripheral positions, and produced particular facial expressions/movements, including neutral, broad smile, raised eyebrows and squinting. Blink detection based on signal magnitude could achieve 100% sensitivity, but generated false-detections on downward gaze (see Fig. 5.3.2.). Thresholding on peak rate of signal change (first derivative) typically distinguished blinks from gaze-related lid movements, and produced an average detection latency of 45.6 ms (±18.9 ms). Facial expressions affected sensor output if they caused substantial squinting or shifted the glasses.

Fig. 5.3.2.

Infrared detector (location #2) output during blink (left column) and downward gaze (right column) when starting from a forward gaze. The detector receives a relatively unobstructed beam during forward gaze, producing an output in the 4-5V range, but drops in voltage when the beam is broken by the lowering upper lid during blink, or looking downward. This drop in voltage is more rapid for blink than gaze-related lid lowering, as shown by the general slope downward pointing arrows) and by the 1st derivative of the output signal (lower panels). The difference in peak derivative fo blink versus downward gaze is highlighted byy the dotted lind and double-headed arrow.



5.3.2. Surface electrical stimulation of the facial nerve

Another half of our investigation has been dedicated to exploring the application of FES to facial nerve branches for the *orbicularis oculi* muscle.

A preliminary FES study was performed on 10 healthy volunteers, who are intended to represent individuals with facial paralysis. A dedicated LabView software built up and triggered custom stimulation trains. An epicutaneous stimulation of the facial nerve branch for the left *orbicularis oculi* muscle was performed on each participant. A webcam recorded the behavioral effect, while a microaccelerometer taped to the upper eyelids was used to study their kinematics. Also, eyeblinks evoked by dynamic vs. non dynamic patterns of stimulation were compared. Muscle recruitment curves were studied and acceleration of the *bionic blink* was measured and compared to the natural one. Kinematics of the natural eyelid is highly variable within subjects. The stimulation pattern frequency was set case by case, in order to obtain the desired eyelid acceleration of the contralateral eye. A custom-fit dynamic stimulation finally led to symmetrical natural-like eyeblinks. Results are discussed in ***Supplement K***.

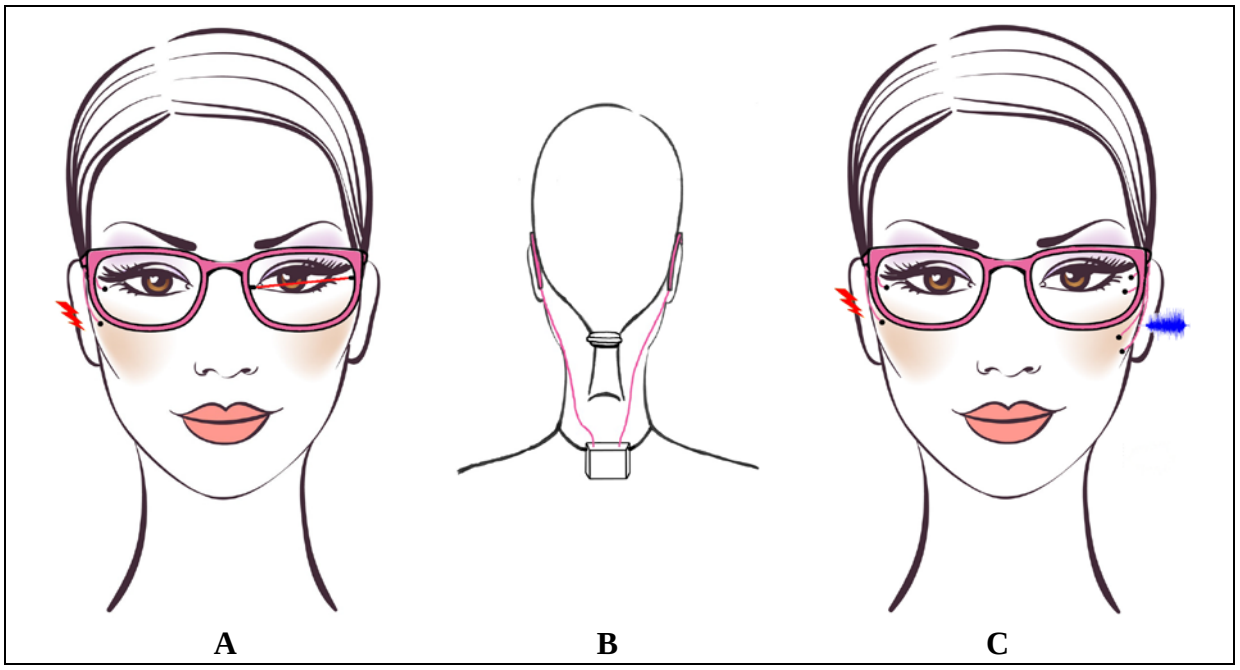
Fig. 5.3.3.

Hypothesis of devices for closed-loop facial pacing.

A. An infrared (IR) eyeblink detection system for the left eye is mounted on the frame of the glasses. The stimulation electrodes wires run into the frame of the right side.

B. The box containing the integrated circuit and batteries hangs behind the neck.

C An EMG eyeblink detection system for the left eye is mounted on the frame of the glasses. The stimulation electrodes wires run into the frame of the right side.



SUPPLEMENT G

Double innervation in free-flap surgery for longstanding facial paralysis.
Journal of Plastic, Reconstructive and Aesthetic Surgery 2012; 65(10): 1343-1349.

Journal of Plastic, Reconstructive & Aesthetic Surgery (2012) **65**, 1343—1349

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Double innervation in free-flap surgery for long-standing facial paralysis

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Received 2 October 2011; accepted 26 April 2012

KEYWORDS
Facial paralysis;
Facial reanimation;
Double innervation;
Masseteric nerve;
Cross-face nerve graft;
Gracilis flap

Summary *Objective:* One-stage free-flap facial reanimation may be accomplished by using a gracilis transfer innervated by the masseteric nerve, but this technique does not restore the patient's ability to smile spontaneously. By contrast, the transfer of the *latissimus dorsi* innervated by the contralateral facial nerve provides the correct nerve stimulus but is limited by variation in the quantity of contraction. The authors propose a new one-stage facial reanimation technique using dual innervation; a gracilis muscle flap is innervated by the masseteric nerve, and supplementary nerve input is provided by a cross-face sural nerve graft anastomosed to the contralateral facial nerve branch.
Methods: Between October 2009 and March 2010, four patients affected by long-standing unilateral facial paralysis received gracilis muscle transfers innervated by both the masseteric nerve and the contralateral facial nerve.
Results: All patients recovered voluntary and spontaneous smiling abilities. The recovery time to voluntary flap contraction was 3.8 months, and spontaneous flap contraction was achieved within 7.2 months after surgery. According to Terzis and Noah's five-stage classification of reanimation outcomes, two patients had excellent outcomes and two had good outcomes.
Conclusions: In this preliminary study, the devised double-innervation technique allows to achieve a good grade of flap contraction as well as emotional smiling ability. A wider number of operated patients are needed to confirm those initial findings.

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doi:10.1016/j.bjps.2012.04.030

Currently, the surgical treatment of long-standing paralysis in the central third of the face is achieved primarily by free-flap surgery.[1–3] Harii[4] first reported facial reanimation by gracilis transposition innervated by the deep temporalis nerve, a branch of the trigeminal nerve. This technique has been considered a great improvement in terms of the vector of contraction, quantity of smiling and aesthetic appearance of the face. The main drawback is the type of contraction stimulus provided, which is related to the voluntary clenching of the teeth, and its imperfect coordination with smiling on the healthy side of the face. To overcome this problem, O'Brien et al.[5] and Vedung et al.[6] achieved the correct stimulus by anastomosing the sural nerve on the contralateral facial nerve. After 10–12 months, when the regenerated axons in the nerve graft had reached the tragus on the paralysed side, they transposed a free gracilis flap and performed a second anastomosis to the free end of the sural graft. Among the various muscle flap techniques proposed, this technique has been the standard procedure since the mid-1990s in most reconstructive centres. To overcome the problem of the length of time required for a two-stage facial reanimation while maintaining the advantage of using the contralateral facial nerve as a nerve source, in 1994, Koshima[7] reported a one-stage facial reanimation technique using the rectus femoris. The quantity of contraction achieved with this method was adequate and the type of neural stimulus was correct, but the bulk of the flap was unacceptable. This idea was refined in 1998, when Harii[8] proposed the use of a *latissimus dorsi* flap harvested with a 15-cm length of the thoracodorsal nerve to be anastomosed immediately to a contralateral facial nerve branch. That flap was thinner and the aesthetic results were improved.[9] Percentages of positive results were close to 90% in most of series.[9–11] The main drawback was the quantity of contraction, which was not always guaranteed.[10,11] This problem may be due to the length of the thoracodorsal nerve and the unavoidable loss of axons when the collateral nerve branches are severed to prepare a 15-cm length.

Zuker et al.[12] proposed the use of a gracilis muscle flap anastomosed to the masseteric nerve to achieve reanimation in Möbius patients affected by bilateral facial paralysis with 100% positive results. Based on the positive experience with this technique, it has gained great popularity and has also been used in adults and in patients with unilateral paralysis, with similar results.[13,14] This technique guarantees the rapid reinnervation of the flap (within 2.5–4 months) and successful contraction. Although Manktelow et al.[15] hypothesised that the conversion to spontaneous nerve stimuli was a type of cerebral adaptation, this has not been observed clinically by Faria[10] or by the authors of the present study. Thus, the primary issue consists of the surgeon's choice between a technique that ensures the reliable recovery of function using a flap directly innervated by the masseteric nerve, and one that ensures the recovery of correct stimulus using the contralateral facial nerve.

In an attempt to obtain guaranteed voluntary contraction as well as spontaneous smiling ability with a single surgery, Watanabe et al.[16] used the method of Harii[8] to create a *latissimus dorsi* flap innervated directly by the contralateral facial nerve, and then created a second neurotisation through close contact with an area of the masseteric muscle.

Based on the observation that a one-stage gracilis transfer innervated by the masseteric nerve achieves a higher percentages of positive results than a one-stage transfer using the *latissimus dorsi*, and given the advantages of the synchronicity and spontaneity of stimuli provided by the contralateral facial nerve, the authors have devised a new one-stage reanimation technique with dual innervation: a gracilis muscle flap innervated by the masseteric nerve receives a second nerve input with a cross-face sural nerve graft anastomosed to a contralateral facial nerve branch. In this article, the technical details and preliminary results of this technique are described.

Materials and methods

Surgical technique (Figures 1 and 2)

This incision begins in the temporal region, passes hidden behind the tragus and under the earlobe, and extends 6–8 cm into the cervical region along a skin crease 2 cm caudal to the inferior mandibular border. An anterior skin flap is elevated to access the lower two-thirds of the face.

To ensure the correct formation of the nasolabial fold, the dissection of the skin flap is extended 1.5–2 cm medially to the ideal fold position. When the flap subsequently contracts, the natural skin crease will form a new nasolabial fold that is as symmetrical as possible to that on the contralateral side. To achieve the best aesthetic results, four to six 2/0 polyethylene sutures are positioned across the residual fibres of the orbicularis oris muscle. If this is not visible, the sutures are passed through the deep subcutaneous tissue. One U-stitch may capture the inner musculature of the philtrum if it deviates from the midline.

The masseteric motor nerve is identified within the muscle parenchyma. The zygomatic arch and the posterior border of the masseter muscle serve as surgical landmarks. One need not detach the muscle insertion from the zygomatic arch because the masseteric nerve is deep in this area. The best approach is to enter the muscle 1 cm below the zygomatic arch and 1 cm medial to its posterior border. The nerve lies 1.5–2 cm beneath the muscle surface and can be readily visualised by gently dissecting the muscle fibres along their nearly vertical axis. The fibres divide readily to reveal the nerve.

One or two small collateral branches of the masseteric nerve may be cut in the craniocaudal direction to harvest 2.5–3 cm of the nerve trunk. The nerve is severed at this level and turned superficially to facilitate anastomosis.

A 10 × 6-cm gracilis muscle flap is simultaneously harvested from the medial thigh following the standard procedure. The flap is transferred into the face pocket and stabilised using only the medial attachment defined by the previously placed sutures. End-to-end vascular anastomosis is performed between the flap and facial vessels. Then, end-to-end neural anastomosis is carried out between the anterior branch of the obturator nerve and the masseteric nerve using 10/0 epineural sutures surrounded by fibrin glue.

On the healthy side of the face, a facelift-type incision is traced posteriorly into the mastoid region with no cervical

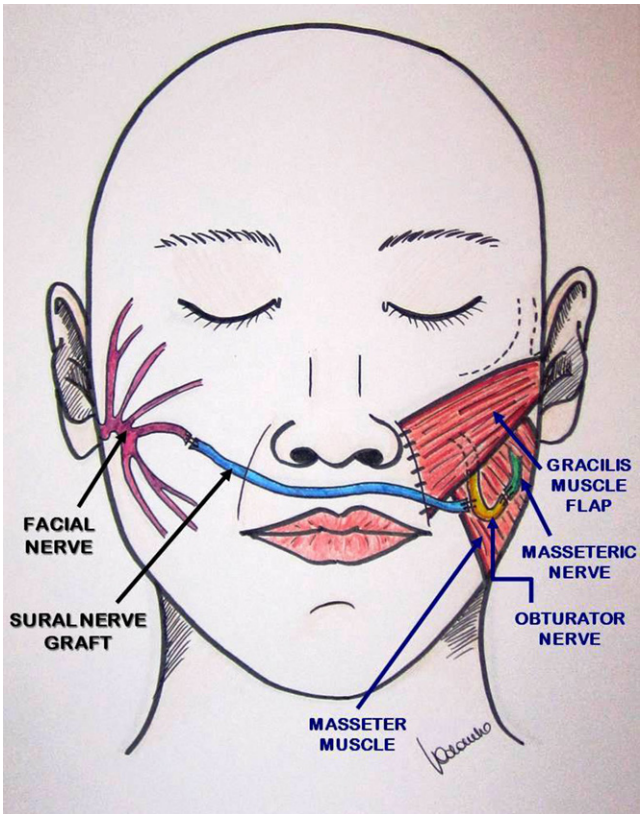

Figure 1 Scheme of surgery. The transposed gracilis muscle flap is innervated by masseteric nerve (end-to-end anastomosis) and contralateral facial nerve (end-to-side anastomosis) through an interpositional sural nerve graft.

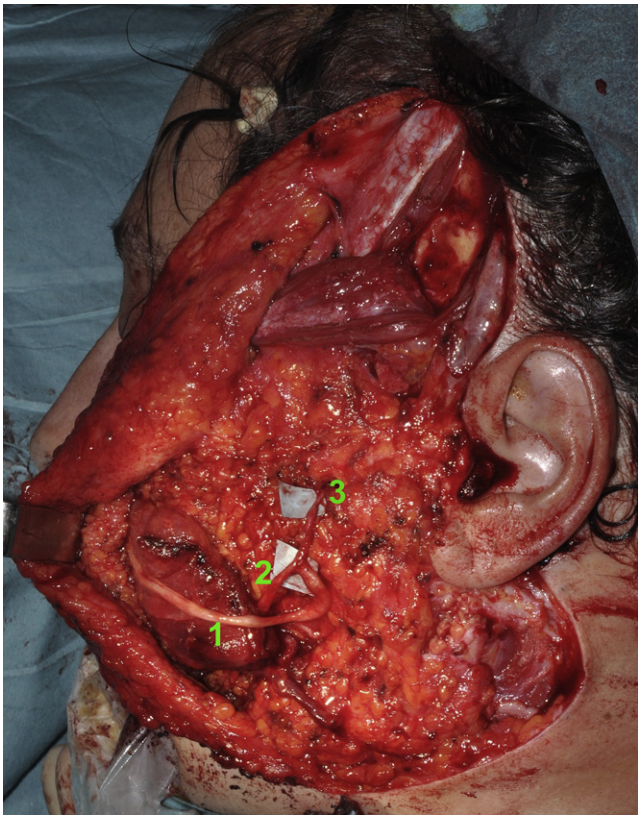

Figure 2 Intraoperative view before setting the masseter muscle over nerve anastomoses. (1) Sural nerve. (2) Anterior branch of the obturator nerve. (3) Masseteric nerve. The intraoperative photograph shows that the patient also underwent the mini-temporalis technique for reanimation of lower eyelid.

extension. Anterior skin flap dissection allows the identification of a middle branch of the facial nerve just medial to the anterior margin of the parotid gland. The involvement of this nerve in a smiling movement is tested with an electrostimulator. A 20—25-cm portion of the sural nerve is then grafted across the face in a reverse manner. The distal end is anastomosed end-to-end with the branch of the facial nerve previously identified. On the paralysed side of the face, the proximal end of the sural nerve is anastomosed end-to-side to the anterior obturator branch, between the hilum of the flap and the anastomosis to the masseteric nerve. An epineural window is opened to allow the end-to-side anastomosis. The inner fascicles and fibres of the receiving nerve are not severed.

Finally, the lateral side of the flap is anchored to the periosteum overlying the zygomatic arch and lateral zygomatic bone. Care must be taken to achieve correct flap tension; insufficient tension will result in inadequate flap contraction, and excessive tension may lead to subsequent spasm of the gracilis.

Patients

Between October 2009 and March 2010, four patients (one man and three women) aged 46—53 years (mean, 49.4 years) with long-standing unilateral facial paralysis received gracilis muscle transfers innervated by the homolateral masseteric nerve and the contralateral facial nerve. Our senior surgeon (FB) performed all the operations. All patients had complete homolateral facial paralysis (House—Brackman stage VI), confirmed by preoperative electromyographic evaluation of the mimetic musculature. The suitability of the masseteric nerve as a donor nerve was also assessed.

Postoperative clinical examinations were performed at 3, 6, 9 and 12 months after surgery. At each office visit, facial objectivity was evaluated at rest and during activation of the mimetic musculature.

Patients were asked to contact the surgical team for an immediate examination when the first voluntary movement of the commissure occurred, or when a relative or friend observed spontaneous activation of the flap during smiling. The patients and people close to them were asked to pay close attention to these types of movement. As soon as voluntary muscle functioning began, the patients were referred to our team's physiotherapist for instruction in physical exercises to be performed in front of a mirror and, later, without a mirror.

Eighteen months after surgery, facial reanimation was assessed in all patients. Standardised photographs were taken and analysed by a team of three persons not involved in the surgery (one physician, one physiotherapist and one

nurse). The results were classified according to the system developed by Terzis and Noah.[17]

Electromyography (EMG) and electroneurography were used to assess reinnervation from contralateral facial nerve, through the grafted cross-face suralis nerve.

The EMG coaxial needle electrode was inserted into the gracilis muscle to verify the voluntary recruitment of motor unit action potentials during smiling without clenching the teeth.

Electrical stimulation of the contralateral facial nerve was applied inferiorly and caudally to the contralateral tragus; motor potentials were recorded using the coaxial needle electrode inserted into the gracilis muscle.

Masseteric innervation of the grafted muscle was tested recording voluntary activity asking the patients to clench their teeth and by direct electrical stimulation of the masseteric nerve: motor potentials were recorded using the coaxial needle electrode inserted into the gracilis muscle.

The spontaneity of contraction could be observed readily by talking with patients during examination, when they were relaxed and smiled involuntarily. The spontaneity of flap contraction in response to emotional stimuli was also evaluated as suggested by Terzis and Noah.[17] The patient was left alone in a room to watch a comedic movie for 10 min. To avoid embarrassing the patient or inhibiting his or her spontaneity, no other person was present at this time.

Results

The average duration of surgery was 5.4 h (range, 5—6.1 h). Clinical examination and colour Doppler images confirmed the complete survival of all microvascular flaps. All patients were available for follow-up and recovered partial facial mimetic function.

All patients also recovered voluntary (video 1) and spontaneous (videos 2 and 3) smiling abilities. Voluntary flap contraction was achieved within a mean of 3.8 months (range, 2—4.8 months) and spontaneous flap activation within a mean of 7.2 months (range, 6—8.8 months) post-surgery. The patients also recovered the ability to smile only on the operated side by voluntarily activating the flap, although bilateral symmetric smiling was the goal.

Supplementary video related to this article can be found at doi:10.1016/j.bjps.2012.04.030.

The quantity of contractions improved within 12 months of the initial flap movement. According to the five-stage classification of reanimation results developed by Terzis and Noah,[17] two patients had excellent outcomes (symmetrical smile with teeth showing, full contraction) (Figures 3—6) and two patients had good outcomes (symmetry, nearly full contraction) at 18 months after surgery.

The EMG coaxial needle electrode inserted into the gracilis during smiling without clenching the teeth showed process of reinnervation led by the contralateral facial nerve (Figure 7).

Motor potentials were recorded during electrical stimulation of the contralateral facial nerve using the coaxial needle electrode inserted into the gracilis muscle, showing

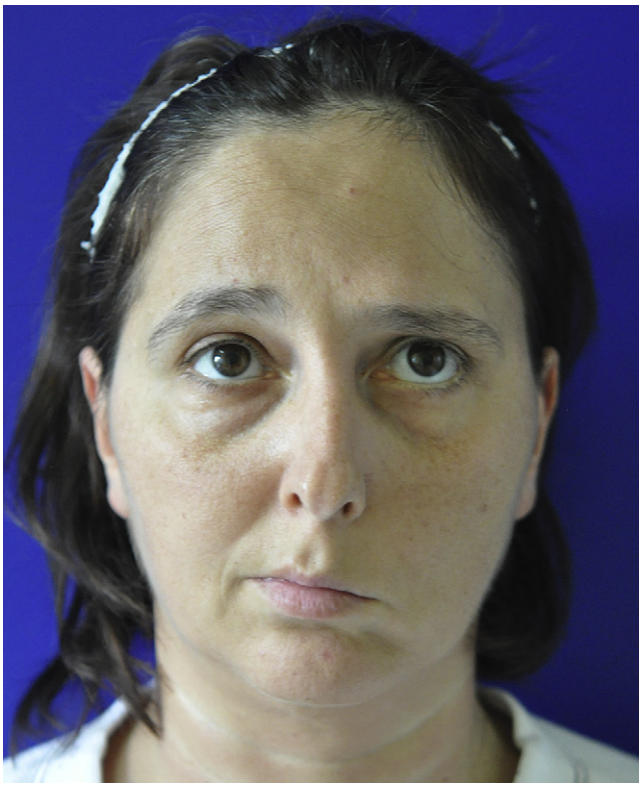

Figure 3 Preoperative view at rest of the patient with a complete long-standing left facial paralysis. Ptosis of facial tissues and asymmetry of the face.

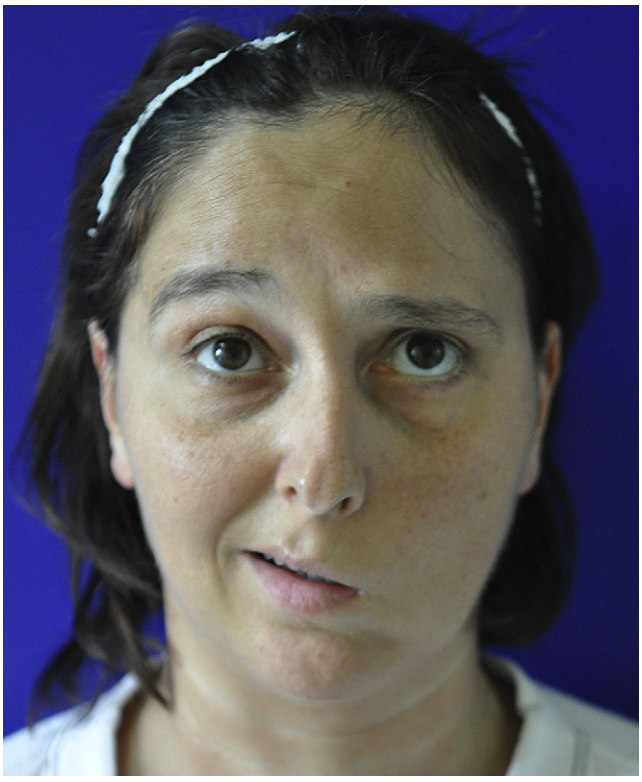

Figure 4 Preoperative view while smiling: note worsening of facial asymmetry.

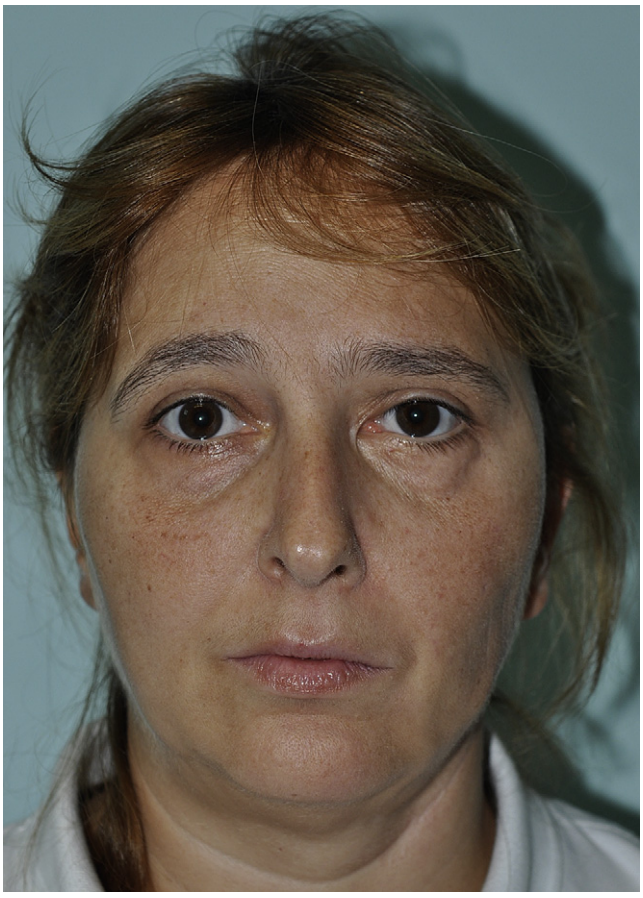

Figure 5 The same patient at rest 18 months after surgery: no gross asymmetry of the face is noticeable.

Figure 6 Nice smile of the patient 18 months after surgery.

the excitability of the grafted (crossed) facial nerve fibres (Figure 8).

Masseteric innervation of the grafted muscle could not be ascertained by electrical stimulation due to artefacts because of direct muscle stimulation while attempting to stimulate masseteric nerve; the presence of motor reinnervation was assessed by EMG voluntary activity recording obtained by clenching the teeth.

Discussion

Most authors agree that the contralateral side of the face provides the correct stimulus for unilateral facial palsy reanimation.[1,4,18] Both two-stage procedures and one-stage transfers based on contralateral facial nerve innervation aim to rehabilitate natural smiling ability, but the efficacy of these techniques is partially impaired by reduced contraction or complete failure in a significant proportion of patients. Negative outcomes are due to several reasons: one is the major length of the flap nerve, known to be an obstacle to nerve regeneration. Another reason may be axonal loss; two anastomoses are created in two-stage procedures reducing the in-growth of regenerated axons, while the collateral thoracodorsal nerve branches are severed in the widely used one-stage *latissimus dorsi*. This technique is also burdened by a long denervation time that leads to muscle atrophy.[10,11]

By contrast, a gracilis transfer with coaptation of the masseteric nerve leads to almost total functional recovery of flap contraction.[14,19] Although a few reports[13,14,20] have

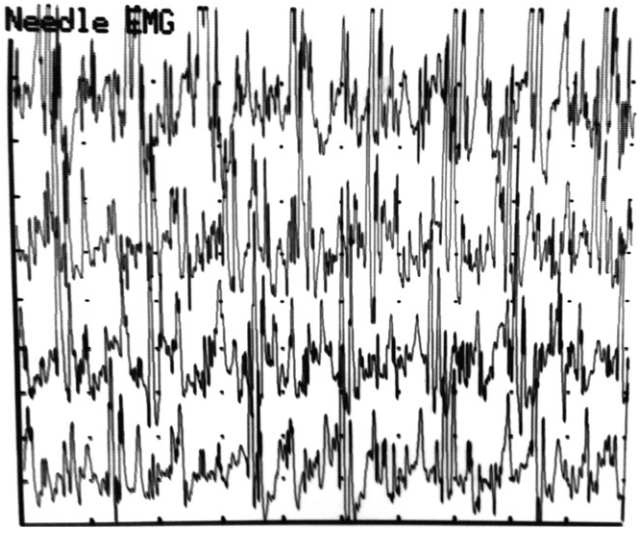

Figure 7 Recruitment of motor unit in gracilis muscle during smiling, without clenching of the teeth.

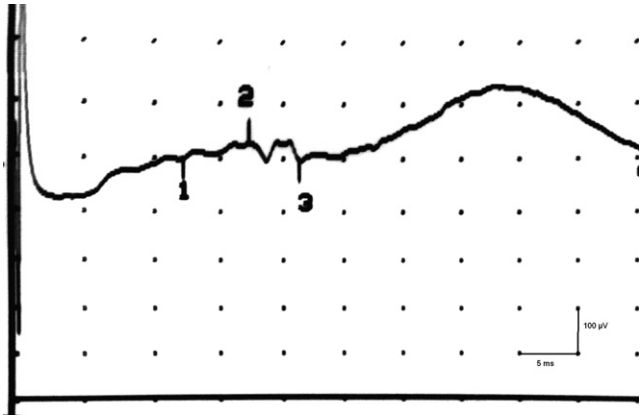

Figure 8 Motor potential recorded into the gracilis muscle while stimulating the contralateral facial nerve.

assessed the recovery of spontaneous smiling, such abilities have not been observed by others[10] or by the authors in clinical practice. As a proof of this, between October 2005 and November 2010, in our Surgical Unit, 11 patients were operated on for long-standing facial palsy by transposition of a gracilis muscle flap innervated only by the masseteric nerve. Follow-up time of all patients was at least 1 year. These patients were examined postoperatively through clinical evaluation and recorded while watching funny videos to check any spontaneity of flap contraction, like the current study. The quantity of contraction was satisfactory in all patients, with achievement of good symmetry at rest and during smile. However, none of the 11 patients recovered the ability to smile spontaneously.

Our idea to combine the use of facial nerve stimulus (to ensure spontaneity) with a masseteric nerve source (to guarantee the quantity of contraction) was borrowed from Yamamoto et al.[21] They introduced the concept of neural supercharge in recent paralysis and demonstrated the effectiveness of using a hypoglossal input in combination with facial nerve stimulus to guarantee an adequate quantity of contraction and the correct facial nerve stimulus. Their concept was based on the observation of reanimation procedures for long-standing paralysis, in which a reduced number of axons reached the muscle as compared to the physiological situation. A double axonal input yields a number of reinnervated fibres that is closer to the normal situation.

Watanabe et al.[16] first reported the use of one-stage free-flap surgery with double innervation for the reanimation of long-standing facial paralysis. They improved *latissimus dorsi* contraction by placing the hilum of the flap in contact with a part of the denuded masseter on the paralysed side. Trigeminal and facial innervation was assessed clinically and by needle electromyography. The authors of the present study devised a similar technique using the gracilis muscle, which has several advantages over the *latissimus dorsi* flap. First, the thickness of the flap is constant, whereas the *latissimus dorsi* is thicker near the hilum and thins distally. Thus, visible bulk may present a problem in the lateral region of the face with the use of Watanabe's technique.[4] Debulking only partly resolves this problem and risks the reduction of contraction. The second advantage of our approach is that all axons passing through the anastomosis between the masseteric and anterior obturator nerves may reach the flap. This is not possible when the contralateral facial nerve branch is anastomosed to the thoracodorsal nerve, as in a one-stage *latissimus dorsi* transfer, because some axons get lost through the collateral branches previously severed to obtain the required 15-cm nerve length.

In a gracilis flap transfer, double innervation is obtained through two epineural anastomoses: an end-to-end anastomosis between the masseteric and anterior obturator nerves, and an end-to-side anastomosis between the distal end of a cross-face nerve graft and the anterior obturator nerve distal to the first anastomosis.

End-to-end anastomosis provides maximal axonal regeneration, but the efficacy of end-to-side neurorrhaphy has also been demonstrated by Viterbo et al.[22] Following their recommendation, we open an epineural window on the side of the nerve when making the end-to-side anastomosis, but do not sever the inner fibres of the receiving nerve.

A potential advantage of this neurotisation technique is that end-to-side neurorrhaphy without disruption of the inner fibres avoids wasting any regenerated axons from the masseteric nerve. Moreover, the masseteric nerve input remains guaranteed, even in case of the failure of axonal input from the cross-face nerve graft to reach clinical significance.[2,9] We did not observe this negative outcome in our patient sample, but many more cases must be studied to confirm our findings.

The favourable quantity of contraction during spontaneous smiling may occur because axons passing through the cross-face nerve graft also trigger the activation of masseteric nerve fibres. This mechanism has also been suggested by Labbè[23] in the double innervation of a lengthened temporalis muscle for facial reanimation.

All single-stage reanimations[24–27] with contralateral facial nerve innervation achieve initial functional recovery within 7—12 months. During the recovery time, muscle fibres are partially but irreversibly atrophied. A more rapid innervation procedure would reduce this phenomenon. This observation gave rise to the concept of babysitting used for recent paralyses.[28] This technique is based on the rapid innervation of the mimetic musculature by cranial nerve XII prior to the 'preferred' innervation by the contralateral facial nerve. Similarly, in case of free-flap transposition, minimisation of muscle atrophy should increase functional results; masseteric innervation may be helpful in reducing muscle flap atrophy during the denervation period because reanimation starts sooner than when cross-facial nerve grafts are used (within a mean of 3.8 months after surgery).[16]

Watanabe et al.[16] have emphasised the importance of a patient's ability to smile on the reconstructed side with or without smiling on the healthy side. Homolateral activation is due to masseteric innervation, as contralateral facial nerve input rarely allows the flap to function independently from the healthy side of the face.[9] Our observations confirmed this, but patients do not frequently use unilateral smiling and the predominant movement is a symmetrical smile.

In this preliminary study, the devised double-innervation technique allows to achieve a good grade of flap contraction

as well as emotional smiling ability. A wider number of patients are needed to confirm these initial findings.

Conflict of interest statement

The authors have no financial interests or personal relationships with other people or organisations that may have inappropriately influenced the work presented here.

We have no funding and we have do not have any conflicts of interest to declare nor ethical approval.

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SUPPLEMENT H

A new gyro-based method for quantifying eyelid motion.
International Journal of Artificial Organs 2012 Dec (Epub ahead of print).

Int J Artif Organs 2012; 00 (00): 000-000 DOI: 10.5301/ijao.5000178

ORIGINAL ARTICLE

A new gyro-based method for quantifying eyelid motion

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ABSTRACT

Purpose: *We present an innovative method to quantify the eyeblink by using a miniature gyroscopic sensor (gyro), which is applied on the upper eyelid. Electrical Stimulation (ES) of the facial nerve is a promising technology to treat dysfunctional eyelid closure following facial paralysis. We used the new gyro-based method to evaluate the biomechanics of both the spontaneous and the ES-induced eyeblink, and to identify the best ES protocol.*

Methods: *During blinking, eyelids rotate about the axis passing through the eye canthi, thus we propose to use a gyro for measuring the angular velocity of the upper eyelid (ω_e). The angular displacement of the eyelid (θ_e) was calculated by integrating the ω_e signal. Two indices were derived from θ_e: 1) the eyelid angular displacement during eye closure (C), calculated as the peak value of θ_e; 2) the eyelid closure duration (D), calculated as the time interval between zero signal and the peak value of θ_e. In a healthy volunteer we used this method to quantify both the spontaneous eyeblink and the blinks elicited by different ES patterns.*

Results: *For the spontaneous eyeblink, indices C = 14.0 ± 1.8° and D = 94.0 ± 10.8 ms were computed. By comparing C and D indices for spontaneous and ES cases, trains of 10 pulses with a frequency ranging from 200 Hz to 400 Hz proved to induce the most effective and natural-like eyeblinks.*

Conclusions: *The new gyro-based method proved to be a valuable tool to provide dynamic and real-time quantification of eyelid motions. It could be particularly useful for evaluating the effective and natural-like eyeblink restoration provided by ES.*

KEY WORDS: *Gyroscope, Eyelid, Electrical stimulation, Eyeblink*

Accepted: October 25, 2012

INTRODUCTION

The facial nerve innervates a group of muscles that perform a variety of complex orofacial functions. Its main function is facial animation, which conveys emotion and mood. The facial nerve also provides complete eye closure (eyeblink) which is necessary for corneal protection. Infections or neurological disorders, such as dysfunction of the facial nerve, are the most common cause of unilateral facial paralysis (1).

Facial paralysis affects up to 0.3% of the population every year in Western Europe and the United States (2). People usually experience unilateral facial paralysis, with the other side of the face moving normally. One of the most bothersome issues are the steadily open eye and loss of the eyeblink, which may cause severe damage to the eye.

Current methods for preserving eye health following facial paralysis include static and dynamic techniques, like the implant of gold weights into the upper eyelid (3-5) nerve and muscle transfer, and tarsorraphy (6-8). Some authors have proposed the implantation of mechanical springs (9) and slings actuated by an artificial muscle (10). While these techniques can help to preserve the eye, there may be unresolved inconvenience issues in terms of optimal aesthetic and functional outcomes. Moreover, harvesting any autologous tissue may be complicated by donor site morbidity issues. Electrical stimulation (ES) of the muscle or nerve controlling the dysfunctional eyelid is recently under study as a valuable technology and a more effective method for eliciting a functional and cosmetically acceptable eyelid closure (11-13). However, a quantitative analysis of the restored eyelid motion has been scarcely investigated and reported for any of these techniques for facial reanimation, (14, 15). A quantitative assessment of this sort would contribute to a better understanding of the potential of each technique to restore effective and natural-looking blinking following facial paralysis.

Many different methods have been employed to measure upper eyelid kinematics during a blink movement (16). High-speed video camera systems and image analysis, direct magnetic search coil techniques, and EMG recordings are the most frequently reported. Video-based systems consist in videotaping the eyelid and using image processing to compute the differences in brightness in images of the palpebral fissure during the closing and opening phases of the blink. Although video techniques are entirely non-invasive, the major drawbacks are that the head must be fixed with respect to the camera, spatial resolution is limited by the size of the video pixel, and the effectiveness of the method is strongly dependent on the contrast between the color of the eyelid skin and the color of the iris, i.e. if a patient has dark-colored skin or a bright-colored iris the contrast may not be sufficient (17).

In the magnetic search coil method (MSC), the subject is placed inside an oscillating magnetic field and a small coil is taped to the upper eyelid close to the margin and above the pupil. Due to the flux generated by the magnetic field, a current is induced inside the coil. This sign is proportional to the sine of the angle between the coil and the magnetic field orientation; because the eyelid rotates over the ocular surface, this measurement is relative to eyelid position (18). Techniques based on MSC have superior spatial and temporal resolution and there are no problems with recordings in darkness, however, the magnetic fields are generated by large field coils (approx. 1 meter in diameter). The large unit constrains the use of this system in a fixed laboratory or clinical setting. Furthermore, the eyes must remain close to the center of the field coils where the three orthogonal fields are homogeneous; thus, the head must be fixed in place or head movements must be restricted in size (19). As for EMG recordings, electrical stimulation induces substantial stimulus artifacts in the EMG signal, thus the adoption of effective filters is required to remove these artifacts (20).

We present an innovative method to quantify the eyelid movement based on a miniature gyroscopic sensor attached to the upper eyelid. To demonstrate its utility, we used this new method to evaluate eyelid closure during both spontaneous blinking and blinking induced by ES. The primary aim of the study was not to validate the clinical utility of the stimulation system itself or the range of stimulus parameters used, but to demonstrate the feasibility of providing a dynamic and real-time quantification of the eyeblink by measuring the angular velocity and displacement of the eyelid by means of the miniature gyroscope.

METHODS

The new method for eyeblink quantification

Assuming that the eyelid movement during blinking can be described as a rotation about the axis passing through the eye canthi, we propose a new method for the quantification of eyelid motion based on a miniature gyroscopic sensor (gyro). In a healthy volunteer, an ultra-small (4 x 8 x 2 mm) and ultra-lightweight (0.2 g) gyro (ENC03-R; Murata Manufacturing Co., Kyoto, Japan) was attached to the upper eyelid and the eyelid angular velocity (ω_e) was directly measured (Fig. 1). Then the ω_e signal was processed in order to compute the values for eyelid displacement during eye closure (C) and eyelid closure duration (D). The eyelid angular displacement (θ_e) was calculated by integrating the ω_e signal and the C index was taken as the peak value of θ_e, while D was defined as the time interval between zero signal and the peak value of θ_e (Fig. 2).

The gyro sensor used in the study is able to detect angular velocities ranging from -300°/sec to +300°/sec and an angular displacement as small as 1°.

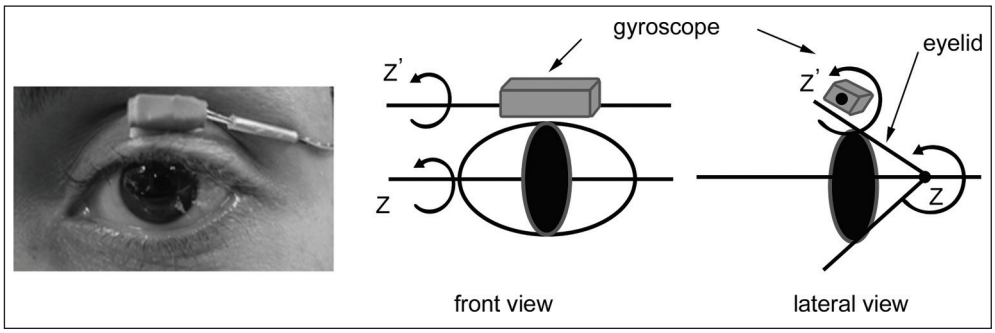

Fig. 1 - *The miniature gyroscope positioned on the upper eyelid for quantifying the eyelid motion during eyeblinking.*

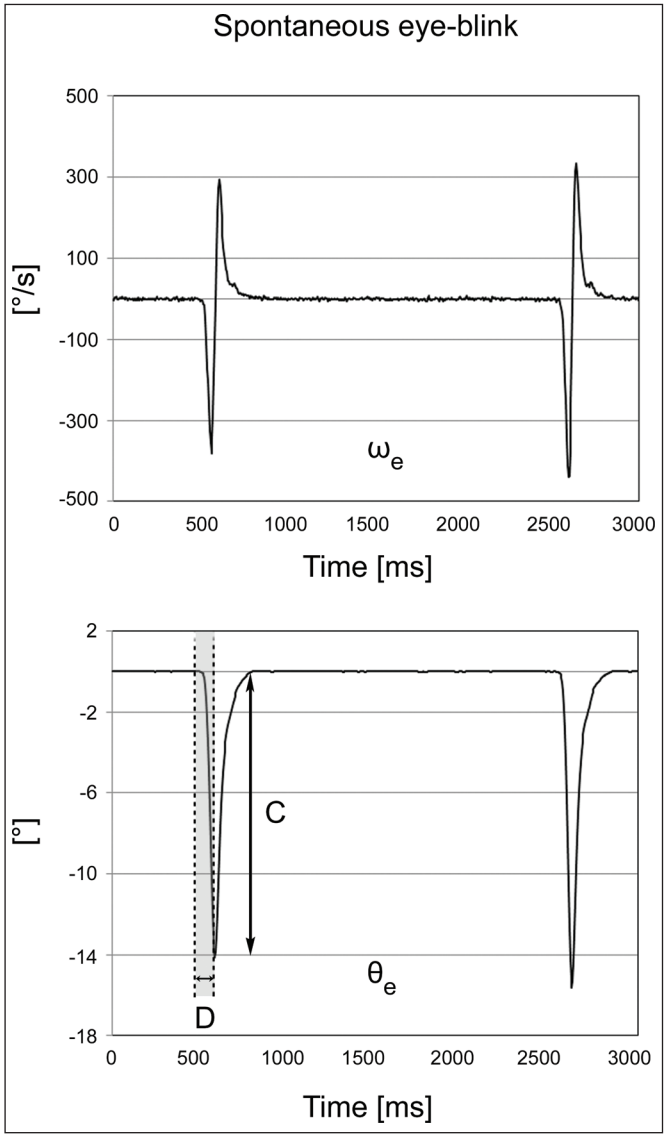

Fig. 2 - *The eyelid angular velocity (ω_e) and the eyelid angular displacement (θ_e) for a spontaneous eyeblink: the computed C and D indices are indicated by arrows.*

Experimental use of the new gyro-based method

As a demonstration of utility, the new gyro-based method was applied to quantify eyelid closure on a healthy subject during both spontaneous blinking and ES-induced blinking. The subject gave written informed consent in performing experiments, following the principles outlined in the Declaration of Helsinki.

The ES device

A prototypal device developed by our group was used for the experiments (Fig. 3). The device is intended for epicutaneous ES of the nerve branch innervating the orbicularis oculi muscle (OOM) which is responsible for eyelid closure. It is mainly composed of:

1. an acquisition unit to detect the EMG of the OOM during spontaneous eyeblink, on one side ("healthy (H) side");
2. a signal processing unit to provide a suitable EMG-based trigger signal to control the delivery of electrical stimulation;
3. a stimulating unit to electrically activate the OOM on the contralateral side ("stimulated (S) side").

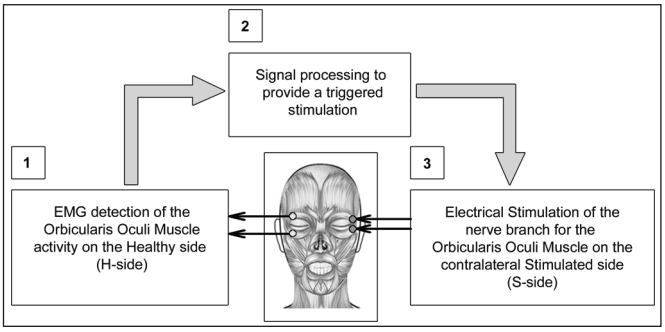

Fig. 3 - *General scheme of the EMG-triggered ES device.*

A graphical user interface developed using LabVIEW software (National Instruments Corporation, Austin, TX, USA) displays the acquired and processed EMG signals and allows the operator to set the stimulation parameters.

A set of surface Ag-AgCl cup electrodes (Disposable Pediatric ECG Electrodes, SilverTRACE; GE Healthcare, WI, USA) were used to detect the EMG signal from the OOM of the H-side. All EMG signals were recorded and processed (20 Hz-low pass filter) using a signal acquisition unit (MP100 Biopac System, Inc., Goleta, CA, USA) and software (Acq 3.9.1, Inc., Goleta, CA, USA). A simple but effective amplitude-threshold method was adopted to detect the occurrence of eyeblink events from the H-side. A programmable controller (compact RIO; National Instruments, Austin TX, USA) connected to the signal acquisition unit was used to implement this amplitude-threshold method on the EMG signal and provide the output trigger signal for the stimulation unit.

ES was delivered through a constant current stimulator (Digitimer DS7A; Digitimer, Hertfordshire, UK) intended for "percutaneous stimulation," which delivers square wave electrical pulses of configurable amplitude and duration. Pulse amplitude (PA) could be set to a value between 0.0 and 99.9 mA by means of a 10-turn rotary dial, while pulse width (PW) could be determined using a switch selector (50-100-200 microsec).

A pair of stimulation surface Ag-AgCl electrodes (ECG electrodes, SilverTRACE; GE Healthcare, WI, USA) were placed on the skin in the proximity of the outer canthus of the eye in order to stimulate the nerve branch for the OOM. Both the stimulation protocol and the stimulation parameters were controlled using the compact RIO controller.

The experimental protocols

The experimental protocols were divided into two stages. During the first stage we evaluated spontaneous eyeblinks and stimulated eyeblinks induced by different patterns of ES. We used the new gyro method to identify the set of stimulation parameters yielding the most functional and natural-looking eyeblink, by comparing the results for both the spontaneous and the ES cases (see below for details). During the second stage of tests, we detected gyro signals from both H- and S-sides and we used the eyelid angular displacement gyro signals to quantify the latency between the two eyelid closures.

For the first set of experiments, the EMG detection unit was disabled and the tests were focused on using the new gyro-based method to quantify eyeblinks induced by different stimulation patterns driven by software triggering. The gyro was attached to one upper eyelid of the subject. In order to evaluate an averaged spontaneous eyeblink, 10 consecutive natural eyelid closures were acquired while the subject was watching ahead, while the subject was unaware data was being collected in order to avoid abnormal blinks. We also tested the gyro during head motions (left-to-right, up-to-down) of the subject in order to verify the independence of gyro measurements from these motions.

Then 10 consecutive ES-induced eyeblinks were delivered, asking the subject to stay as relaxed as possible and to avoid any spontaneous blinking for a few seconds and an averaged stimulated eyeblink was computed. The collected data were then averaged in order to obtain mean eyeblink values.

First, single square-wave pulses with PW = 2 ms and PA ranging from 2 to 8 mA were delivered; then, pulse trains consisting of 10 monophasic square wave pulses with PW ranging from 2 to 0.5 ms, PA ranging from 3 to 5.5 mA and various pulse train frequencies (chosen by varying the duty cycle of the square-wave pulse trains) were delivered (Tab. I).

The pulse train stimulation patterns were selected according to the following criteria:

– the PW was fixed at one of the following three values: 2 ms, 1 ms, 0.5 ms;

TABLE I - THE TESTED PULSE TRAIN STIMULATION PATTERNS (ONE PATTERN FOR EACH FREQUENCY VALUE EVALUATED FOR EACH PW-PA COMBINATION).

PW [ms]	PA [mA]	Frequency [Hz]
2.0	4.0	50, 100, 150, 200, 250
	3.5	50, 100, 150, 200, 250
	3.0	50, 100, 150, 200, 250
1.0	4.0	100, 200, 300, 400, 500
	3.5	100, 200, 300, 400, 500
	3.0	100, 200, 300, 400, 500
0.5	5.5	200, 400, 600, 800, 1000
	4.5	200, 400, 600, 800, 1000
	4.0	200, 400, 600, 800, 1000

– for each PW, the PA was set to an initial value which would ensure complete eyelid closure; the PA was then progressively reduced (by step of 0.5 mA) until a PA value yielding ineffective stimulation (no complete eyelid closure) was reached;
– for each PW-PA combination, five frequencies were considered, corresponding to 10%, 20%, 30%, 40% e 50% of the pulse train duty cycle (d. c.), as indicated by the following expressions:

*d. c.** 100

where T is the period of the pulse train, which is related to frequency (f) as:

T

In order to evaluate the ES-induced eyeblink in terms of "functionality" (efficacy in providing a complete eyelid closure) and "natural look" of the response (amplitude and duration of the ES-induced eyeblink similar to the spontaneous one), percent variations of the stimulated eyelid closure (ΔC) and eyelid closure duration (ΔD) with respect to spontaneous eyeblink were calculated from the gyro measurements.
Human visual information updates at rates of about 30 to 33 Hz; therefore any latency around 30 ms or lower would be impossible for people to perceive. Thus, considering that the duration of the closure phase of a spontaneous eyeblink is approximately 100 ms (21, 22) a maximum variation Δ_{max} = 25% (corresponding to 25 ms over 100 ms) for eyelid closure duration was considered acceptable (not visually appreciable). The same Δ_{max} = 25% was assumed for the eyelid closure. Therefore, the ES-induced eyeblink was considered "functional and cosmetically acceptable" if both $|\Delta C|$ and $|\Delta D| \leq \Delta_{max}$.
In the second stage of tests, both upper eyelids were provided with gyros in order to detect eyelid motion on both H- and S-sides and to compute the mechanical latency between the two sides. The EMG detection unit was reconnected and the EMG signal from H-side was used to trigger stimulation delivered to the S-side.
In order to provide natural-looking and synchronous blinking, the latency between blinks of the H- and the S-sides should be minimized. Latency in contralaterally-triggered ES systems is linked to the presence of time lags along the ES process pipeline: detection of healthy eye muscle activity and identification of blinking events; generation of an electrical stimulus; contraction of the OOM on the affected eyelid.
In healthy subjects, blinking occurs naturally and simultaneously in both eyes. In our tests performed on a healthy volunteer it was therefore difficult to discriminate between spontaneous and stimulated eyelid closure on the S-side. To overcome this issue and to properly compute the latency between the H- and S-sides while avoiding artifacts due to natural blinks superimposed onto the ES-induced blinks, we intentionally introduced a delay (t_0 = 500 ms) between the time when the trigger eyeblink event is identified and the time when stimulation is delivered. We then measured the overall delay (t_{TOT}) between the onset of the spontaneous eyeblink from the H-side and the onset of the stimulated eyeblink on the S-side, as detected by the gyros. Finally, we computed the latency (L) as follows:

$$L = t_{TOT} - t_{0.}$$

RESULTS

The new gyro-based method proved to be a valuable tool to provide dynamic quantification of eyelid motion. From the gyro measurements, the spontaneous eye blink was characterized by a mean value of C = 15 ± 2° and D = 94 ± 11 ms (Fig. 2), consistently with physiological ranges.
During head motions, the gyro recordings were found to be insensitive to translational (left-to-right) head motions. During up-down head motions, an angular velocity of 20 ÷ 40°/sec was detected. This is much smaller, however, than the eyeblink angular velocity for spontaneous blinking in healthy subjects, which ranges between approximately 100 to 400°/sec (21).
During single-pulse stimulation experiments we generally observed a non-physiological eye blink response: only the 2 ms – 8 mA stimulation settings yielded adequate eyelid closure (ΔC = -24%), however, a painful sensation was experienced by the subject and an eyeblink reflex was induced on the contralateral side. Moreover, the eyeblink duration was longer than the spontaneous one (ΔD = +38%). For PA values < 8 mA no eyelid closure was obtained ($|\Delta C| > 25\%$).
Conversely, the delivery of 10-pulse train stimulation proved to be more effective. Pulse trains with frequency between 200 Hz and 400 Hz achieved the best results in terms of functional and natural-looking eyelid closure and eyeblink duration, as shown by the measured ΔC and ΔD plotted against pulse train frequency (Fig. 4). As clearly shown by

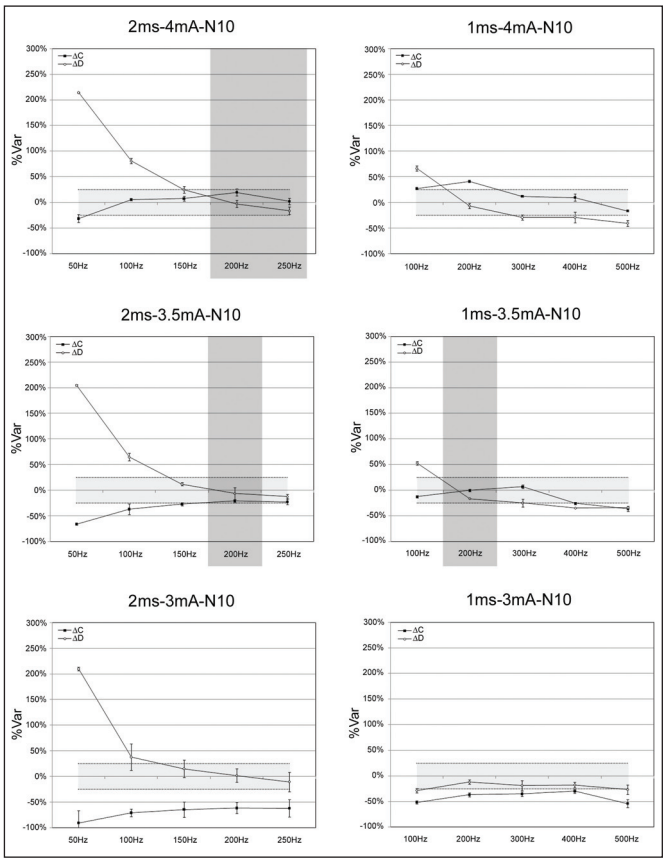

Fig. 4 - *Examples for PW = 2 ms (**left**) and PW = 1 ms (**right**) of percent variations of ES-induced eyelid closure (ΔC) and eyelid closure duration (ΔD) with respect to spontaneous eyeblink, as derived from gyro detections. ΔC and ΔD were plotted against pulse train frequencies and the region of acceptable variations (Δ_{max} = 25%) was indicated by light gray area framed by dotted lines. In dark gray shadow the "functional and cosmetically acceptable" pulse train frequencies for each PW-PA combination were indicated.*

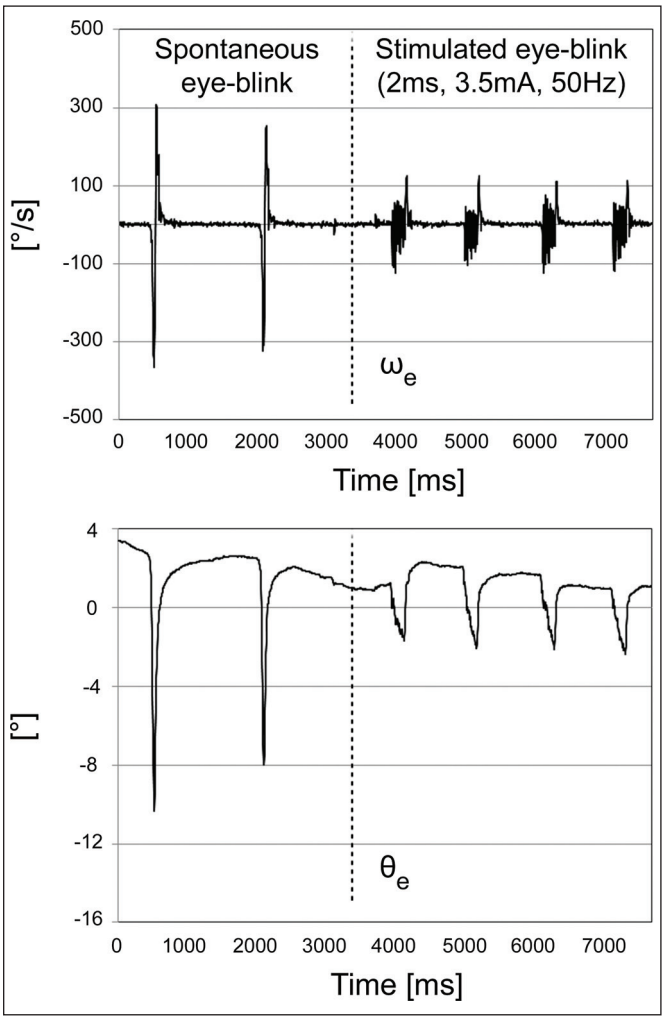

Fig. 5 - *Example of gyro detections obtained for 50 Hz-pulse train stimulation (**right**) compared with detections for spontaneous eyeblink (**left**).*

the gyro signals (Fig. 5), the worst result was found for stimulation at very low frequency (50 Hz), which was also perceived by all subjects as unpleasant and cosmetically unacceptable due to incomplete eyelid closure ($|\Delta C| > 50\%$) and excessive eyeblink duration ($|\Delta D| > 200\%$) (Fig. 4).

The gyro-based method allowed us to identify a set of optimal stimulation patterns from among the different pulse train stimulation protocols used in our experiments. For each PW, we selected the minimum PA yielding complete eyelid closure and the pulse train frequency providing the most natural-looking eyeblink duration (minimum ΔC and ΔD) (Tab. II).

In the second stage of tests, while using the overall EMG-triggered ES device and delivering one of these optimal stimulation patterns (1 ms, 3.5 mA, 200 Hz), the gyro signals allowed for quantification of the mechanical latency between the spontaneous eyeblink occurring at the H-side and the stimulated blink event at the S-side (Fig. 6). A latency L = 80 ms was calculated.

TABLE 2 - THE SELECTED OPTIMAL PULSE TRAIN STIMULATION PATTERNS

PW [ms]	PA [mA]	Frequency [Hz]
2.0	3.5	200
1.0	3.5	200
0.5	4.0	200 - 400

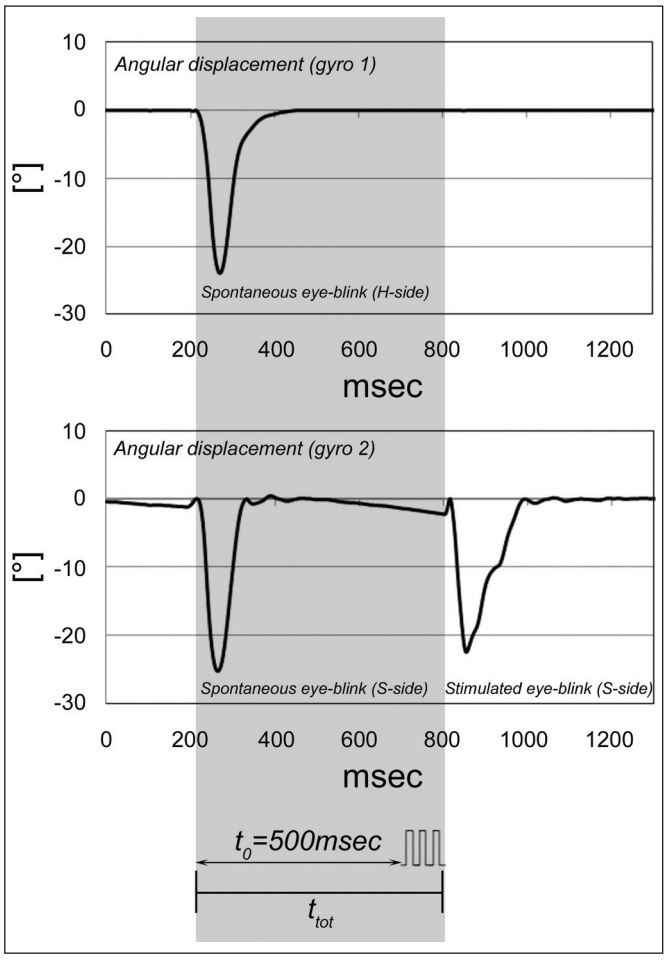

Fig. 6 - *Gyro signals used to evaluate the mechanical latency between the spontaneous eyeblink occurring at the H-side (gyro 1) and the stimulated blink event at the S-side (gyro 2). An intentionally delay (500 ms) was introduced to discriminate between spontaneous and stimulated eyelid closure on the S-side.*

DISCUSSION

An important contribution of our results is the introduction of a new method for the quantitative assessment of eyelid movements based on the use of a gyroscope. The sensor allows to compute both the eyelid angular displacement and the duration of eyelid closure during blinking, by processing the eyelid angular velocity signal which is measured directly.

This novel use of a gyro sensor to quantify eyelid motion may offer several advantages over existing eyeblink recording techniques:

– a real time and dynamic detection of eyelid angular velocity and displacement can be provided without the need for post-processing time as required in the video-based eyelid motion-measuring systems;
– head-free movements are possible during eyelid motion recordings as the gyro intrinsically senses exclusively the angular velocity around its sensitivity axis (the axis passing through the eye canthi) and possible artifacts due to facial movements can be avoided;
– the gyro signal is unaffected by the electrical stimulus delivered to evoke an artificial eyeblink which instead may interfere the EMG recordings.

No evident restrictions were reported by the subject in performing eyeblink with the small gyro attached on the eyelid. The new gyro-based method showed consistent results (D = 94 ± 11 ms) with previously reported values for closure duration (included in a range of 50 ÷ 100 ms) during spontaneous eyeblink in humans (21). Moreover, it was particularly useful for comparing different ES patterns and identifying a set of optimal stimulation parameters which can yield effective and natural-looking ES-induced eyelid closure.

However, in order to assess the properties of this new gyro-based method it is essential to analyze how the gyro signal relates to an eyelid movement assessed by established methods. To accomplish this, further tests are underway to compare the gyro data to simultaneous video recording-based measurements, also including more subjects in the study. As previously reported (11, 22) stimulation with trains of pulses achieves greater eyelid closure than single pulses by delivering a stimulus which is more similar to that sent by motoneurons to muscles. In fact, delivery of consecutive pulses in a train at appropriate frequency modulates the OOM tension, allowing adjustability of the blinking force. The close onset of two stimuli causes the muscle twitches to fuse, thus creating a sustained contraction (wave summation and tetanization mechanism) which generates greater eyelid closure at a lower pulse amplitude. Increases in PW, PA, and number of pulses have been shown (11) to improve effective closure; however, each of the three parameters provides diminishing returns as it increases above a certain point. A limit has been reported for PA above which current spread may cause activation of adjacent neural structures. Also, the effect of increasing the number of pulses appears to plateau, peaking at about 10 pulses (11).

In our experimental pulse train stimulation protocols we investigated the effect of varying PW, PA, and frequency of the pulse train, while maintaining a fixed tnumber of puls-

es (n = 10). Our quantitative assessment of eyelid motion by means of gyro measurements confirmed that trains of pulses are more effective than single pulse delivery, which also tended to be unpleasant and activate eyeblink reflex on the contralateral, non-stimulated side. Moreover, the gyro-based method was useful to identify a range of optimal pulse train frequencies which may induce effective and cosmetically acceptable eyelid closure at minimal PA and PW. This could be particularly interesting for future design and development of an implantable eyelid ES device, which should minimize power consumption to be successful. Moreover, the possibility to preliminarily and non-invasively tune the stimulation parameters by means of gyro detections will be of great interest in the case of a future implantable stimulation device.

In our study, we evaluated only pulse train stimulation delivered at constant frequencies. Trains of pulses with varying frequencies could be considered, as suggested by previous studies (23-25). Electrical stimulation with a train of pulses which include the motoneuron dynamic sensitivity induce eyeblinks with fewer pulses and a lower carrier frequency than those needed with trains at constant frequencies.

Stimulation of the OOM must be sufficient to produce complete eye closure but it must not excite adjacent facial musculature. Our proposed gyro method allows for effective measurement of upper eyelid motion during blinking; however, it does not provide any quantification of possible activation of portions of the surrounding musculature that are not directly related to blinking function. Further solutions must be studied to estimate such potential alterations of facial mimicry associated with ES.

CONCLUSIONS

The new gyro-based method was effective in providing dynamic quantification of the eyelid motion for both spontaneous and ES-induced blinks. As a demonstration of its utility, the method was used to evaluate stimulation patterns that would induce functional and natural-looking eyelid closure. Future work could involve the use of the gyro-based method to evaluate further stimulation patterns, which may provide effective eyeblink recovery at very low currents and minimal power consumption. As well as its potential use in combination with ES, the presented gyro-based method could also be clinically useful to quantify results of eyeblink restoration provided by currently performed surgical procedures for facial reanimation.

Conflict of Interest Statement: [AUTHOR: Please provide]

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SUPPLEMENT I

Facial movement before and after masseteric-facial nerves anastomosis: A three-dimensional optoelectronic pilot study.

Journal of Cranio-Maxillo-Facial Surgery 2012; 40(5): 473-479 .

Journal of Cranio-Maxillo-Facial Surgery 40 (2012) 473–479

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Facial movement before and after masseteric-facial nerves anastomosis: A three-dimensional optoelectronic pilot study☆

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ARTICLE INFO

Article history:
Paper received 8 March 2011
Accepted 23 July 2011

Keywords:
Facial nerve paresis
3D
Motion analysis
Mimetics
Asymmetry

ABSTRACT

To quantify the effects of facial palsy reanimation, 14 patients aged 17–66 years were analysed. All patients had unilateral facial paralysis, and were candidates for surgical masseteric to facial nerve anastomosis. Two patient groups were measured: seven patients were waiting for surgery, the other seven patients had already been submitted to surgery, and had regained facial mimicry. Each patient performed three facial animations: brow raise; free smile; lip purse. These were recorded using an optoelectronic motion analyser.

The three-dimensional coordinates of facial landmarks were obtained, their movements were computed, and asymmetry indices calculated (differential movements between the two hemi-faces: healthy and paretic/rehabilitated). Before surgery, mobility was larger in the healthy than in the paretic side; after surgery, the differences were reduced (brow raise and lip purse), or even reversed (smile). Before surgery, lip purse was performed with significant labial asymmetry ($p = 0.042$; larger healthy side movement). After surgery, asymmetry indices reduced. Total labial asymmetry during smiling was significantly different from 0 before surgery ($p = 0.018$, larger healthy side movement). After surgery, all asymmetry indices became non-significant. Before surgery the lateral displacements of all labial landmarks were towards the healthy side, while they normalized after surgery.

1. Introduction

Unilateral facial paralysis is a pathological condition involving asymmetry of the face at rest, worsened by activation of facial (mimetic) musculature while smiling and during facial expression. Facial morphology is grossly distorted, while eye lubrication, nasal inspiration, labial competence, cheek and lip mobility are partially impaired. Social communication and interaction, phonation and speech articulation are also altered (Wachtman et al., 2001; Nicholls et al., 2004; Mehta et al., 2008; Popat et al., 2010). The patients have serious alterations in their quality of life, and may develop a reactive depression.

Because of this, a large number of surgical techniques have been devised to reanimate the paralytic patients early by anastomosing the facial nerve to a donor nerve (Ballance et al., 1903; Körte and Bernhardt, 1903; Smith, 1971; Scaramella and Tobias, 1973; Terzis, 1990; Biglioli et al., 2010, 2011). In 1978, Spira first reported the use of the masseteric nerve as a new axonal source for the cervico-facial branch of the impaired facial nerve, and this has been used to reanimate both recent and long-standing facial paralysis (Zuker et al., 2000; Coombs et al., 2009). A specific technique consisting of a masseteric to facial nerve anastomosis with a 4 cm great auricular interpositional nerve graft was devised by the Authors and has been used since October 2007 (Biglioli et al., 2011). A quantitative, objective assessment of results was become necessary to evaluate the effectiveness of the technique.

☆ The current investigation was supported by annual grants from the Università degli Studi di Milano to CS and VFF.

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1010-5182/$ – see front matter © 2011 European Association for Cranio-Maxillo-Facial Surgery.
doi:10.1016/j.jcms.2011.07.004

Facial dysfunctions can be graded by both clinical and instrumental methods that analyse spontaneous and instructed facial movements. Clinical assessments focus on total and local facial motion, synkinesis and movement asymmetries (Coulson et al., 2005), while quantitative methods can assess both the movements of selected facial landmarks and their direction (Wachtman et al., 2001; Linstrom et al., 2002; Trotman et al., 2003; Nicholls et al., 2004; Rogers et al., 2007; Frey et al., 2008; Hontanilla and Aubá, 2008; Mehta et al., 2008; Popat et al., 2010; Sforza et al., 2010a,b).

Currently, three-dimensional motion analysers seem to be the best choice for the non-invasive assessment of soft tissue facial movements, permitting a minimally disturbing quantitative evaluation that overcome the subjective nature of the clinical scales (Coulson et al., 2005; Trotman et al., 2003; Nicholls et al., 2004; Frey et al., 2008; Hontanilla and Aubá, 2008; Mehta et al., 2008; Popat et al., 2010; Sforza et al., 2010a,b).

In our laboratory, we developed a method for the non-invasive, three-dimensional assessment of facial movements using an optoelectronic motion analyser (Sforza et al., 2010a,b). The method was found to be minimally disturbing, reliable, and to accurately detect total and local motion during the performance of standardized facial animations (Sforza et al., 2010a,b).

The aim of this investigation was to quantitatively assess facial movements in a group of patients before and after masseteric to facial nerve reanimation. The patients were recorded while performing a set of standardized symmetric facial movements, and the displacement of selected facial landmarks was measured in three dimensions. Movements involving parts of the face submitted to the surgical rehabilitation (middle and lower facial thirds), and movements involving parts of the face not submitted to the surgical rehabilitation (upper facial third), were investigated.

2. Materials and methods

2.1. Patients

Fourteen patients (seven men, seven women; age range 17–66 years, mean 44 years, SD 15) were analysed. All patients were affected by unilateral facial paralysis lasting not longer than 19 months (between four and 16 months, mean 11 months, SD 4). All of them had signs of mimetic muscle fibrillations at preoperative electromyography and were candidate for surgical masseteric to facial nerve anastomosis. Those without signs of fibrillations were reanimated by free-flap surgery (Biglioli et al., 2009, 2011), and excluded from the present study.

The patients were subdivided into two groups: seven patients were waiting for surgery, while the other seven patients had already had surgery, and were analysed at least 4 months after they had clinically started to regain facial movement. All patients were instructed to call clinicians for an examination as soon as they felt and observed in a mirror, the first facial movements on the operated side.

All patients were operated on at San Paolo Hospital and Galeazzi Hospital (Milano, Italy) by one of the authors (FB). After the nature and possible risks of the study had been completely described, written informed consent was obtained from each patient and/or from the parents of the patients younger than 18 years of age. The protocol used in the current study was approved by the Ethics Committee of the Department of Human Morphology, and it did not involve dangerous or painful activities, in accord with the Helsinki Declaration.

2.2. Data collection

The data collection protocol was previously described (Sforza et al., 2010a,b). In brief, facial movements were recorded using an optoelectronic three-dimensional motion analyser with a 120 Hz sampling rate (SMART System, BTS, Milano, Italy). The instrument uses nine high-resolution infrared sensitive charge-coupled device video cameras coupled with a video processor that define a working volume of 60 (width) × 60 (height) × 60 (depth) cm^3; metric calibration and correction of optical and electronic distortions are performed before each acquisition session using a 20-cm wand, with a resulting mean dynamic accuracy of 0.121 mm (SD 0.086), corresponding to 0.0158% (Sforza et al., 2010b).

The patient sat inside the working volume on a stool, and was asked to perform a series of standardized facial movements. During the execution of the movement, for any camera special software identified the two-dimensional coordinates of 16 passive markers positioned on facial landmarks (Fig. 1). Subsequently, all the coordinates were converted to metric data, and a set of three-dimensional coordinates for each landmark in each frame that constituted each movement was obtained.

For each patient, the 16 soft tissue landmarks were identified by a set of 2-mm round reflective markers (Trotman et al., 2003; Hontanilla and Aubá, 2008; Sforza et al., 2010a,b): n, nasion; prn, pronasale; f, right and left frontal; ft, right and left frontotemporale; t, right and left tragion; ng, right and left naso-genian; cph, right and

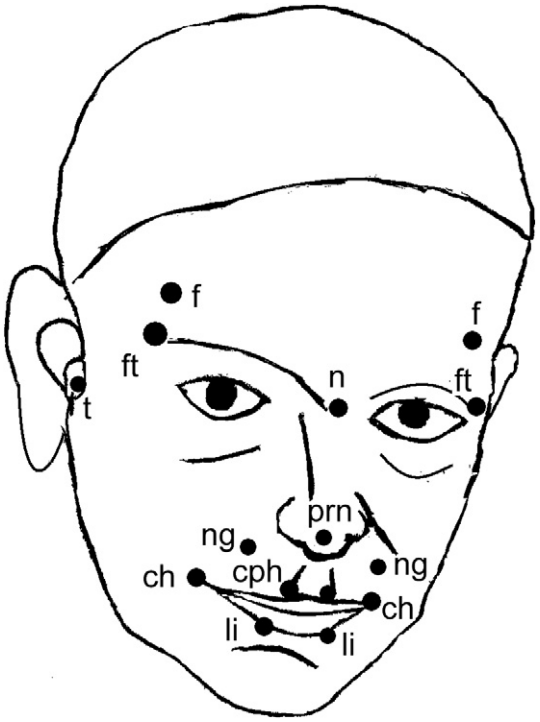

Fig. 1. Soft tissue landmarks: n, nasion; prn, pronasale; f, right and left frontal; ft, right and left frontotemporale; t, right and left tragion; ng, right and left naso-genian; cph, right and left crista philtri; ch, right and left cheilion; li, right and left lower lip midpoints.

Table 1
Analysed patients in the pre- and post-surgical groups.

	Before surgery ($n = 7$)			After surgery ($n = 7$)		
	Mean	SD	Range	Mean	SD	Range
M:F	2:5	–	–	5:2	–	–
Age (years)	45	14	17–59	42	17	18–66
Paresis duration before surgery (mo)	13	3	9–16	9	4	4–15
Mobility recovery after surgery (mo)	–	–	–	6	2	4–11
Recovery follow-up (mo)	–	–	–	14	6	4–21

left crista philtri; ch, right and left cheilion; li, right and left lower lip midpoints (Fig. 1). The positions of the markers were carefully controlled to avoid any interference with facial movements.

Each patient performed three standardized, maximum facial animations from rest (Wachtman et al., 2001; Rogers et al., 2007; Hontanilla and Aubá, 2008; Mehta et al., 2008; Sforza et al., 2010a,b): brow raise (upper facial third); free (natural) smile (middle and lower facial thirds); lip purse (middle and lower facial thirds). Each animation was explained and shown to the patients, which they practiced before data acquisition. For each patient, five repetitions of each expression were recorded without modifications of the marker positions.

For brow raise, pronasale and tragi landmarks defined a head reference plane that was used to mathematically eliminate head movements during the animation, and to standardize head position within and between subjects. The origin of axes was set in the left tragus. For free smile and lip purse, the head reference plane was defined by nasion and frontotemporale landmarks (origin of axes: left frontotemporale).

2.3. Data analysis

The method has been described in detail by Sforza et al. (2010a,b). At first, head and neck motion was subtracted from the raw facial movements using the three cranial (reference) markers, so only movements occurring in the face (activity of mimetic muscles) were further considered. Subsequently, for each facial marker, the three-dimensional movements during each facial animation were computed, the modulus (intensity) of the three-dimensional vector of maximum displacement from rest was calculated. For free smile, the latero-lateral (right-left direction) component of the maximum displacement of the analysed landmarks was computed.

Considering the unilateral kind of facial palsy, in patients with a right-side paresis all paired landmarks were mirrored on the other side of the face, and all movements were further considered relative to the healthy or paretic side.

For each animation, the total movement of the relevant facial part was obtained as the sum of the movement of selected facial markers: the larger the value, the larger the facial movement. For the smile and lip purse movements, markers ng, cph, ch and li were considered; for brow raise, markers f were considered.

To assess differential movements between the two hemi-faces, percentage indices of asymmetry were computed as: (healthy side displacement − paretic side displacement)/(healthy side displacement + paretic side displacement) × 100. The indices were computed for the total movement, as well as for the single landmarks. The indices range between −100 (complete paresis during the movement) and +100 (complete movement on the health side) (Linstrom et al., 2002; Sforza et al., 2010b).

2.4. Method error

Within- and between-session repeatability was previously assessed in healthy subjects. Within session, the technical error of the measurement for single landmarks (random error) was, on average, 0.5–3.38 mm, showing good reproducibility. Between sessions, all facial movements had standard deviations lower than 1 mm (Sforza et al., 2010a,b).

2.5. Statistical calculations

For each patient, the five series of facial animations were averaged. Descriptive statistics were obtained for the total movement for each facial area, the lateral displacement and the asymmetry indices separately for the patients analysed before and after surgical facial reanimation. The total movements for each facial area obtained in the two groups were compared by two-way analyses of variance (between subjects factor: group, before and after surgery; within subject factor: facial side, healthy and paretic; the group × side interaction was also computed); post hoc tests were made by Wilcoxon signed rank tests. To assess if the asymmetry indices significantly deviated from the expected value of 0, Wilcoxon signed rank tests were made. Fisher's exact test and Mann–Whitney U test were used to compare the sex, age and paresis duration of the two patient groups.

The level of significance was set at 5% ($p < 0.05$).

3. Results

The sex, age and paresis duration distributions in the two analysed groups were not significantly different (sex, Fisher's exact test, $p = 0.286$; age, Mann–Whitney U test, $p = 0.654$; paresis duration, U test, $p = 0.054$) (Table 1).

Fig. 2 shows the static and dynamic facial characteristics of an 18-year-old patient before and 5 months after the functional recovery of the anastomosis.

Before facial surgery, mobility was larger in all animations in the healthy compared to the paretic side; after surgery, the differences reduced (brow raise and lip purse), or even reversed (smile) (Table 2). In no occasion, the between-group differences were significant, but for all animations a significant ($p < 0.05$) or nearly significant (lip purse, $p = 0.056$) between-sides difference was found. In the smile movement, a significant group × side interaction was found; post hoc tests demonstrated that the side difference was significant only in the pre-surgery patients (Wilcoxon test, $p = 0.02$).

Before surgery, the patients performed the lip purse animation with significant asymmetry of the cheilion landmark (Wilcoxon test, $p = 0.042$; larger healthy side movement), and a nearly significant total labial asymmetry ($p = 0.063$). After surgery, all asymmetry indices but that of the lower lip midpoints reduced (Fig. 3).

Total labial asymmetry during the smile animation was significantly different from 0 before surgery (Wilcoxon test, $p = 0.018$ for both total asymmetry, and landmarks ch, cph, li), with a larger movement of the healthy side (Fig. 4). After surgery, all asymmetry indices became not significantly different from 0 (Wilcoxon test, $p > 0.05$). In particular, before surgery the lateral displacements of all labial landmarks (cph, ch and li) were all in the healthy side direction, while they normalized after surgery (Fig. 5).

4. Discussion

Data were collected in two groups of patients with unilateral facial palsy, assessed before and after masseteric to facial nerve reanimation according to Biglioli et al. (2011). This is a new reanimation technique for early facial nerve repair, to be performed when the facial paralysis has not been present for more than 24 months. The presence of fibrillation potentials at the preoperative electromyographic examination is essential, as it guarantees a chance for the reinnervation. Fibrillations document that mimetic muscle fibres still exist and may regain function with appropriate reinnervation. Masseteric to facial nerve anastomosis allows a quick functional recovery of movement (about 5 months). This timing is comparable to the results of the traditional hypoglossus to facial nerve anastomosis (Körte and Bernhardt, 1903), while the much lower morbidity represents a great advantage for the patients (Yetiser and Karapinar, 2007).

At the end of clinical follow-up, final results were assessed by an objective method, allowing quantification and comparison to those obtained with other procedures.

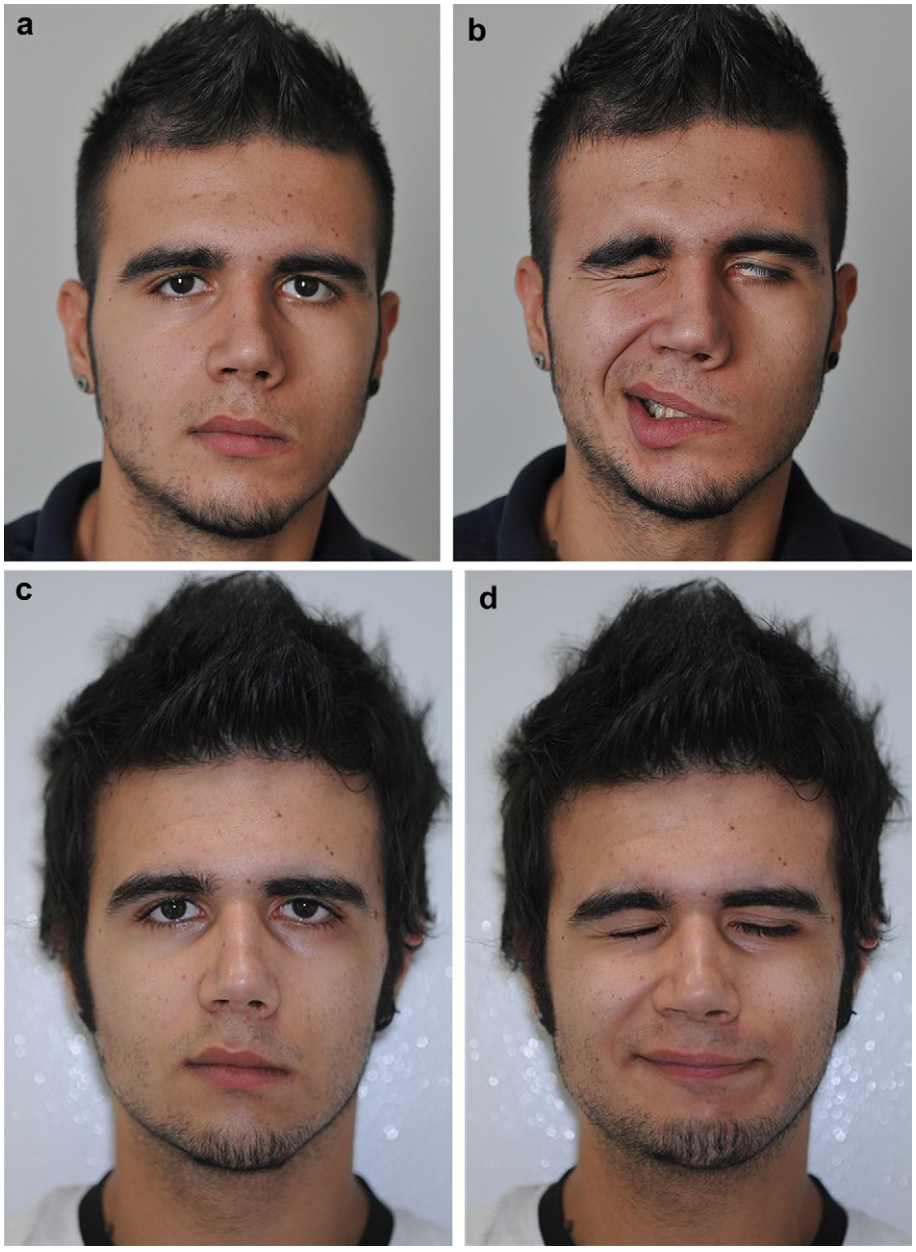

Fig. 2. Static images of the face (a, c) and dynamic ones (b, d) of an 18 years old patient before (a, b) and 9 months after (c, d) the surgical masseteric to facial nerve anastomosis. The patient clinically started to regain facial mimicry 4 months after surgery.

Table 2
Total facial mobility during standardized movements before and after surgery.

Side	Before surgery ($n = 7$)				After surgery ($n = 7$)				Comparisons		
	Healthy		Paretic		Healthy		Paretic				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Group	Side	G × S
Brow raise	7.1	2.7	2.1	0.8	5.9	0.8	2.0	0.6	0.321	<0.001	0.348
Lip purse	35.3	11.0	26.6	12.0	35.8	12.3	32.6	9.6	0.554	0.056	0.348
Smile	37.4	19.8	19.4	8.8	24.9	9.1	26.6	7.6	0.664	0.014	0.005

All values are mm. Comparisons were made by analyses of variance; 1;12 degrees of freedom for both factors and interactions.

The computerized method previously developed in our laboratory (Sforza et al., 2010a,b) was used for the automatic recording and analysis of facial motion: an optoelectronic motion analyser detected the three-dimensional position of small, weightless, passive markers glued on the face in correspondence of selected anatomical landmarks. Marker displacements were used to investigate facial motion without interfering with the movement, and custom algorithms allowed compensation for head motion, without the need for head holding (Mehta et al., 2008).

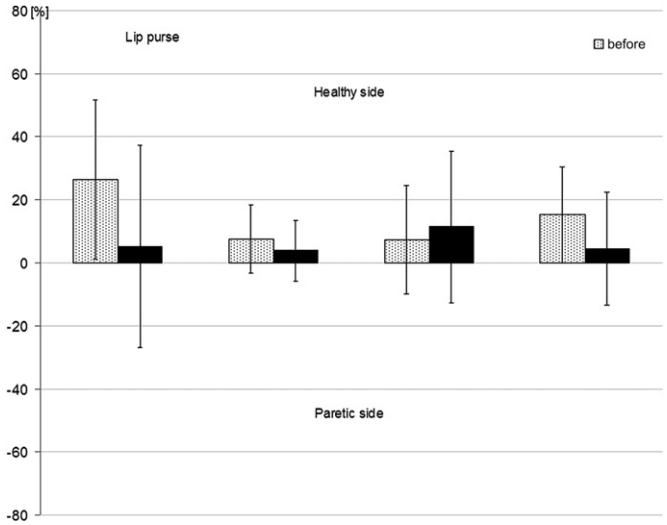

Fig. 3. Lip purse animation: total labial asymmetry and asymmetry of selected landmarks before and after surgery (mean ± 1 SD).

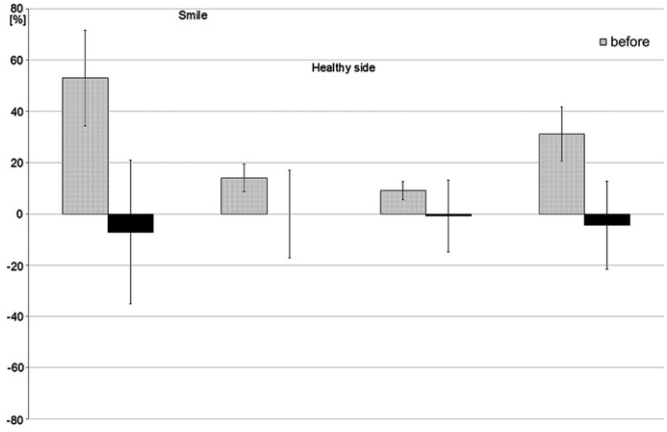

Fig. 4. Smile animation: total labial asymmetry and asymmetry of selected landmarks before and after surgery (mean ± 1 SD).

As discussed in previous investigations (Sforza et al., 2010a,b), when assessing facial motion the use of passive markers glued on the face is common (Trotman et al., 1998, 2003; Linstrom et al., 2002; Hontanilla and Aubá, 2008). Alternatively, the landmarks can be drawn directly on the face using an eyeliner pencil (Frey et al., 2008). Both protocols need the semi-automatic tracking of the markers to obtain their three-dimensional reconstruction. A distinct method is the automatic individualization of the facial features of interest without previous marking (Wachtman et al., 2001; Rogers et al., 2007). This last method is likely to be less disturbing and invasive for the patient, and faster for the investigator than the use of physical markers. Nonetheless, current applications are only two-dimensional (Wachtman et al., 2001; Rogers et al., 2007). The method may be difficult to apply in patients with facial scars or hairs. Stereophotogrammetry and laser scanning have also been used to assess facial motion in three dimensions, but both methods require a sufficiently large non-moveable part of the face (typically the forehead), thus restricting the kind of movements analysable and necessitating carefully controlled experimental conditions (Mehta et al., 2008; Sawyer et al., 2009; Popat et al., 2010). Additionally, facial hairs prevent correct detection of the facial features of interest (de Menezes et al., 2010).

To detect actual variations between and within individuals, the signal-to-noise ratio of each measuring system should be known. The optoelectronic instrument used in this study was calibrated with an accuracy lower than 0.02%. This means that the movement of each 2-mm marker could be detected within 0.12 mm, a value similar (Hontanilla and Aubá, 2008), or even better (Trotman et al., 1998, 2003) than those reported in previous studies.

Overall, the error of the current method was limited, and in good accord with data reported by other investigators. According to Trotman et al. (1998), reproducibility in non-verbal facial movements can be met when variations are lower than 4 mm. If this criterion is valid, all our expressions can be considered reproducible (mean TEMs all lower than 3.3 mm). For the inter-session variations, all the movements analysed had standard deviations lower than 1 mm. The current intra- and inter-session variability in single landmark movements was comparable (or even better) to previous reports (Trotman et al., 1998, 2003; Mehta et al., 2008).

Recently, better reproducibility has been reported for verbal animations (speech) than for non-verbal ones (Popat et al., 2010), but in the current study we limited our analysis to conventional clinical movements (Coulson et al., 2005; Frey et al., 2008).

In this preliminary study two different groups of patients were analysed, and the current results can be considered only indicative of the possibilities of the surgical rehabilitation technique. Nonetheless, the two groups of patients had similar pre-surgical clinical characteristics, as well as similar ages and duration of facial palsy. Together with this study limitation, there is the reduced number of facial animations, where not all movements previously proposed in the literature (for instance, eye closure, grimacing, cheek puff, and even verbal expressions) were used (Wachtman et al., 2001; Popat et al., 2010; Sforza et al., 2010a,b). The number of facial movements should be a compromise between the detailed examination of the patients, and the time necessary for the test, considering both recording and semi-automatic tracking. In the current study we limited our analysis to the maximum displacement of the landmarks, neglecting their directions (Wachtman et al., 2001; Trotman et al., 2003; Frey et al., 2008).

Previous studies have underlined the need to select facial animations that could detect regional mobility in the various parts of the face, according to the anatomical branches of the facial nerve (Coulson et al., 2005; Frey et al., 2008; Mehta et al., 2008; Sforza et al., 2010a,b).

In this study, both movements involving parts of the face submitted to the surgical rehabilitation (smile and lip purse, performed in the middle and lower facial thirds), and movements involving parts of the face not submitted to the surgical rehabilitation (brow raise, made in the upper facial third), were investigated. Brow raise was not expected to be different because the temporal branch is a very thin one, without significant anastomoses among adjacent ones that could partially accomplish its function. Indeed, the highly significant asymmetry between the movements of frontal landmarks was similar in the two patient groups: the paretic side movement was on average only 30–34% of the healthy side movement. This similar behaviour in the two groups further confirms the homogeneous facial conditions of the patients, except the surgical intervention.

In contrast, both smile and lip purse were influenced by the surgical treatment, with significant reductions of labial asymmetry during the movement: on average, before surgery the paretic side movement during the lip purse was only 75% of the healthy side movement, and became more than 90% after surgery. During the free smile, the modification was even larger: from 52% (before) to 101% (after). After surgery, asymmetry indices became similar to those found in healthy control subjects (Sforza et al., 2010a,b).

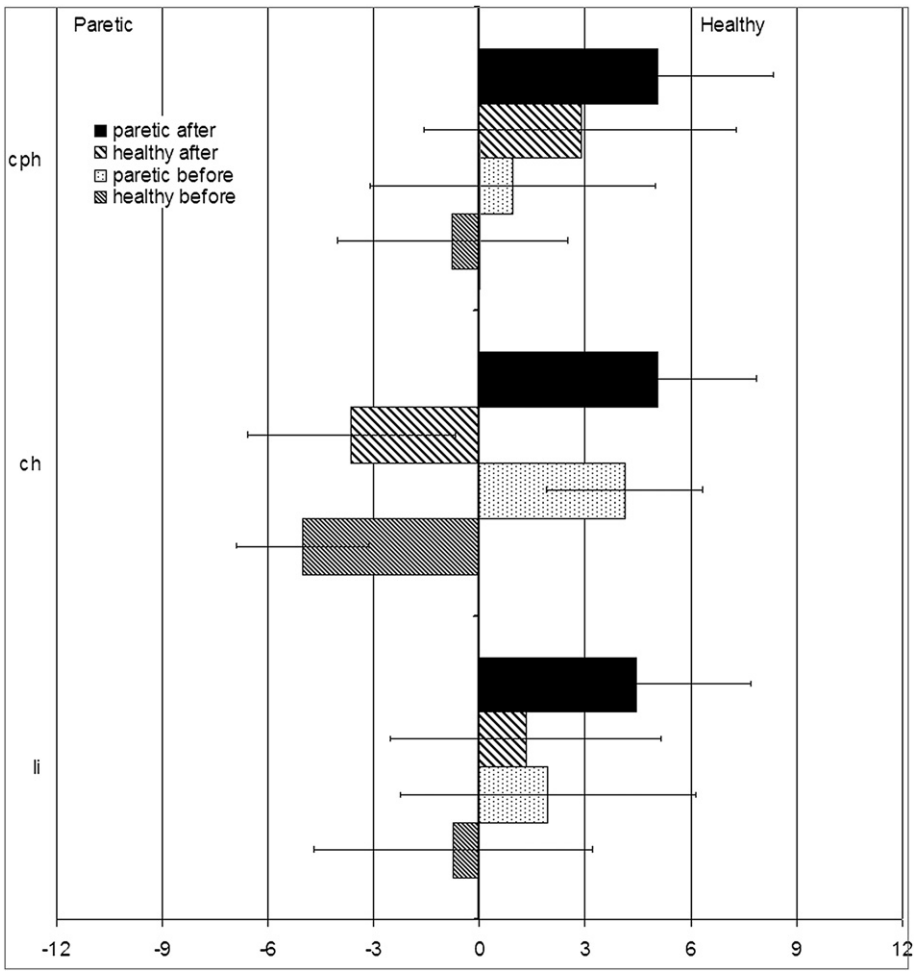

Fig. 5. Smile animation: lateral displacement (right–left direction, mm) of labial landmarks before and after surgery (mean ± 1 SD). Positive displacements: healthy side prevalence; negative displacements: paretic side prevalence.

The successful effect of surgery can be appreciated better by analysing the lateral displacement of the labial landmarks, as suggested by Frey et al. (2008). Before surgery, all six labial landmarks analysed (paretic and healthy side cph, ch, li) had considerable lateral movements, all in the healthy side direction (Figs. 2b, 5). After surgery, only the ch landmark maintained a lateral displacement, while both the other two landmarks remained nearer to the symmetry plane, as expected in healthy persons (Sforza et al., 2010a,b).

It has been reported that the assessment of synkineses and of the actual components of a movement may be difficult for a clinical observer because they require switching from a global, broad-external view to a local, narrow-internal focus on the animation being performed (Coulson et al., 2005). Computerized motion analysis can easily overcome this problem (Rogers et al., 2007).

On going investigations in our laboratory are following up the same patients before and after surgical reanimation, to document the actual individual modifications in facial movements and asymmetry (Frey et al., 2008).

5. Conclusion

The method used in this investigation allowed us to quantitatively detect both the alterations in facial movements in patients with unilateral palsy, and their rehabilitation after surgical reanimation. The significant asymmetry in the amount of facial movements that characterized the patients analysed before surgery reduced after surgery in those facial areas involved in the masseteric to facial nerve anastomosis.

Conflict of interest

The authors have no conflicts of interest in relation to the current investigation.

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SUPPLEMENT J

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Otolaryngology Head and Neck Surgery 2012 Dec (Epub ahead of print).

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery XX(X) 1–6

DOI: 10.1177/0194599812469352
http://otojournal.org
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Surface Electromyography Recording of Spontaneous Eyeblinks: Applications in Neuroprosthetics

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. We are designing an implantable neuroprosthesis for the treatment of unilateral facial paralysis. The envisioned biomimetic device paces artificial blinks in the paretic eyelid when activity in the healthy orbicularis oculi (orbicularis) muscle is detected. The present article focuses on electromyography (EMG)–based eyeblink detection.

Study Design. A pilot clinical study was performed in healthy volunteers who were intended to represent individuals with facial paralysis. Spontaneous eyeblinks were detected by a surface EMG recording. Blink detection accuracy was tested at rest and during voluntary smiling and chewing.

Setting. Fifteen participants were asked to wear surface recording electrodes on the left side of their face, detecting the orbicularis oculi, the masseter, and the zygomatic muscle EMG activity.

Subjects and Methods. Participants were asked to look ahead, voluntarily smile, and chew according to an experimental protocol. Custom software was designed with the purpose of selectively filtering the multichannel EMG recordings and triggering a digital output.

Results. The software filter allowed elimination of spurious artificial eyeblinks and thus increased the accuracy of the EMG recording apparatus for the spontaneous blinking.

Conclusion. Orbicularis oculi EMG recording worked as a real-time eyeblink-detecting system. Moreover, the multichannel EMG recording coupled to a proper digital signal processing was very effective in specifically detecting the spontaneous blinking during other facial muscle activities. With regard to closed-loop biomimetic devices for the pacing of the eyeblink, the EMG signal represents a valid option for the recording side.

Keywords

facial paralysis, eyeblink, surface EMG, neural prosthesis

Received May 11, 2012; revised October 3, 2012; accepted November 6, 2012.

Facial paralysis affects up to 0.3% of the population every year in Western Europe and the United States.[1] People usually experience unilateral facial paralysis, with the other side of the face normally moving. One of the most bothersome issues is the steadily open eye and loss of the eyeblink, which may cause severe damage to the eye. Besides functional impairments, facial paralysis is a major psychological barrier to social life.

Preliminary studies laid the groundwork for the application of neuroprosthesis to the treatment of paralytic eyelid closure.[2-12] Since spontaneous eyeblinks are normally symmetrical, in the case of unilateral paralysis, a biomimetic device can record and process a biopotential signal when the healthy eye spontaneously blinks. The signal can be processed to trigger a train of electrical pulses that would initiate an artificial blink on the paralyzed eye. This solution is referred to as closed-loop eyelid reanimation and does not require external control to activate the biomimetic blinking mechanism.[11]

Our laboratory is designing an implantable closed-loop eyelid reanimation system. The neuroprosthesis detects the spontaneous blinks on the healthy side via electromyography (EMG) recording and elicits the eyeblink of the contralateral paralyzed eyelids via an electrical stimulation (**Figure 1**). The present article focuses on the EMG-based eyeblink recording that is aimed at detecting the onset of the electrical activity of the healthy orbicularis oculi muscle, before the movement starts.

Methods

Experiments, carried out in 15 adult volunteers (9 women and 6 men; mean age, 30.5 years), were approved by the ethical committee of the University of Milan Medical School in accordance with the standards of the 1964 Declaration of Helsinki. All participants were fully informed about the procedure and provided written consent. No

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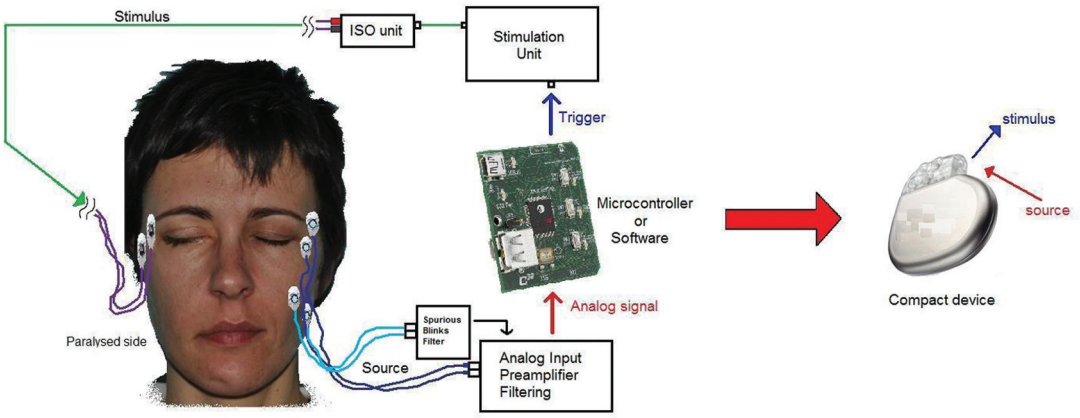

Figure 1. Project of a closed-loop implantable device detecting the onset of the electromyographic (EMG) activity of the patient's left (healthy) orbicularis muscle and triggering the stimulation of the contralateral (paralyzed) muscle.

subject showed any neurological or ophthalmologic abnormalities. Each volunteer participated in all phases of the procedure. With informed consent, setup time, and cleanup time, the entire procedure took less than 30 minutes. The experiments were well tolerated by the participants, with no reported discomfort.

Participants were asked to wear recording EMG electrodes on the left side of their face (**Figure 2**). Pairs of disposable Ag/Cl skin recording electrodes (Kendall/Tyco ARBO, 10-mm diameter, type H124SG) were taped at the lateral orbital rim, detecting orbicularis oculi (orbicularis) EMG activity, and along the jaw angle bisector line, recording the masseter and zygomaticus major and minor (zygomatic) muscle EMG activity, respectively. The inter-electrode distance was within the range of 2 to 3 cm (intercenters). A seventh electrode taped onto the left forearm skin served as a ground.

First, participants were asked to sit still and look ahead for 1 minute. Then, they were asked to perform 10 voluntary smiles, 1 every 6 seconds, for 1 minute. The entity of the smiles was not differentiated between gentle and big smile; participants were asked to perform their own natural smile, without making any particular effort. Finally, they were asked to chew gum for 1 minute.

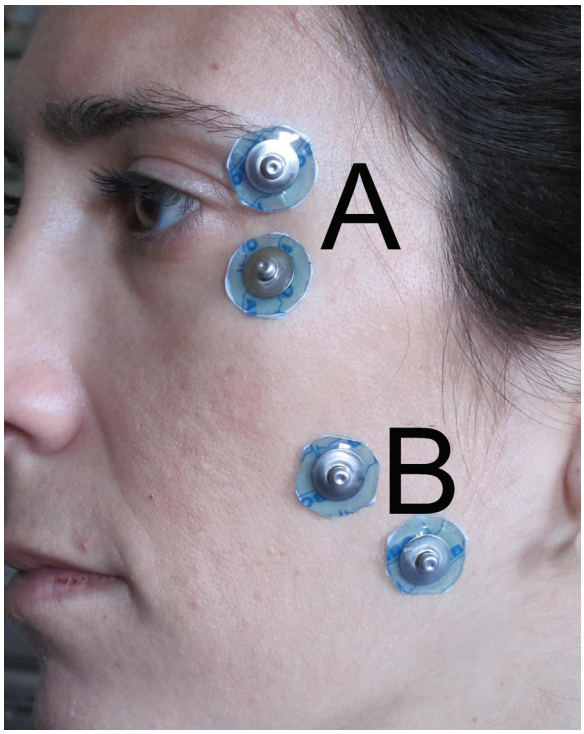

Figure 2. Recording electrodes' position on the left side of the face. (A) Lateral orbital rim, detecting the orbicularis electromyographic (EMG) activity. (B) Angle of the jaw and cheek, recording the masseter and zygomatic muscles' EMG activity.

Software Filter

Surface EMG signals were amplified, integrated, and filtered at a high-pass frequency of 0.5 Hz and a low-pass cutoff frequency of 1 kHz. The in-band gain was regulated from 0 db to 40 db on the basis of the amplitude of the source signals. Successively, the analog-to-digital conversion was performed at a sampling frequency of 5 kHz by the internal ADC of a National Instrument BNC-2090 I/0 acquisition board. Customized LabVIEW software allowed us to store, elaborate, and display the multichannel EMG signal and trigger a computer digital output based on a multithreshold algorithm. This algorithm applied a standard deviation (SD) evaluation over a time window of 20 milliseconds (typical, but it can be set arbitrarily) on both the signal samples.

The threshold-and-stimulate system was realized as follows. A time window, tunable from 5 to 30 milliseconds, is applied to the digital signal to evaluate its SD. Under resting conditions, no significant EMG signal is recordable, and a low SD value is measured. During muscular activity, instead, depolarization of motor units produces an increase

of the detected signal as well as of its SD. At constant mechanical conditions and initial position of the muscle, stronger activation of motor units is thus correlated with an increased electrical activity of the EMG signal and a faster increment of its SD. Five SD thresholds were programmed in our software. All threshold values are set according to measurement conditions (electrodes, skin condition, general quality of the signal) and preamplification parameters. Increasing SD thresholds were set to carefully discriminate the intensity of the right orbicularis EMG onset. In presence of activity from masseter or zygomatic muscles, independently from the orbicularis oculi muscle signal, the digital output is prevented. The stimulation terminal is turned off as long as the masseter EMG SD is over threshold. In this way, no spurious blinks for mimic or moderate chewing activity can occur.

In the absence of activity from the same muscles, the orbicularis EMG signal is detected and classified in intensity by the SD threshold scheme discussed above. Over-threshold signals trigger the stimulation of the contralateral orbicularis muscle. The orbicularis EMG standard deviation is compared with a progressive threshold scale to quantify the intensity of the electrical activity and trigger an equivalent pattern of stimulating pulse train. Different pulse trains are also programmed in the software. After each stimulation, a resting time interval prevents from any EMG feed-through effect from the stimulated side of the face to the other, which would result in an uncomfortable positive feedback loop. The masseter and/or zygomatic muscles' EMG SD is compared with a single threshold value. Threshold values are tailored for each individual to guarantee a correct signal detection. Thus, SD evaluation, comparison, and stimulation trigger are all performed by the software.

Our experiments were carried out both with and without the activation of the software filter.

Data Analysis

The high variability of the calibration of the multithreshold system does not allow a standardization of the recordings. Thus, the criteria of data analysis excluded the use of sensitivity and specificity parameters. As an alternative parameter, we calculated the gain of the system as the ratio between the true-positive outputs and the true-positive inputs. A second parameter to take into consideration is the presence of spurious triggers, not to be included in the gain calculation.

Results

When participants were asked to look ahead for 1 minute while keeping the face at rest, the number of pulses delivered by the computer digital output corresponded to the number of natural eyeblinks, independently from the on-off state of the software filter (**Figure 3**), since activity in the masseter and zygomatic muscles was absent. Thus, the apparatus gain (the ratio between the true-positive outputs and the true-positive inputs) was 1, and no spurious triggers were recorded. Among the 15 subjects, the natural blink frequency was 10 to 26 blinks per minute (mean, 16.1 ± 6.7).

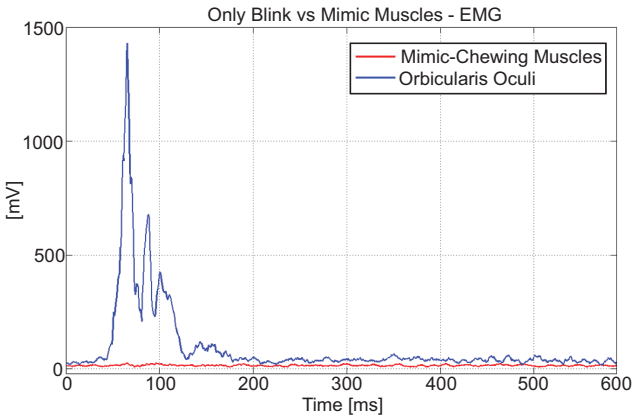

Figure 3. Spontaneous eyeblinks. The graph shows orbicularis electromyography (EMG; blue line) and masseter/zygomatic EMG (red line) during natural eyeblinks. No other facial movements were performed.

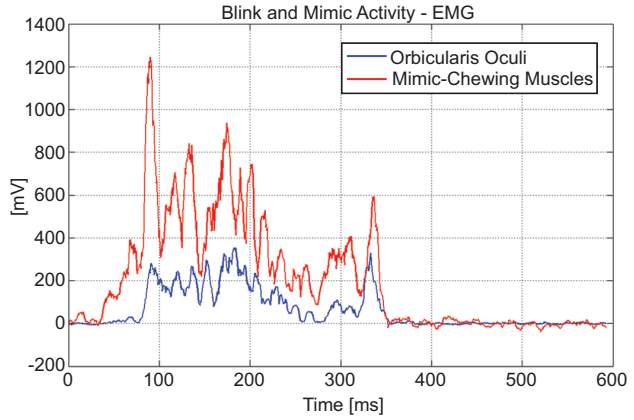

Figure 4. Voluntary smile. The graph shows orbicularis electromyography (EMG; blue line) and masseter/zygomatic EMG (red line) during voluntary smiles. The EMG activity of the zygomatic muscles is recorded by both channels and may trigger a computer digital output (spurious eyeblinks). Note that the amplitude of the EMG signal is more than twice the voltage of the orbicularis EMG shown in **Figure 3**.

Subjects were then asked to voluntarily smile every 6 seconds for 10 times. When the software filter was off (**Figure 4**), the zygomatic EMG interfered with the orbicularis EMG and triggered the computer digital output in 40% to 60% of the trials (mean, 51% ± 8%). Recording the voluntary smiles together with the spontaneous eyeblinks for 1 minute resulted in 15.4% to 33.3% of spurious triggers (mean, 23.9% ± 6.7%) per minute. The gain was still 1, but despite a mean of 16.1 natural blinks/min, the digital output was recorded 21.2 times in 1 minute. The mismatch is related to the presence of 23.9% spurious triggers from the adjacent muscle activity. When the zygomatic EMG signal was filtered, the digital output was prevented, independently from the spontaneous eyeblinks. Thus, the smiling activity

did not activate the closed-loop system. In this case, spurious triggers were suppressed, and despite a mean of 16.1 natural eyeblinks/min, a mean of 14 digital outputs was recorded. The gain of the system was 0.86 (14% lower than with the filter off).

Video 1 (available at otojournal.org) shows that when the participant smiles and the software filter is on, the zygomatic muscle EMG activity is read by the apparatus, and any computer digital output is prevented, independently from the blinking.

When subjects were asked to chew gum (moderate chewing activity, average 40 bites/min) for 1 minute, a digital output signal was recorded in 50% to 60% (mean, 54% ± 5.1%) of the chewing movements. Observing the chewing activity together with the spontaneous eyeblinks for 1 minute, the gain was still 1, but the percentage of spurious triggers was about 43.5% to 68.6% (mean, 55.8% ± 8.8%) per minute. After the multichannel EMG recording was coupled with the software filter for masseter muscle, it was possible to selectively detect the eyeblink, with no spurious eyeblinks related to moderate chewing activities. In this case, spurious triggers were suppressed, and despite a mean of 16.1 natural eyeblinks/min, a mean of 13 digital outputs was recorded. The gain of the system was 0.8 (20% lower than with the filter off).

Discussion

Research in biomimetics has progressed rapidly in recent years, fueled by the interdisciplinary efforts fusing medicine and engineering. Since the 1980s, the possibility of rehabilitating a paralyzed hemiface by an implantable stimulator controlled by functioning hemiface muscle activity has been shown. In fact, the onset of the electrical activity of the healthy facial muscles may be processed to trigger the electrical stimulation of the paralyzed side to elicit matching patterns of movement. The feasibility of a functional electrical stimulation of the paralyzed orbicularis muscle has been assessed in animal models (eg, rabbit and dog) to find effective stimulation locations and patterns.[2-11] Moreover, similar stimulation experiments have also been performed in anatomically intact human volunteers who are intended to represent individuals with facial paralysis, and recent findings on healthy subjects indicate that the best stimulation pattern for eliciting natural-like movement of the eyelids without discomfort is 100- to 200-Hz pulse trains.[12] This topic has been an area of ongoing investigation for more than 25 years, and substantial effort has been put forth by researchers to overcome several design issues and realize a device based on the above-described concept.

One of the issues is recording natural eyeblinks with a system that is harmless, has real-time detecting, has a proper signal strength, is accurate, and is eventually implantable. Neural and muscular recordings are the basis of biomimetic devices that could record signals and provide motor functions to patients with paralysis. Our study represents a preliminary work with the aim of discussing advantages and downsides of the EMG recording as a possible eyeblink-detecting system for neuroprosthetic applications.

Eyeblink Symmetry

The described eyeblink-recording system is aimed at detecting the onset of healthy orbicularis EMG activity, before the movement starts. Indeed, it is known that regardless of their origin (reflexive, voluntary, or spontaneous), all blinks exhibit a similar pattern: 10 to 12 milliseconds after the onset of orbicularis EMG activity, the upper lid rapidly lowers (down phase), after which it rises more slowly (up phase) to nearly its starting position.[13] Recording the orbicularis EMG prior to the starting of the movement would help minimize the delay of the closed-loop system, that is, the time to pace the stimulation of the contralateral paralyzed side and thus facilitate a symmetrical synchronous eyeblink. EMG data can be measured with surface, needle, or wire electrodes. The advantage of surface electrodes is that they are not painful and record from a relatively large volume of muscle. For this reason, they have been chosen to perform pilot studies on healthy human volunteers. The disadvantage of surface electrodes may be their low selectivity when recording small muscles.

Recent studies have hypothesized to record and process the EMG signal from the levator palpebrae of the same paralyzed eyelid as an alternative to the contralateral orbicularis EMG.[14] This idea is suitable for a fast and symmetric response, because cessation of the levator palpebrae activity anticipates the orbicularis signal for trigeminally evoked eyeblinks, but stimulation and EMG artifacts could be more critical technical challenges than in cases of healthy orbicularis EMG recording. The extracellular neural action potential (ENAP) of the zygomatic branches of the healthy facial nerve would be another alternative, with 2 advantages: a shorter delay and a potentially higher accuracy. However, its signal amplitude would be 20 times smaller than that of EMG[11]; signal strength represents one of the parameters that ensure the detection of the blink in noisy environments. Moreover, ENAP accurate recording is localized to nerve routes, and this implies a challenge for correct surface electrode placement. A high chance of signal artifacts due to localization error may be a further inconvenience in using ENAPs in this specific application.

Interference from Adjacent Muscles

From our preliminary data, it emerged that a potential downside to the surface EMG is that the cross-talking from adjacent facial muscle activities could interfere with the blink recording and thus alter the output response. Of greatest concern are the chewing muscles during mastication and the zygomatic muscles during smiling. Eivinger et al[13] reported that 2 miniature silver electrodes (<2-mm diameter), taped to the lateral and medial portions of the upper lid near its lower margin, monitor orbicularis muscle activity without picking up signals from adjacent muscles. Despite the broad investigation of the upper eyelid movements in 4 conditions (voluntary, spontaneous, and reflex

blinks, and the lid movements that accompany vertical saccadic eye movements), their experiment lacked data of recording while chewing or voluntarily smiling. We agree that the position of the recording electrodes is of paramount importance, and further investigation is needed. For example, the medial quadrants of the orbit, where the orbicularis muscle is in close contact with the frontal and nasal bones and farther from other muscles, should be an ideal position to record the orbicularis EMG activity, partially overcoming the noise issue. Any electrical noise exceeding the predetermined threshold would trigger the computer digital output, resulting in an asynchronous eyeblink during chewing or smiling. This potentially socially embarrassing feature could limit its use in the public setting. The activation of artificial blinks while performing other voluntary facial movements would correspond to a synkinesis-like effect. Synkinesis, referring to the abnormal involuntary facial movement that occurs with voluntary movement of a different facial muscle group, has been described as one of the most distressing consequences of facial paralysis.[15]

Our software was implemented with a filter able to differentiate natural eyeblinks from spurious EMG activity from adjacent muscles, for example, correlated with smile. Theoretically, it would be ideal to record each muscle individually; however, to reduce the number of electrodes, masseter and zygomatic muscle electrical activity is detected by a single channel that still gives an accurate recording. For our purposes, the data provided by a single channel are in excess of the requirement for this specific application, since the EMG signal from smiling and chewing muscles is more than twice the voltage of the orbicularis EMG signal, as shown in **Figures 3** and **4**.

A supplementary third channel should be activated to read the activity from the temporalis muscle (co-responsible with the masseter for the chewing activity) and improve the selectivity of the filter.

Activation of the filter prevents any computer output, independently from the orbicularis EMG activity. The loss of gain is not considered a limit to this specific application. Indeed, the main aim of the envisioned neuroprosthesis is preserving the health of the eye, and we believe that skipping about 20% of the eyeblinks during smiling or chewing activities would still allow this device to be functionally effective anyway. Moreover, since a cosmetically desirable eyeblink represents another paramount goal of the application, avoiding spurious triggers has been our priority while writing the software.

An alternative approach to the software filter would be recording noisy muscle EMG and orbicularis EMG separately and then subtracting the second signal from the first. This conceptually allows the cut of masseter interference for better accuracy of the system. However, differences in attenuation between the 2 acquisition points and electrodes are hardly predictable, and a partial cancellation of the chewing muscle EMG signal, much larger than that of the orbicularis muscle, may result in a system failure. Other issues would be the increased circuit complexity, needed for signal subtraction, and the consequent rise of power requirements.

Other conditions that may affect the accuracy of blink detection include the changes in EMG signal level from person to person as well as the changes in electrode impedance. Blink detection circuitry should thus be able to adapt to each patient by automatic parameter training. Electrode impedance does contribute to noise, and higher impedance electrodes are expected to have a lower signal-to-noise ratio. In addition, high electrode impedance in combination with the distributed capacitance between the electrode and the recording amplifier will reduce the electrodes' high-frequency response.[16]

Author Contributions

Alice Frigerio conceived the study, took part in the experiments, interpreted the data, performed statistical analysis, drafted the manuscript; **Stefano Brenna** conceived and wrote the software filter, took part in the experiments, interpreted the data, and performed statistical analysis; **Paolo Cavallari** conceived the study, wrote the software for data acquisition, coordinated lab activity, acquired the funding, and revised the manuscript.

Disclosures

Competing interests: None.

Sponsorships: Università degli Studi di Milano, Italy.

Funding source: None.

Supplemental Material

Additional supporting information may be found at http://oto.sagepub.com/content/by/supplemental-data

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SUPPLEMENT K

A closed-loop stimulation system supplemented with motoneurone dynamic sensitivity replicates natural eye blinks.

Otolaryngology Head and Neck Surgery 2012; 146(2): 230-233.

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
146(2) 230–233

DOI: 10.1177/0194599811427255
http://otojournal.org
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A Closed-Loop Stimulation System Supplemented with Motoneurone Dynamic Sensitivity Replicates Natural Eye Blinks

Alice Frigerio, MD[1], and Paolo Cavallari, MD[1]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. The authors are designing an implantable device that will electrically stimulate a paretic eyelid when electrodes implanted into the contralateral healthy orbicularis oculi muscle detect a spontaneous blink activity. As a novelty, the stimulation pattern includes the dynamic sensitivity of motor units, thus obtaining complete eyelid closure, tailored on the kinematics of the natural eye blink.

Study Design. A preliminary study was performed on 10 healthy subjects, to observe, first, the kinematics of their natural eye blink and, second, the eye blink stimulated by a dynamic vs nondynamic pattern.

Setting. A microaccelerometer taped onto the left upper eyelid detected its kinematics. A dedicated LabView software built up and triggered the stimulation pattern. A webcam recorded the behavioral effect.

Subjects and Methods. The kinematics of spontaneous eye blinks was detected. Then, an epicutaneous stimulation of the facial nerve branch for the left orbicularis oculi muscle was performed on the same subjects. Muscle recruitment curves were studied, and acceleration of the bionic blink was measured and compared with the natural one.

Results. Kinematics of the natural eyelid is highly variable within subjects. The stimulation pattern frequency was set case by case in order to obtain the desired eyelid acceleration of the contralateral eye. A custom-fit dynamic stimulation leads to a symmetrical natural-like eye blink.

Conclusions. By adding the dynamic pulse, the authors were able to tailor a bionic eye blink, which was hardly distinguishable from the subject's natural one.

Keywords

facial paralysis, eye blink, motoneurones dynamic sensitivity

Received July 5, 2011; revised September 16, 2011; accepted September 29, 2011.

Ipsilateral peripheral facial nerve palsy (FNP), caused by the impairment of the facial nerve, affects 0.3% of the population per year in Western Europe and the United States.[1] The most common cause of FNP is idiopathic (Bell palsy), with an annual incidence in a population of 100,000 people of around 20 afflicted individuals, but there are many other causes: traumas, infections, neoplasms, iatrogenic palsies, and congenital palsies. Besides the impairment of mimetic and smile, its most severe damage is the loss of the blink reflex and eyelid closure, with corneal exposure.

Although the idea of a bionic reanimation of a paralyzed hemiface is not new,[2-4] functional and cosmetically acceptable eyelid closure results have been poorly documented. Thus, we are proposing a closed-loop implantable device (**Figure 1**) capable of detecting the onset of the electromyographic (EMG) activity of a healthy orbicularis oculi muscle and triggering the stimulation of the injured side. This device will contain a microchip that generates patterns of stimulation, mimicking the dynamic sensitivity of motor neurons,[5] hence leading to a natural-like eye blink.

Methods

Experiments, carried out in adult volunteers, were approved by the ethical committee of the University of Milan, Medical School, in accordance with the standards of the 1964 Declaration of Helsinki. All subjects gave written consent to the procedure.

First, the kinematics of normal eye blinks was studied. Ten healthy subjects (6 women and 4 men; mean age, 33.5 years) were asked to look ahead for 1 minute. Their blink frequency, speed, and duration were recorded by taping a microaccelerometer (weighing < 0.5 g) onto the left upper eyelid. After the kinematics data were recorded, they were analyzed offline and average peak acceleration was calculated.

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Part of this article was presented at the 16th IFESS Annual Conference; São Paulo, Brazil; September 8-11, 2011.

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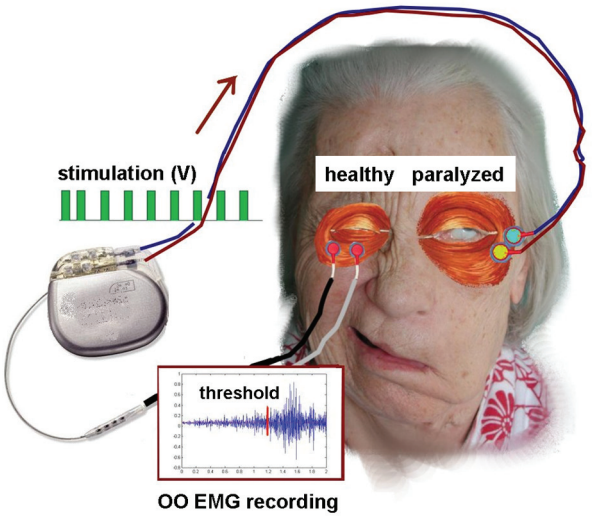

Figure 1. Project of a closed-loop implantable device detecting the onset of the electromyographic (EMG) activity of the patient's right (healthy) orbicularis oculi (OO) muscle and triggering the stimulation of the contralateral (paralyzed) one.

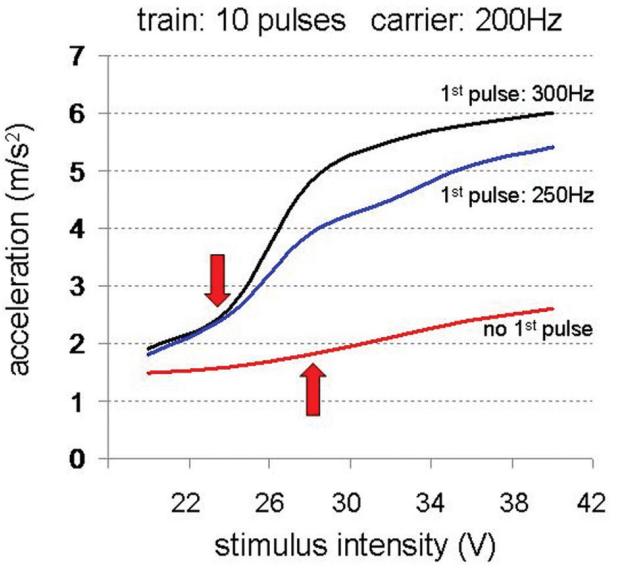

Figure 2. Recruitment curves of the eye blink showing the role of the motoneurones dynamic sensitivity. Eyelid acceleration is plotted against stimulation intensity. When a train of 10 pulses (carrier frequency 200 Hz) was added with an additional first pulse of variable frequency (250 Hz, blue line, and 300 Hz, black line), the threshold for a complete eyelid closure (arrows) was lower.

In the second phase, the process was tested on the same subjects. Surface-recording EMG electrodes were placed on the right orbicularis oculi, masseter, and temporalis muscles. The skin of the left orbital region was medicated with a topical anesthetic cream (a 5% emulsion preparation containing 2.5% each of lidocaine and prilocaine).

The electrical activity of the right orbicularis oculi muscle was used as a trigger for the stimulus. The computer digital output was connected to a Grass S88 stimulator. Percutaneous stimulation (0.8 mm silver electrodes) of the left facial nerve branch controlling the eyelid movement was then performed. The stimulating electrodes were placed along a facial nerve branch for the orbicularis oculi muscle, distal enough not to trigger the nearby facial nerve branches to signal. This avoided undesirable synkinesis movements. On the other hand, the eventual electrical activity of the right masseter and temporalis muscles, active while chewing, fed a software threshold circuit, blocking the stimulation process.

Dedicated Labview software was designed to read the trigger signal and deliver a pattern of stimulation. The pattern of stimulation consisted of a train of 10 pulses (width 0.8 ms) at a constant carrier frequency (range, 20-200 Hz), with the interval between the first and second pulse adjustable in length (dynamic pulse range, 250-300 Hz). For every testing, the whole train was given identical voltage. This special pattern confers the eyelid movement natural speed and acceleration properties. Different combinations of first intervals and carrier frequencies were tested on each subject.

The same 10 volunteers were stimulated with clusters of trains at different frequencies. The kinematics effects of stimulations with or without dynamic sensitivity were compared.

Finally, the behavioral effect was recorded by a webcam and analyzed offline. Muscle recruitment curves were then studied, and average peak acceleration was computed and compared with the kinematics data of the spontaneous eye blink for each subject. Moreover, the carrier frequencies were plotted against eyelid average peak acceleration.

Results

Among the 10 subjects, the natural blink frequency was 11 to 26 blinks per minute (mean, 17.2 ± 5.6), while blink duration and its average peak acceleration were 83.5 to 118.2 milliseconds (mean, 110.5 ± 11.3) and 1.4 to 5.1 m/s^2 (mean, 3.4 ± 0.6), respectively. From these data it emerges that a high variability of the natural blink parameters occurs within subjects; thus, for each subject, a custom-fit approach is needed to reproduce the blink in the paralyzed side.

From the recruitment curves (**Figure 2**) it is inferred that the average peak acceleration of the eyelid was higher when subjects were given stimulation trains containing a dynamic pulse than when achieved by the sole carrier frequency. From the same experiment it is also apparent that to obtain a full eyelid closure, the intensity of the stimulation was much lower (–15%) when using dynamic pulses. As an example, in the case illustrated in **Figure 2**, full eyelid closure was obtained at 26 V, rather than 30 V. By comparing the red curve and the black and blue curves, note also that by adding a single dynamic pulse, the acceleration range dramatically widens, attaining maximum values comparable with those recorded in the natural blink.

In the tailoring process, it is also important to underline that by keeping a constant first interval delay, the proper peak acceleration may be obtained by simply changing the carrier frequency value. The desired eyelid acceleration (in the range of 1.4-5.1 m/s^2) may be obtained by setting the most suitable carrier frequency (75-200 Hz). **Figure 3**, where the carrier

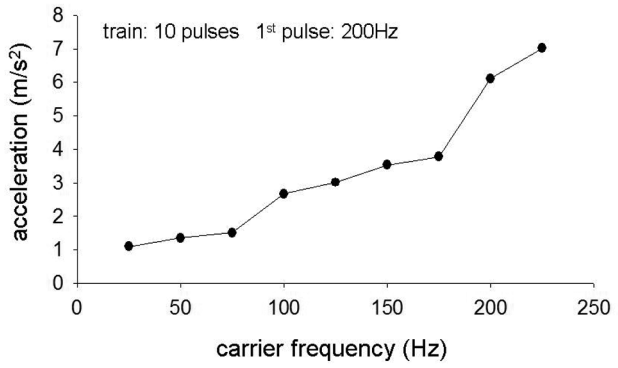

Figure 3. The carrier frequency of the train is plotted against the average peak acceleration of the eyelid (Pearson R = 0.95).

frequency is plotted against the eyelid average peak acceleration, shows that the desired acceleration (in the range of 1.4-5.1 m/s^2) may be obtained by setting the proper carrier frequency (75-200 Hz). Epicutaneous stimulation, at frequencies lower than 100 Hz, leads to an uncomfortable or painful thrill if given without premedicating the skin with a topical anesthetic.

Discussion

Eyelid paralysis impairs the eyelid's closure and may lead to severe corneal damage since natural eye blink movement spreads tears over the surface of the cornea and protects the eye from external damage. So far, great effort has been made by facial reanimation surgeons to restore eyelid movement in patients with irreversible facial paralysis with static and dynamic procedures, which consist of cross-facial nerve grafting, direct neurotization of the orbicularis oculi muscle, nerve transfers, and local and free muscle transfers. The best functional result of the most sophisticated eyelid reanimations is about 80% compared with the contralateral healthy side.[6] However, with these techniques a perfectly synchronous and natural-like eye blink is very hard to obtain.

Many preliminary studies on the feasibility of an implantable device restoring a bionic blink have been performed so far. Since facial paralysis is mostly unilateral, functional electrical stimulation of a paralyzed hemiface may be triggered by the contralateral healthy-side activity. First attempts were published in the 1970s, when injured laryngeal muscles were stimulated in dogs, with stimuli triggered by the contraction of contralateral healthy laryngeal muscles.[7] A few years later, Tobey[8] used the same method in rabbits' faces in order to restore a symmetric mimetic function. Otto et al[9] also demonstrated the feasibility of electrically stimulating the paralyzed orbicularis oculi muscle of the canine, using the EMG activity of the contralateral healthy orbicular oculi muscle as a trigger. Finally, the possibility of a restoration of eyelid closure using an artificial muscle has been investigated on a cadaver model by Tollefson and Senders.[10] An implanted sling device driving an artificial muscle[11] would represent an alternative to electrical stimulation, especially for patients whose muscles underwent complete atrophy because of an established paralysis. However, long-term biocompatibility and function may be an issue of artificial muscle technology.

A key point for reproducing a natural-like blink seems to be the right pattern of stimulation. Somnia[12] compared single- and multichannel electrical stimulation of denervated orbicular oculi canine muscles and concluded that only the latter may lead to complete eyelid closure (blink) at lower electrical stimulation thresholds. A few years later, Sachs and colleagues[13] found out that trains of 10-millisecond biphasic pulses delivered at 50 Hz were the most effective stimuli to elicit eyelid closure. Cao and colleagues,[14,15] who first attempted a functional nerve stimulation of the injured facial nerve, used pulse width of 200 milliseconds and frequency of 100 Hz. Kurita,[16] instead, stimulated the human paralyzed frontalis muscle with square pulses, which had a width proportional to the maximal amplitude of the healthy-side EMG signal.

To generate a natural-like blink, we are also working on an implantable programmable device that "selectively" detects the EMG activity of the healthy homologous contralateral muscle and electrically stimulates a paretic orbicularis oculi. As a novelty, as shown in this article, the stimulation pattern includes the motoneurons dynamic sensitivity,[5] which allows us to easily and effectively obtain complete eyelid closure and to tailor it on the kinematics of the subject's spontaneous eye blink. This would represent not only a functional upgrade but also an aesthetic improvement for patients with implants.

Moreover, since it is known that a train of stimuli is able to reduce the current required to eye blink (of about 40%)[17] further reduction (of about 15%) may be achieved when introducing the dynamic sensitivity in the pattern of stimulation itself.

The rationale of choosing a nerve stimulation was to lead to a full contraction of the orbicularis oculi muscle, according to Sachs et al.[13] The nerve stimulation may be indicated for those patients who suffer from partial impairment of the nerve conduction (paresis), for patients recovering from paralysis, and for patients who underwent a surgical reinnervation, ie, an anastomosis of the distal trunk of the facial nerve with a local motor donor nerve (masseter, hypoglossal).[18]

Finally, to avoid activation of the loop when the subject bites or activates other facial muscles, our device was supplemented with a multichannel EMG recording coupled to a software filter. This was very effective in specifically detecting the blinking activity of the healthy side.

The preparation of a multichannel analog-to-digital conversion card, supplemented with a microcontroller to process the signal and trigger the stimulation pattern, represents the next step toward miniaturization. According to a preview, traditional batteries will be replaced by an electromagnetic wireless power system with use of supercapacitors.

Conclusions

We propose a method to reproduce patient-tailored natural eye blink. Assembling an implantable microdevice allowing the recovery of the eye closure would be a life-changing opportunity for patients affected by facial paralysis. Moreover,

from this first step, a multichannel device may also be envisaged to restore both the eye blink and the smile.

Author Contributions

Alice Frigerio conceived the study, took part in the experiments and interpreted the data, performed statistical analysis, drafted the manuscript. **Paolo Cavallari** wrote the software for stimulation and data acquisition, conceived and coordinated the study, acquired the funding, revised the manuscript.

Disclosures

Competing Interests: None.

Sponsorships: None.

Funding Source: Università degli Studi di Milano, Italy.

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6. DISCUSSION

Facial nerve disorders encompass a broad spectrum of dysfunction, ranging from subtle dynamic facial asymmetry to complete, dense paralysis. The most common unilateral facial paralysis is Bell's, which affects 20-30 people per 100,000 every year. Bell's palsy is thought to be a result of Herpes simplex virus reactivation in the geniculate ganglion of the facial nerve, and accounts for approximately two-thirds of all new facial paralysis cases (*Kennedy, 2010*). Approximately 80% of Bell's palsy patients recover spontaneously, and over 90% will improve to near normal function if treated with oral steroids (*Sullivan et al., 2007*). Despite the generally favorable prognosis of Bell's palsy, many patients do not recover fully, particularly those with either complete flaccid paralysis or prolonged recovery periods. Other common causes of facial paralysis include: varicella zoster virus reactivation (Ramsay-Hunt syndrome), Lyme disease, removal of skull base tumors (most commonly acoustic neuromas), parotid gland malignancy, temporal bone fractures, autoimmune disease, and iatrogenic injury. Facial nerve regeneration following injury can vary greatly and may result in hypofunction (persistent weakness or poor excursion of facial muscles), hyperfunction (hypertonicity, spasm) or aberrant regeneration (synkinesis).

None of the disabilities encountered (i.e. corneal exposure, speech impairment, drooling) is perhaps as significant as the social isolation these patients often succumb to based on their perceived disfigurement and inability to convey emotion through facial expression. Because of the profound effect of this disorder on patient quality of life, a great deal of effort has been focused toward rehabilitation of the paralyzed face. A review of the current gold-standard surgical strategies for facial reanimation has been provided in Chapter 3. Facial reanimation experts all agree that this field still remains a challenge. Substantial effort has been put forth by surgeons to improve techniques for restoring eyelids movement and smile in patients with facial paralysis. The best functional results from the most current reanimations techniques restore about 80% range-of-movement compared with the contralateral, healthy side. Despite the advances in surgical grafting and repair techniques over the past 60 years, the functional outcome from attempted facial nerve repair or reanimation techniques is often disappointing, leaving patients with substantial impairment and in poor facial muscle control. In particular, the asymmetry of movements is emotionally devastating. Moreover, reanimations imply rerouting or harvesting autologous tissues -nerves, muscles and/or fascia- with partial or complete sacrifice of their original function. For example, sural nerve harvesting is a commonly performed procedure (for cross-face jump grafting) that implies the loss of skin sensitivity from the outer surface of the ipsilateral foot. Surgical procedures are all accompanied by risks, and may not be appropriate for many patients. Not only are surgical patients subjected to pain and the risks of bleeding, scarring, and infection, but periocular procedures are also frequently disfiguring. Eyelid springs and weights frequently lead to ptosis and are visible as masses beneath the skin surface. Bulky gold weights have, in many cases, been replaced by lower-profile platinum implants, but are still perceptible as upper eyelid contour irregularities. In addition to the cosmetic drawback, indwelling foreign bodies increase the risk of postoperative infections (particularly in diabetic patients or patients receiving chemotherapy), may ultimately extrude through the thin skin of the eyelid, and have been known to cause astigmatism from pressure on the cornea (*Saleh et al.,*

2007). While it is often more convenient for a patient to undergo eyelid weight placement or tarsorrhaphy than to use constant eye drops, if *orbicularis oculi* muscle function ultimately returns, the weight will need to be removed or the tarsorrhaphy reversed surgically.

This research aims at realizing a biomimetic application that might be associated or partially replace facial reanimation surgerical prcedures. Prosthetically assisting eyeblink, and eventually other facial movements, will produce a huge change in the actual context, and the reasons will be further discussed throughout this chapter.

The knowledge of the different clinical scenarios accompanying facial palsy is a premise of paramount importance. For the purposes of treatment planning, patients with facial paralysis may be classified by category:

a) recent acute onset with prognosis for complete recovery within 3 months, *i.e.* Bell' s palsy;
b) recent acute onset with prognosis for complete recovery over 4 to 12 months, *i.e.* Lyme disease or longitudinal temporal bone fracture;
c) acute onset with an injured but intact or grafted facial nerve with prognosis for prolonged, incomplete recovery, *i.e.* acoustic neuroma;
d) chronic paralysis with severely injured or extirpated facial nerve and no recovery over the course of 12 months, *i.e.* parotid gland malignancy;
e) chronic paralysis of congenital or childhood origin, *i.e.* Möbius syndrome or traumatic forceps delivery.

The first 3 of these categories would benefit from a biomimetic device to facilitate eye closure during waking hours, until the recovery process is complete. The last 2 groups of patients would require more conventional treatment regimens, such as lid loading or periocular reanimation surgery with free or regional muscle transfer. Ultimately, engineered muscle tissue and implantable electrodes with movement detection systems for the non-paralyzed side may supplant micro-neurovascular surgery as the gold standard for facial reanimation in these patients.

With regards to the rehabilitation of the eyeblink, application of facial nerve pacing to patients with acute facial paralysis would provide immediate restoration of periocular function and could be used all day long, until either the patient recovers sufficient function to no longer require assistance for eye closure, or the decision is made to proceed with further surgery. As long as there is an elicitable *orbicularis oculi* muscle, which should persist to some degree for at least 18 to 24 months in the absence of innervation, the patient can potentially avoid periocular surgery and still maintain normal eye closure via *functional electrical stimulation* (FES), with all its attendant benefits (*Gutmann and Young, 1944*). Since spontaneous mimetic movements are mainly symmetrical, in case of unilateral paralysis a biomimetic device can record and process a biopotential signal when the healthy hemiface spontaneously moves. The signal recorded from the healthy side can be processed to create a train of electrical pulses that would initiate an artificial movement on the paralyzed side. This solution is referred to as closed-loop eyelid reanimation and does not require external control in order to activate the biomimetic blinking mechanism.

Facial pacing applications would have two main biologic advantages. First, the potential saving of autologous tissues with avoidance of any donor site morbidity as a consequence of tissue harvesting. Secondarily, in case of acute reversible paralysis with periocular issues, an external device facilitating the eyeblink would significantly reduce the need for alloplastic weight or spring implants into the upper eyelid. Also, the costs for ophthalmologic care would be dramatically reduced, representing a highly desirable advantage for the community. Finally, a cosmetic and functional advantage of a closed-loop device, with a real-time trigger and stimulation system, is facilitating symmetrical and synchronous movements.

Synchrony. "Real-time trigger" means that the overall delay (between the movement of the healthy side and the movement of the prosthetically-assisted side) is shorter that 33ms. Indeed, human visual information updates at rates of about 30-33 Hz; therefore any latency around 33 ms or lower would be impossible for people to see. The EMG-based detection system discussed in ***Supplement J*** particularly fits this need, since the onset of the electrical activity of the muscle is recorded 10 to 12 ms prior to the start of the movement. Considered that the signal processing takes less than 1ms and the stimulation part of the loop would take about 15-20ms, the loop can be easily completed in time. An innovative method for early detection of the EMG activity of facial muscles (i.e. smiling muscles) could be detecting anticipatory postural adjustments (APA) related to specific movements. No studies have been performed so far on the topic. On the other hand, any recording system that detects the eyelids movement might cause a noticeable trigger delay, depending on the instant the movement is recorded. With regards to the infrared (IR)-based eyeblink detection system described in paragraph 5.3.1., the timing of the trigger depends on the relationship between the IR beam and the eyelids.

Symmetry. Normal eyelids movements in humans are highly conjugated (*Stava et al., 1994*). Spontaneous blinks have some degree of variation in their profiles, which the natural motor system that controls bilateral blinking compensates for to maintain conjugacy. Using simple stimulation profiles to generate binary blink functions wouldn't adjust for these differences, leading to some degree of mismatch in movements between the lids of the two eyes. To overcome this issue, we reproduced the natural ability to create a symmetrical movement by tuning the dynamic pattern of stimulation (see ***Supplement K***).

Strategies discussed so far are strictly for binary restoration of eyelid function. In normal subjects, however, there is fine control of lid position that is exhibited during such actions as squinting. Adjustment of various electrical stimulation parameters could provide a wide range of degrees of lid closure. Some could also be developed to match the duration of stimulation with the duration of closure in the healthy contralateral lid.
Recent studies have hypothesized to record and process the EMG signal from of the *levator palpebrae* of the same paralyzed eyelid, as an alternative to the contralateral orbicularis EMG (*Deng et al., 2010*). This idea is suitable for a fast and synchronous response, because the cessation of the *levator palpebrae* activity anticipates the orbicularis signal for trigeminally evoked eyeblinks, but stimulation and EMG artifacts could be a more critical technical challenge than in case of healthy orbicularis EMG recording. We think that the *levator palpebrae* EMG signal could rather be a valid option to approach cases of bilateral facial paralysis. Other methods of ipsilateral triggering may also be available.

First attempts to develop a closed-loop facial pacing date back to the late 70s (*Tobey and Sutton, 1976*). Possible explanations of the lack of success of previous research projects might be: the challenge of the topic, the lack of preliminary data on human subjects, the weakness of the interdisciplinary collaboration between scientists, clinicians and engineers, and finally the shortage of funding for a "humanitarian device" research. Our envisioned closed-loop eyelid reanimation system is an assembly of three different components, aimed at:

a) recording the biopotential signal from the healthy eye and thus providing the trigger signal for the closed-loop stimulation;
b) signal processing, i.e. a microcontroller included into an application-specific integrated circuit (ASIC) processes the signal and triggers a microstimulator;
c) stimulating the facial nerve or *orbicularis oculi* muscle on the paralyzed side, in order to elicit matching patterns of movement.

Any of these three components is object of a dedicated research & development (R&D).

Indeed, the main aims of the current project have been:

1) exploring biosignals representing spontaneous blinking activity in healthy individuals. Alternative eyeblink detecting systems, providing the trigger signal for a closed-loop facial pacing, have been designed and tested on healthy human volunteers.

Recording of the *OO* EMG onset has been studied as a possibility. EMG-based recording represents a valid tool to detect spontaneous eyeblinks, as part of closed-loop facial pacing systems. The early onset of the trigger signal allows a real-time pacing for the reasons discussed above. Moreover, an EMG detection system can be integrated both in external devices and implantable neuroprostheses. A potential downside is the crosstalk from adjacent muscles, but multi-channel EMG recording coupled to proper digital signal processing resolves most cross-talks and other spurious EMG events. ***Supplement J*** describes an EMG-based real-time eyeblink detection system for facial pacing. Further investigation is needed, mapping the OO surface with smaller electrodes and exploring alternative recording sites.

Alternatively, the detection of the eyeblink with infrared (IR) light technology has been explored and compared to the previously studied EMG-based method. IR light is commonly used in commercial eye-tracking systems and has been for long time used to detect blinks in animal research. A similar approach may be adopted for the envisioned application in humans. Our prototypal IR-based blink detection system provides a reliable, non-invasive indication of eyelid closure using an invisible beam of light passing in front of the eye. A potential downside is the generation of false detections on downward gaze, and during the production of some facial expressions. Facial expressions might affect sensor output when they cause substantial squinting or shift the eyeglasses. Future versions will aim to mitigate detection errors associated with downward gaze by using multiple IR emitter/detector pairs mounted on the glasses, and alternative frame designs may reduce shifting of the sensors in relation to the eye during facial movements.

2) Understanding neuromuscular excitability parameters in healthy and paralyzed individuals. By FES standards, bionic reanimation of the eyelids is a relatively simple, low-risk application. There are technical challenges (many of which are dealt with in this thesis), however the level of control needed to restore useful function is low and the consequences of system failure are tolerable. Blink restoration essentially involves single muscle (*orbicularis oculi*) acting in a binary fashion (relaxing when the eye is open or contracting to close it), that can either be paced or triggered by a readily accessible and robust command signal (the closing of the contralateral eye in patients with unilateral facial paralysis). If eye blink is not fully restored by the stimulation, the patient will not suffer any immediate physical harm (such as would result from a fall due to inadequate coordination in FES walking) and can simply be reverted to one of the pre-existing ophthalmic treatment methods for facial palsy. This makes the pursuit of FES-enabled eyelid reanimation a natural step in the current progression of clinical neuromuscular stimulation.

Excitability thresholds and effective stimulation parameters stricty depend on the neurophysiological state of nerves and muscles, and vary with the degree of muscle denervation. For this reason, a stimulation system created for individuals with Bell's palsy would not work when applied to patients with a denervated muscle. Patients with an elicitable nerve may benefit from nerve stimulation, while patients with a denervated muscle need a muscle stimulation at different (higher) stimulating current levels.

Supplement K describes a preliminary trial conducted in anatomically intact human volunteers. Epicutaneous stimulation of the left facial nerve branch for the *orbicularis oculi* was performed in order to elicit natural-like eyeblinks. Findings indicate that the best stimulation pattern for eliciting natural-like movement of the eye lids without discomfort is 100-200 Hz pulse trains. The desired eyelid acceleration (in the range of 1.4-5.1 m/s^2) was obtained by setting the most suitable carrier frequency (75-200 Hz). Dynamic properties of motoneurones were artificially reproduced and custom-fit biomimetic eyeblinks were facilitated.

An ongoing clinical trial on individuals experiencing paralysis of *orbicularis oculi* muscle, enrolled at 6-42 days from onset, represents a feasibility study of whether eyeblink can be elicited by surface electrical stimulation in this selected cohort of patients, and to obtain real-time sensation feedback from participants to determine whether stimulation would be tolerable for daily eye blink restoration (see Fig. 6.1.). By studying an initial 20 individuals (10 males and 10 females) we are establishing useful descriptive statistics regarding the average stimulation thresholds for initial twitch, complete closure, and the relationship between those thresholds and the corresponding level of stimulation discomfort (Wong-Baker Pain Rating Scale scores). Moreover, we are obtaining pilot data regarding the variability of these measures. Pulse train repetitions (see Fig. 6.2.) end for each stimulation location when one of three conditions have been met: 1) the highest stimulation value has been reached at the end of the pre-programmed repetitions (i.e. 15 mA), 2) complete eyelid closure has been achieved, or 3) the subject reports discomfort and wants the stimulation series to stop. Preliminary data indicate that the current threshold eliciting an eyeblink is 7-12mA pulse amplitude and that the best stimulation pattern is 150Hz pulse train frequency, with a first couple of pulses at 250Hz, pulse width 0.8ms, train duration 37-40ms. Nine participants have been studied so far and further experiments are needed.

Fig. 6.1.
Clinical trial: FES of the facial nerve in patients with acute facial palsy.

Pulse trains are defined in software (Clampex 10.2, Molecular Devices, LLC., Sunnyvale, CA), generated by a high-precision digital-to-analog converter (DigiData 1440A, Molecular Devices, LLC.) and amplified by a constant-current stimulator (STMISOL, BIOPAC Systems Inc., Goleta, CA). Pulse trains are repeated every second and begin at a sub-threshold amplitude. With each repeated stimulation train, the amplitude increases by a pre-determined delta level, and eyelid movement is recorded with a high-speed video camera. The relationship between stimulation parameters and cutaneous sensation is obtained using the Wong-Baker Faces Pain Rating Scale in a continuous manner throughout stimulation trials. Participants control a rotary knob mounted on a small hand-held plastic box which can be switched among 6 discrete knob positions. Each knob position represents a different level of sensation on the Wong-Baker Faces Pain Rating Scale, and illuminates a visual representation of the scale "faces" (continuum of happy to sad) in a sign located a few feet directly in front of the participant. This allows participants to maintain a forward gaze while continuously reporting what sensation (degree of discomfort) they are experiencing as repeated pulse train amplitudes are incrementally increased by the stimulation software. The different knob positions also generate different discrete voltage levels of an output signal that is sent to the data acquisition system so that subject pain scale responses can be saved in data files along with delivered pulse train characteristics and the video synchronization TTL signal.

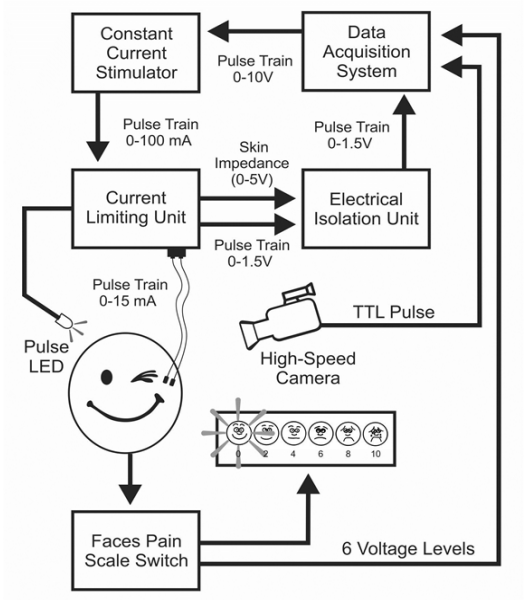
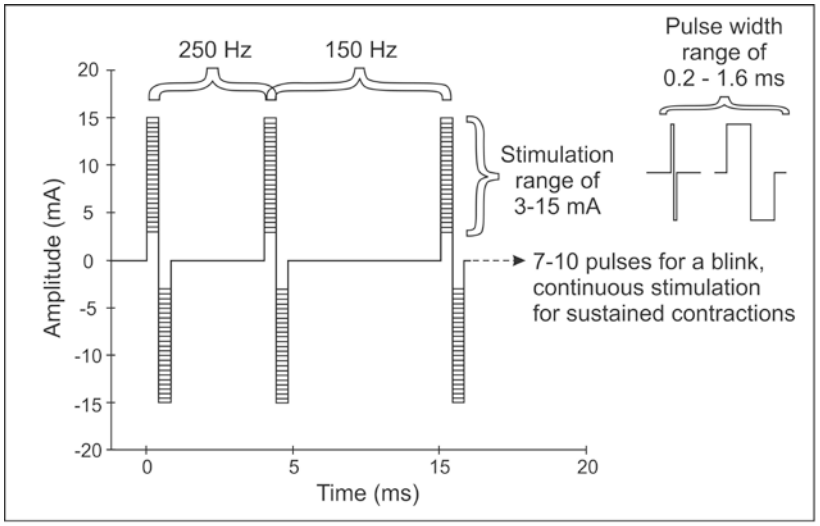


Fig. 6.2.

Illustration of the range of stimulation pulse train parameters for eliciting blinks. Pulses are biphasic, charge-balanced square waves ranging n pulse width from 0.2-1.6ms (see upper right). The inter-pulse interval for the first two pulses is 4ms (250Hz), and inter-pulse intervals are 6.666ms (150 Hz) thereafter. Stimulation amplitudes typically range from 3-15mA, shown here to vary in steps of 0.5mA acoss the range. Pulse train durations for eliciting a single blink range from 7-10 pulses, or are continuosly delivered when eliciting other facial movements (for the duration of the desired movement) with stimulation amplitude proportional to the extent of the movement (e.g. big smiles elicited with stronger stimulation than more subtle smiles.



Two factors might limit the envisioned FES application: 1) tolerability of stimulation in humans and 2) safety limits.

1) Tolerability of stimulation in humans. The most immediate question that must be addressed is whether the delivery of electrical stimulation pulses above the facial skin can cause adequate contraction of the *orbicularis oculi* muscle to elicit eyelid closure at tolerable stimulation levels. No human studies defining sets of stimulation parameters that can provide nearly complete to complete eyelid closure at tolerable stimulation levels were available until our first trial (see ***Supplement K***).

Moreover, the trial described in Fig. 6.1. is aimed at obtaining participant feedback regarding the relationship between electrical stimulation parameters at targeted face surface locations and the level/nature of sensation (i.e. *is effective stimulation too uncomfortable/painful for practical use in restoring blink?*). Participants are forewarned in the informed consent process that potentially painful electrical stimulation will be delivered to their face in an attempt to stimulate motor nerves controlling their eyelids. They are given the opportunity to terminate a stimulation series at any point in the study by asking that we stop during a stimulation series, or by defining a Wong-Baker Faces Pain Rating Scale rating that represents the greatest discomfort they are willing to experience. The Wong-Baker Faces Pain Rating Scale (Wong, D. and Whaley, L. 1986. Clinical handbook of pediatric nursing, ed., 2, p. 373. St. Louis: C.V.Mosby Company) is a popular visual scale featuring 6 facial expressions. These expressions help the patient express what kind of level of discomfort/pain they are experiencing. These expressions are often associated to a numerical category as follows:

- Face 0 is very happy because he doesn't hurt at all.
- Face 2 hurts just a little bit.
- Face 4 hurts a little more.
- Face 6 hurts even more.
- Face 8 hurts a whole lot.
- Face 10 hurts worst.

The subject can choose to have a given pain rating scale level automatically terminate the stimulation trial, and participants are able to terminate the stimulation at any point with a verbal request (e.g. "stop") regardless of their current rating scale level.
Preliminary data show that all delivered currents are tolerable by participants.
2) Safety. Electrical stimulation of superficial motor nerves to elicit muscle contraction can be accomplished safely and with little or no discomfort, but does present risks of pain or even tissue damage. The equipment used in our preliminary studies is commonly employed for human research and it is designed to stimulate sensory and/or motor responses through the skin surface without presenting risk of injury when used properly. Electrical stimulation can be characterized in terms of stimulation voltage (the force or push of the electricity into the person), current (the amount of energy conduced), and charge density (current per unit area of electrode contact). The first two characteristics are interrelated, and stimulation devices typically hold one aspect constant (voltage or current), while allowing the other aspect to vary. Because stimulation current is the aspect that can damage tissue, current is held constant in our current experiments while voltage varies according to what amount is needed to achieve the target current. For example, stun guns can deliver a continuous 500,000 volts to a person, but because they deliver very little current (<3mA), the stimulation has little or no lasting impact on body tissues. Likewise, static electrical shocks we experience in the dry winter months often exceed 30,000 V (and can be painful), but deliver little current and therefore cause no lasting harm. The stimulation current required to elicit complete eye closure (full blink) in anatomically intact individuals is approximately 4-5 mA. Prior research has demonstrated that the voltage required to generate this level of current through the skin is tolerable for most participants (*Frigerio and Cavallari, 2012*). However, the current required to generate complete closure in paralyzed individuals might be substantially higher than for intact individuals, and may therefore require uncomfortable/painful voltages. Our goal is to determine whether eliciting blinks is feasible in patients with acute facial nerve palsy, or if doing so requires stimulation levels that are too uncomfortable/painful to experience with each blink (i.e. about 20 per minute) and are therefore impractical. The upper limit of pulse train current delivered in our experiments is 15 mA. Although preliminary data show that complete closure is achieved in most individuals with acute facial palsy at stimulation levels below 15mA, and few people would be willing to tolerate stimulation above 15 mA for daily blink restoration. This upper limit will not be harmful, and is lower than currents typically delivered during a standard facial nerve functional testing (which all patients with acute palsy undergo as part of their medical care). Specifically, electroneuronography (ENoG) tests often deliver 20-25 mA of current to the face surface (above the facial nerve) in order to elicit maximal facial contractions, and can reach levels of 40 mA in the course of a test (Beck *DL and Hall JW, 2001*). The charge density limit in our study has been set at 0.5 μC/mm2/pulse. At a current of 15mA (the upper limit in this study), the charge density would be 0.05 μC/mm2/pulse for VIASYS Ag/Cl disposable rectangular electrodes, 0.48 μC/mm2/pulse for the BIOPAC EL254 electrodes (diameter 4mm) and 0.12 μC/mm2/pulse for the BIOPAC EL258 electrodes (diameter 8mm) that we are using. The charge density limit of 0.5 μC/mm2/pulse is more than four times lower than the amount anticipated to present a risk of injury to the skin coming into contact with the electrode(s), and therefore can be considered safe. For example, Merril et al. (*2005*) report that charge-balanced biphasic stimulation (like what we are currently delivering) does not cause significant tissue damage at levels up to 2 μC/mm2/pulse (*Merril et al., 2005*).

Electrical Stimulation Hardware. Transcutaneous electrical stimulation is delivered using a constant current stimulator (STMISOL; BioPac Inc). The stimulator receives a driving waveform (train of pulses) from a commercially available, high quality digital-to-analog converter (DigiData 1440A; Molecular Devices, Inc.). The stimulator delivers a bipolar constant-current output waveform matching the input waveform pattern, such that ±1 V input generates a ±10 mA output (current signal). The STMISOL stimulator is marketed by BioPac Inc. for human experimentation, but is not FDA approved as a medical device. Hardware safety precautions are in place to ensure that use of this device does not present a significant risk. The STMISOL

electrically isolates the research participant from potentially harmful input voltage (1500 VDC HiPot or Dielectric Withstanding Voltage), with 90 pF of coupling capacitance. When the stimulator is powered on, it enters a safety (operational but no output) state and requires that a Reset button be pressed for 3 seconds in order to enter a fully operational state. This prevents a participant from receiving stimulation on power-up or if the unit power should cycle on/off (either intentionally or not). Moreover, should the unit attempt to deliver a stimulus that exceeds ±200V, then it immediately enters a locked-out Protect state, and requires a manual reset before stimulation can continue. The unit can deliver a painful stimulation to the face prior to achieving the Protect state if the STMISOL receives an inappropriate (large) input signal, but the unit becomes locked-out before tissue-damaging current is applied. In other words, the worst-case scenario during face surface stimulation would be an instantaneous, painful shock, but without a burn or other lasting tissue effects.

Any physiological stimulator can potentially deliver a lethal electrical stimulation if current is passed through the heart. Multiple precautions are followed to ensure the cardiac safety of the research participant and experimenters in our protocol, including the following:

1. Prior to stimulating a participant, all pulse train programs is be pre-tested in a "phantom" testing run where a resistor (e.g. 50 K Ohm) is placed between the electrodes to simulate the human face. During the phantom testing, the volts delivered through the stimulation leads is monitored/recorded by the data acquisition system to verify the expected relationship between programmed pulse current and the volts delivered to achieve that current (in relation to the resistor representing the face). This ensures that the stimulation programs are error-free, and that the pulse generating hardware and stimulating hardware are working properly.
2. Stimulating electrodes are positioned no further than 3 cm apart from each other (center-to-center) on one side of the face, and never touch the body in a way that would direct current through the chest (e.g. not placed on the two limbs or held independently by two hands).
3. The stimulator remains in the Protect mode during electrode placement and is not put into the fully operational state (where output can occur) until after the electrodes are in their intended positions and the experimenter is no longer touching the electrodes or the participant.

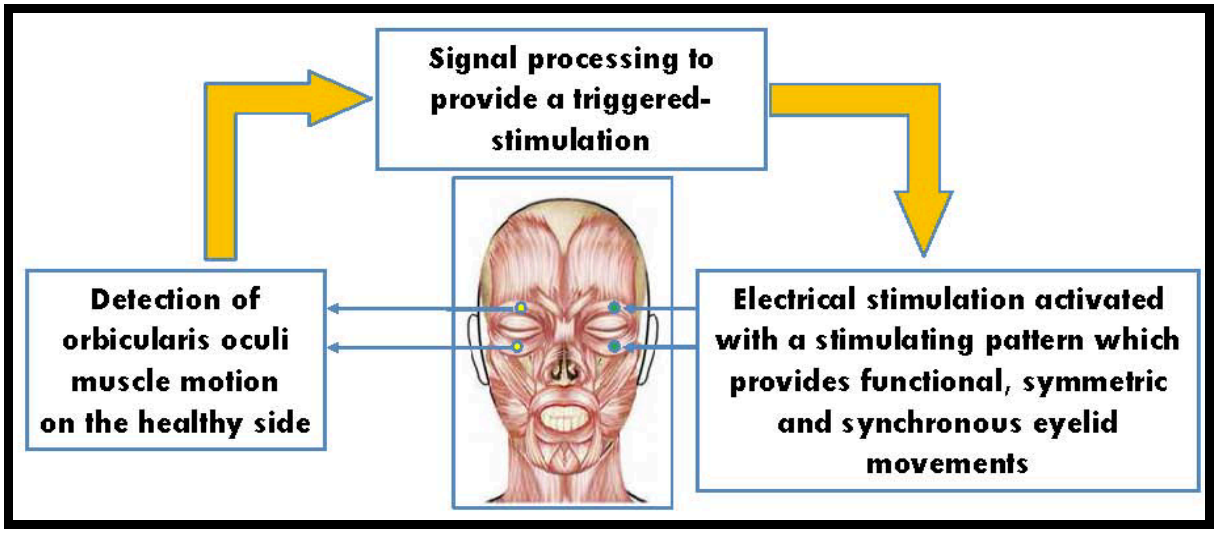
The last topic to discuss about is the controversial effect of FES on facial nerve regeneration and functional recovery. Recent studies describe that brief electrical stimulation immediately following crash injury enhances functional recovery of the rat facial nerve (*Foecking et al., 2012*). Farragher (*1987*) described a remarkable response to eutrophic FES in patients with apparentrly intractable Bell's palsy. Positive results have also been observed after long-term FES in patients with chronic facial paralysis (*Targan et al., 2000*). The methodological differences between available studies make comparisons difficult. In fairness, eyeblink restoration in the animal model should be studied taking into account the activity of the *retractor bulbi* muscle, that is still intact after facial nerve injury. We believe that investigation of the effects of FES on neuromuscular recovery should continue.

7. GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

Research in the area of electrical stimulation for eyeblink reanimation has demonstrated promising results in multiple animal studies that span as far back as 30 years. It is time to declare that this is no longer simply an interesting exercise in electrophysiological research and recognize it as grounds for development of an actual clinical system that can provide tangible benefit for these patients. Current treatment measures of facial palsy are often inadequate and medical technology has advanced too far to allow this to continue.

This thesis has explored:

1. the use of surface EMG recording as real-time eyeblink detection system;
2. the realization of an external prototypal device, for the detection of the eyeblink with IR sensors.
3. the use of surface FES of the facial nerve branch for the *orbicularis oculi* muscle as a means of eliciting eyeblink in healthy individuals who are meant to represent patients with facial paralysis.



The upcoming steps are:

1. Completing the feasibility study on the use of surface FES of the facial nerve branch for the *orbicularis oculi* muscle as a means of eliciting eyeblink in healthy individuals with acute recent facial paralysis.
2. Microcircuitry design and development, On the base of data gathered from clinical trials, stimulation and power circuits will be designed, followed by the controlled circuit through a microcontroller (firmware programmation included). At the end of the circuital project a protoboard (PCB, Printed Computer Board) will be printed. The list of the components necessary for the assembly of the

printed circuit will be defined. The design of the closed-loop device requires the creation of an ASIC with three distinct parts: the input filtering, the microcontroller with Printed Circuited Assembly (PCA), and the output circuit. The first part of the circuit must be able to collect the EMG or IR data from the spontaneous eyeblinks of non-palsied eye and filter any existing noise. From here, the signal enters a microcontroller, which decides (based on our program) whether a blink has occurred or not. When the microcontroller decides that a blink has occurred, it sends an output stimulus into the output circuit. The stimulating system is composed by a constant-current microstimulator, an isolation unit and stimulating electrodes.

3. Testing of the developed closed-loop prototype. A final clinical trial will be performed to test whether eye blink can be elicited by using the new developed closed-loop system in patients affected by recent facial palsy, and to get feedback regarding how the prototype works and if it can provide an effective and natural-looking eyeblink.

At the end of the above described journey, our project will hopefully be ready for a technological transfer.

If we think of facial palsy as of a dynamic phenomenon where the neurophysiologic state of muscles and nerves varies with time and from case to case, we can agree that the research conducted so far represents the tip of the iceberg. The bionic blink project leads the groundwork for the opening of a broad research field, potentially spanning from epicutaneous FES for apraxia (the case of a lucky Bell's palsy), to implantable epineural electrodes for irreversible nerve injury (for example an unlucky surgery), to implantable muscle electrodes for denervated muscles (i.e. loss of the nerve), to the artificial muscle for cases where the musculature is lost (like in long-standing paralysis). Moreover, multichannel systems could potentially assist different anatomical units of the face and thus rehabilitate forehead movements, eyeblinks, smiling and lower lid movements.

Finally, tissue engineering and regenerative medicine is an emerging interdisciplinary field that applies the principles of biology and engineering to the development of viable substitutes that restore, maintain, or improve the function of human tissues and organs. Tissue engineering science has provided critical new knowledge that will deepen our understanding of the phenotype of an important category of cell types-the muscle cells-and this knowledge may enable meaningful advances in musculoskeletal tissue engineering. There are two principle strategies for the replacement of impaired muscle tissues. One approach uses the application of isolated and differentiated cells (in vivo tissue engineering), using a transport matrix for the cell delivery; the other uses in vitro-designed and pre-fabricated tissue equivalents (in vitro tissue engineering). Future developments of this field include the elucidation of the relationships among cell growth and differentiation, the three-dimensional environment, the architecture of the cells, and gene expression of the developmental process and the survival of the cells and integration in the host in vivo experiments. As the techniques of tissue engineering become more sophisticated and as issues such as vascularization and innervation are addressed, the usefulness of these methods for reconstructive surgery may grow significantly and hopefully some application for the bionic reanimation of the face in individuals missing a viable musculature will be possible.

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