Orbital decompression in Graves’ orbitopathy: state of the art and novel perspectives
Baldeschi, L.

Citation for published version (APA):
Baldeschi, L. (2011). Orbital decompression in Graves’ orbitopathy: state of the art and novel perspectives
Graves' orbitopathy affects hundreds of thousands of people in the world every year. It causes pain, discomfort, double vision, disfigurement, and sometimes blindness. People suffering with Graves' orbitopathy have a poor quality of life and long-term psychosocial morbidity. The quality of care received by the majority of people affected by this condition can be improved. Conventional treatments are effective when used appropriately and by centers with expertise. Not all patients are offered effective treatments either because they present an atypical orbital appearance or are not referred at all. People at high risk of developing Graves' orbitopathy can be identified, and effective risk management can potentially lessen the severity of the disease.

The care of people with Graves' orbitopathy can be vastly improved by making centers of excellence more accessible to them.

In October 2009, international experts on Graves' orbitopathy, representatives of professional organizations, and patient representatives met in Amsterdam and unanimously agreed on the following:

Health care providers and professional organizations should recognize the need to improve the care of people with Graves' orbitopathy and support plans for implementing better care and prevention.

The general objectives are:

- To minimize the morbidity associated with Graves' orbitopathy and improve patients' experience and quality of life
- To prevent the development of Graves' orbitopathy in people at high risk

The specific targets are:

- Raise awareness of this condition among health care professionals and managers
- Establish pathways of referral and care
- Support existing centers of excellence in management of this condition
- Create new centers of excellence in localities where they are lacking
- Establish audit and monitoring mechanisms of quality assurance of provision of care to people with Graves' orbitopathy
- Implement measures to reduce the incidence and morbidity of the disease by:
  - Halving the time from presentation to diagnosis
  - Halving the time from diagnosis to referral to a center of excellence
  - Appropriate management of thyroid dysfunction including use of radioiodine
  - Vigorous antismoking measures in patients at risk of or with Graves' orbitopathy
- Improve the existing research networks and develop further international collaborative research

The Amsterdam Declaration (Thyroid 2010;3:351-2)
Orbital Decompression in Graves’ Orbitopathy:

State of the Art and Novel Perspectives
Orbital Decompression in Graves’ Orbitopathy:

State of the Art and Novel Perspectives

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. D.C. van den Boom

ten overstaan van een door het college voor promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 14 januari 2011, te 10.00 uur

doors

LELIO BALDESCHI

geboren te Pisa, Italië
Promotiecommissie

Promotores
- Prof. dr. W.M. Wiersinga
- Prof. dr. M.J.D. de Smet

Overige leden
- Prof. dr. D.A. Bosch
- Dr. G. Rose
- Prof. dr. G.P.M. Luyten
- Prof. dr. H.P. van den Akker
- Prof. dr. P.T.V.M. de Jong

Faculteit der Geneeskunde
This thesis is dedicated to Leo Koornneef one of the most bright minded and talented surgeons in the field of orbit and ophthalmic plastic surgery

“behind every problem lies an opportunity”

Galileo Galilei
Pisa 15 February 1564 - Florence 8 January 1642
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Preface

I am grateful to my patients and to many people who have helped me in different ways. I am grateful to my promoters whose constant advice and encouragement kept me going, and I am also grateful to those who could not be my promoters, but whose attitude provided me with positive motivations as well. I am also indebted to colleagues, ortoptists, paramedical and administrative personnel, and former fellows of the Department of Ophthalmology AMC all of them have never failed to lend me their support. I particularly thank my former secretary Mrs Ineke Ompi whose hard secretarial work was behind most of my publications. I wish to express my feelings of gratitude to all the friends of the NVGP, the EUGOGO, and the AMORE group AMC, all of whom I shared years of work and commitments. Marc Prummel has a special place among them. Twenty years back my ophthalmic plastic adventure started in London with Mr. Richard Collin and Mr. Geoffrey Rose and thereafter continued in Amsterdam with Professor Leo Koornneef. At that time I met other fellows and new colleagues, Professor Christoph Hintschich, Dr. Christopher Neoh and Dr. Jane Dickinson who have become friends for life. All these people have been instrumental in my professional and human development with their culture and friendship. Thank you! Finally, I of course thank my wife Antonella, our son Giovanni and my parents for their patience during the production of this thesis, and for being the never ending source of support and confidence which made my life so happy.
Introduction

Part I: General Introduction and Current Concepts on Decompression Surgery for Graves' Orbitopathy

1. A MISNAMED DISEASE WHICH CONTINUES TO REQUIRE SURGICAL ATTENTION
2. AN OVERVIEW OF GRAVES' "ORBITOPATHY AND ITS CURRENT MODALITIES OF TREATMENT: THE PLACE OF SURGERY
3. SURGERY FOR GRAVES' "ORBITOPATHY: THE PLACE OF ORBITAL DECOMPRESSION


4. ORBITAL DECOMPRESSION IN GRAVES' "ORBITOPATHY: STATE OF THE ART

Chapter 1

Introduction

Part I:

General Introduction and Current Concepts on Decompression Surgery for Graves’ Orbitopathy

1. A MISNAMED DISEASE WHICH CONTINUES TO REQUIRE SURGICAL ATTENTION

2. AN OVERVIEW OF GRAVES’ ORBITOPATHY AND ITS CURRENT MODALITIES OF TREATMENT: THE PLACE OF SURGERY

3. SURGERY FOR GRAVES’ ORBITOPATHY: THE PLACE OF ORBITAL DECOMPRESSION

4. ORBITAL DECOMPRESSION IN GRAVES’ ORBITOPATHY: STATE OF THE ART

Part II:

Outline and aims of this thesis
1. A MISNAMED DISEASE WHICH CONTINUES TO REQUIRE SURGICAL ATTENTION

The multi-systemic disease which may include autoimmune thyroid disorders, goitre, exophthalmos, pretibial myxedema, and acropachy has been recognized as such for a very long time.

According to Jan-Gustaf Ljunggren 1, a Persian physician, Sayyid Ismail Al-Jurjani was the first to have noted the association of goitre and exophthalmos in the 12th century, and reported his observation in Thesaurus of the Shah of Khwarazm, the most famous of his five books, and the major medical dictionary of its period.

In more recent times, the Italian anatomist and surgeon Giuseppe Flajani in 1802 2, followed by another Italian physician Antonio Giuseppe Testa in 1810 3 described "exophthalmic goiter", though it was earlier recognized by Caleb Hillier Parry in 1786 and reported in his "unpublished medical writings" which appeared 3 years after his death in 1825. 4

Robert James Graves in 1835 5, and the German Karl Adolph von Basedow in 1840 6 independently reported the constellation of signs and symptoms which typifies the disease.

Long before any description of the association between exophthalmos and goitre appeared in the medical literature, a clear iconographic report of the disease was already available. In 2003, a painting in an Etruscan grave of the fourth century B.C., found in Sarteano, a small village in the Tuscan countryside of Siena depicts clearly these manifestations (Figure 1). 7

Figure 1. A painting in an Etruscan grave of the IV century B.C. in Sarteano, Siena, Italy. Charun the demoniac creature who transferred the defunct to the Ade, the Etruscan beyond, is depicted on his quadriga, as a patient with Graves' hyperthyroidism, and orbitopathy (left photo). The grave is named after this picture as "the grave of the infernal quadriga". An enlargement of the Charun's head and neck regions (right photo) clearly shows the presence of exophthalmos, lid retraction, frown, hyperaemic eyelids, cheek and lips. The presence of the goitre is further emphasized by the shadow behind the figure. (Photographs Civic Archeologic Museum of Sarteano; courtesy of Dr. Alessandra Minetti, reproduced with permission of the "Soprintendenza per i Beni Archeologici della Toscana").

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![Figure 1](image1.png)

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As manifestation of the disease, orbital involvement has been given a multitude of names, including: thyroid eye disease, autoimmune orbitopathy, thyroid related or dysthyroid orbitopathy / ophthalmopathy, Basedow’s or Graves’ orbitopathy / ophthalmopathy. All of them are misnomers as they lack etiopathogenetic precision or eponymic priority. Until the pathogenesis of the disease is known and a more specific nosologic nomenclature is available, this bizarre orbital disorder should at least respect eponymic priority. For this reason, the adjective “Etruscan” should be mentioned when defining this orbitopathy and conversely the thyroid disease. This logical but regionalistic suggestion, however, might not sound appropriate to the international character of the two large consortia which at present are committed to research in the field of this disease, and which are both already named after it as European Group on Graves’ Orbitopathy (EUGOGO) and International Thyroid Eye Disease Society (ITEDS). Additionally, just for a coincidence..., it might appear parochially motivated by the Tuscan birth and Etruscan ancestry of the writer, together with the medieval but still strongly deep seated Ghibelline vicinity of Pisa, the author’s home town, to Siena.

By an astonishing twist of fate, and the serendipitous location of the Etruscan painting, Graves’ orbitopathy (GO), fulfils the writer’s proposal in part, that such a definition is maintained in this PhD thesis. This is also consistent with the writer being a member of EUGOGO. The painting in the Sarteano grave in which Charun is depicted resembling a patient with Graves’ disease and GO (Figure 1) suggests that the somatic alterations and psychosis due to untreated hyperthyroidism might have already in that ancient culture been a source of prejudices resulting in social isolation for the affected patients.

Visible deformity, particularly involving the face, has always induced society’s aversion. Patients with facial disfigurement suffer from intrusions such as staring or comments. At the root of the patient’s distress lies a social pressure to conform to an idealized appearance. This obsession with appearance in our culture devalues those who do not match the perceived ideal and stigmatizes those with visible disfigurement. Despite the long-lasting social implications and medical recognition of GO, its exact pathogenesis remains unknown. As a consequence a specific medical therapy is lacking,
Chapter 1

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Despite the long-lasting social implications and medical recognition of GO, its exact pathogenesis remains unknown. As a consequence a specific medical therapy is lacking, and for many patients orbital surgery continues to represent an essential cornerstone in the treatment of their disabling and socially alienating disease.

2. AN OVERVIEW OF GRAVES' ORBITOPATHY AND ITS CURRENT MODALITIES OF TREATMENT: THE PLACE OF SURGERY

GO is an autoimmune disorder representing the most frequent and important extrathyroidal expression of Graves' disease. It may also be found, although less frequently, in patients with no present or past history of hyperthyroidism (so-called euthyroid or ophthalmic Graves' disease) or in patients who are hypothyroid due to chronic autoimmune (Hashimoto's) thyroiditis. In most affected individuals GO is mild and self-limiting, and only in 3-5% of cases, it is severe and potentially sight-threatening. The exact pathogenesis of GO is unknown. It is, however, worth highlighting the clear-cut link between the orbit and the thyroid, because this has important clinical and therapeutic implications. In addition to endogenous (non-preventable) factors, such as genetics, age- and gender-related factors, GO occurrence and progression are influenced by environmental (preventable) factors, such as cigarette smoking, thyroid dysfunction, and different treatments for hyperthyroidism. This implies that control or correction of these risk factors is an integral part of GO management.

Independently of the complex association with thyroid dysfunction and its treatment, management of GO is difficult: decisions need to be made regarding the need for specific treatment or whether spontaneous regression is likely. The natural history of GO is of gradual increase in severity followed by a plateau phase then gradual improvement. These are the active phases. The inactive phase follows with no change in severity. GO is thus self-limiting, although it often does not return to baseline. Treatment is aimed at accelerating recovery, preventing serious sequelae, and eventually functional and cosmetic rehabilitation.

Therapeutic options consist of medical therapy, radiotherapy, surgery, or frequently a combination of these. Consensus as to indications and timing of these options has been reached by the EUGOGO consortium (Figure 2). More specifically the role of orbital decompressions in the state of the art rehabilitative surgery has been published in the
Figure 2. Management of Graves’ orbitopathy. Rehabilitative surgery includes orbital decompression, squint surgery, lid lengthening, and blepharoplasty/browplasty. i.v. GCs, intravenous glucocorticoids; OR, orbital radiotherapy; DON, dysthyroid optic neuropathy.25, 26

The next two sections of this chapter describe these further.

3. SURGERY FOR GRAVES’ ORBITOPATHY: THE PLACE OF ORBITAL DECOMPRESSION

Graves’ orbitopathy (GO) is a debilitating disease which adversely interferes with the quality of life of affected patients.27 It is characterised by different degrees of disfigurement and alterations in vision, both of which contribute to loss of self-confidence, psychosocial stability and ability to function.

In GO, surgery, which may be necessary to protect visual function in the active phase of the disease or to correct the stable typical disfigurement and symptoms in the static post-inflammatory phase, should always be considered rehabilitative as it is aimed at restoring the individual integrity disrupted by the disease and ultimately the lost ability to function.

Commonly, however, surgery performed primarily to treat potentially sight threatening conditions such as optic neuropathy or exposure keratopathy is referred to as functional, while procedures primarily aimed at correcting disfigurement and symptoms are referred to as rehabilitative. For didactic purposes, we like to maintain this distinction between

Figure 3. A patient affected by left, moderate severe, not-active GO with exophthalmos, mild restrictive esotropia and large angle restrictive hypotropia. An upper lid aponeurotic ptosis was also present left side. The general health condition of the patient and his scarce cooperation suggested to reduce as much as possible the number of surgical interventions. (a) Upon admittance for simultaneous orbital decompression and strabismus correction. (b) Five weeks after left deep lateral wall decompression through an upper skin crease approach followed by recession of the left inferior rectus muscle in the same surgical session. An adequate reduction of exophthalmos was achieved and the field of binocular single vision extended for more than 20° around primary position of gaze.
functional and rehabilitative surgery, although it is necessary to admit that besides the above-listed semantic considerations, a clear-cut distinction between the two does not exist as surgery aimed primarily at restoring function also has positive effects on disfigurement and vice versa.

The definition cosmetic surgery, which does not stress the impact of the orbital disease in affected patients, appears inadequate and should be avoided. Surgery is in fact aimed at restoring a patient’s appearance as closely as possible to that preceding the onset of GO, and not at changing his or her somatic tracts to make them more beautiful. Cosmetic/aesthetic rehabilitation has often been used and can be considered an acceptable compromise when defining surgery mainly aimed at correcting disfigurement due to GO.

Figure 3. A patient affected by left, moderate severe, not-active GO with exophthalmos, mild restrictive esotropia and large angle restrictive hypotropia. An upper lid aponeurotic ptosis was also present left side. The general health condition of the patient and his scarce cooperation suggested to reduce as much as possible the number of surgical interventions. (a) Upon admittance for simultaneous orbital decompression and strabismus correction. (b) Five weeks after left deep lateral wall decompression through an upper skin crease approach followed by recession of the left inferior rectus muscle in the same surgical session. An adequate reduction of exophthalmos was achieved and the field of binocular single vision extended for more than 20° around primary position of gaze.
3.1. **What Are the Steps and Timing of Rehabilitative Surgery?**

During the post-inflammatory phase of GO, after a 6- to 8-month stable endocrinological and ophthalmic clinical picture, surgical rehabilitation can be performed if required. Depending on the severity of the disease, surgical rehabilitation can be more or less extensive, the full treatment consisting of decompression surgery, squint surgery, eyelid lengthening, blepharoplasty and eyebrow plasty.

The first rehabilitative step mainly consists of orbital bony decompression and early intervention soon after stabilisation has been advocated. Fibrosis due to long-lasting orbital disease or as a possible consequence of retrobulbar irradiation administrated in the early phase of GO has been questioned as a possible cause of poor distensibility and plasticity of the soft orbital tissues, resulting in scarce effectiveness of orbital expansion surgery. Recent studies, however, have demonstrated that long-lasting GO or preoperative radiotherapy do not adversely interfere with the results of orbital bony decompression; thus, when the stabilisation of Graves’ disease and orbitopathy has occurred, rehabilitative surgery can be started at any time and no adverse effects from common preceding treatments such as retrobulbar irradiation are to be expected. Decompression surgery causes a reduction in exophthalmos as well as reduction in upper and lower eyelid displacement. It may positively influence extra-ocular muscle restriction, but displacement of the soft orbital tissues caused by decompression procedures may also cause strabismus. Possible squint surgery should therefore follow orbital decompressions, but considering that vertical tropias may influence eyelid position, squint surgery should precede possible correction of eyelid position. Finally, when necessary, the finishing touch can be given by eyebrow lift, forehead plasty and blepharoplasty.

In short, surgical rehabilitation needs to respect the given order since the preceding step may influence the necessity and the extent of the step that follows. When all the steps are necessary, the entire rehabilitation may require between 1.5 and 2 years. In particular cases, exceptions are possible and the rehabilitation can be favourably speeded-up by carrying out more than one procedure at the same time (Figure 3). The traditional management algorithm has not been respected in only a few series, and simultaneous decompression and strabismus surgery (in severe orbitopathy) or simultaneous decompression and correction of upper eyelid retraction (in mild to moderate, or in moderate to severe orbitopathy).
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3.2. How Should Patients Be Selected for Rehabilitative Surgery?

Patients should be selected on the basis of their motivation to undertake a long-lasting, potentially risky, and somewhat exhausting trail. Multiple interventions may also be necessary in cases where full treatment, starting with orbital decompression, is not required. Patients should be fully aware of the risks and benefits of each possible procedure and should accept the possibility of partial results or temporary worsening of their inability to function in the course of rehabilitation. Information provided by the physicians, although precise, may be inadequate to the patients, and potential candidates for surgery can better build up realistic expectancies by contact with patient associations. The psychological impact of GO on the affected patient is consistent, but should not itself be a reason to undertake a surgical treatment with potentially distressing effects in the same respect. It is up to the physician to understand when the patient has matured the adequate consciousness to be admitted to surgical rehabilitation, and the ophthalmologic controls necessary to assess disease stability should also be finalised according to this. Besides the patient’s determination to accept major surgeries, the possibility to aim for only partial results should always be weighed in the light of patients’ characteristics, such as age, general health conditions, profession, education and psychosocial environment. Often conservative surgery is of maximal benefit to the patient, in spite of modest final results that may be unattractive to the surgeon.
4. ORBITAL DECOMPRESSION IN GRAVES’ ORBITOPATHY: STATE OF THE ART

4.1. What Is Orbital Decompression?

The autoimmune process at the basis of Graves’ orbitopathy (GO) induces swelling of the soft tissues contained within the boundary of the bony orbit, this causes impairment of the venous out flux towards the cavernous sinus and reverses the flux in direction of facial circulation. This positive feedback circle leads to an increase in the intraorbital pressure which is first responsible for the progression of GO and later for its typical signs and symptoms. Any surgical procedure aimed at decreasing the raised intraorbital pressure and its effects by means of enlargement of the bony orbit and/or removal of the orbital fat is defined as orbital decompression.

4.2. What Are the Aims of Orbital Decompression?

For one century decompression surgery has been used to treat GO. First it was used only to address sight-threatening conditions such as optic neuropathy refractory to medical therapy, or exposure keratopathy unresponsive to local measures, and/or minor eyelid surgeries. More recently, the indications of orbital decompression were extended to the treatment of disfiguring exophthalmos and symptoms. Eyeball subluxation (which may be a possible cause of acute optic neuropathy and exposure keratopathy), postural visual obscuration in patients with congestive inactive GO and choroidal folds due to eyeball indentation by enlarged extraocular muscles represent other more recently recognised functional indications for decompression surgery.

*Functional Aims*

According to a large retrospective study, decompression surgery can offer a rapid solution to dysthyroid optic neuropathy with an acceptable list of adverse effects (Figure 4).
Chapter 1

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**Functional Aims**

According to a large retrospective study, decompression surgery can offer a rapid solution to dysthyroid optic neuropathy with an acceptable list of adverse effects (Figure 4). A more recent randomised controlled clinical trial comparing surgical to medical decompression as a first-line treatment for dysthyroid optic neuropathy led to the conclusion that immediate decompression surgery did not result in a better outcome in terms of increased visual acuity, and therefore intravenous followed by oral glucocorticoids appeared to be the first-choice therapy. In line with these latter results, the same trend was shown by clinicians from three European professional organisations potentially involved in the treatment of patients with GO, in response to a questionnaire sent by the European Group on Graves' Orbitopathy (EUGOGO). In GO exophthalmos, increased palpebral fissure width, blink rate alterations, lid lag, lagophthalmos, deficit of elevation and poor Bell's phenomenon can all be potentially connected with drying of the ocular surface. In the course of active GO, ocular surface damage correlated significantly with a reduced tear secretion due to autoimmune lacrimal gland impairment, but not with increased ocular surface or impaired upgaze. Other studies had shown that in patients with a short duration of GO, tear secretion was not abnormal and exophthalmos, lid lag and lagophthalmos did not correlate with ocular surface damage, while the damage to the ocular surface depended principally on a widened...
palpebral fissure, which is the cause of increased ocular surface evaporation resulting in an elevated tear film osmolarity similar to that of sicca keratoconjunctivitis. The influence of decompression rehabilitative surgery on increased eyelid aperture has recently been reported. A decrease in eyelid aperture based equally on decreased upper and lower lid displacement was found in about 50% of the patients presenting with preoperative increased eyelid aperture and decompressed by means of a 3-wall coronal approach which leaves the upper and lower lid retractors undisturbed.  

The effect of decompression surgery on severe corneal alteration had never been studied specifically, and although most of the studies on orbital decompression report a reduction in symptoms associated with exposure keratopathy, a case of severe corneal ulcer refractory to decompression surgery has also been published.  

Eyeball subluxation is a rare (0.1%) recurrent complication of GO that deserves urgent referral to a specialist centre as it represents a potential cause of visual loss. In light of the current literature, eyeball subluxation seems to occur in the type I, ‘lipogenic’ variant of GO as described by Nureny and never in the type II ‘myopathic’ variant. Globe subluxation in fact requires extensibility of the extraocular muscles. For this, it is conceivable that a definitive treatment of this sight-threatening condition can benefit either from bony and/or orbital fat decompression, but studies addressing this issue are lacking.  

Among patients with inactive congestive orbitopathy there appear to be some with borderline optic nerve perfusion: a blood flow that is just able to maintain neural function. Such patients can present with recurrent visual obscuration associated with transient postural hypotension; diabetics appear particularly susceptible to this phenomenon. The vascular embarrassment of the optic nerve depending on elevated intraorbital pressure is very effectively relieved by orbital decompression and leads to an immediate cessation of postural visual obscuration.  

Organised choroidal folds consecutive to eyeball indentation by enlarged extraocular muscles had been thought to be refractory to orbital decompression until recently when a positive response of this complication to bony decompression surgery has been reported.  

4.3. Which Surgical Technique Should Be Preferred?  

The raised intraorbital pressure and its consequences can be surgically addressed by expansion of the bony orbital boundary and/or by means of fat removal. For about one century, the two possibilities developed through parallel routes; only recently did it become clear that they should no longer be considered alternatives but complementary approaches concurring in tailoring the most adequate treatment to the specific patient’s needs (Figures 7, 8). Through the years, there have been many proposed techniques and variations. This has been largely due to the multifaceted nature of the disease, the different indications for decompression surgery, surgeon preferences and expertise, variations in orbital osteology, and patients’ expectations and attitude towards intervention. Furthermore, the constant attempt to implement the beneficial effects of this type of surgery while simultaneously decreasing the aesthetic impact of surgical scars, convalescence periods and
Rehabilitative Symptomatic Aims

In GO, severe functional complications due to increased intraocular pressure are rare, different degrees of venous congestion, strabismus, eyelid puffiness and retraction, exophthalmos, and symptoms such as retroocular pressure and/or grittiness due to chronic corneal exposure are more frequent. Decompression surgery is the mainstay method to treat stable disfiguring alterations and/or symptoms that can typify the inactive post-inflammatory phase of the disease (Figure 5). Decompression surgery is not necessarily required only when exophthalmos exceeds the normal reference range. Patients with a flat forehead, scarce brow bossing, and scarce anterior projection of the zygomatic eminence or patients with deep-set eyes before GO may be or feel disfigured at normal exophthalmometric values (Figure 6). Evaluation of pre-GO facial photographs may help the surgeon to restore a patient’s appearance as close as possible to how it was before the onset of orbital disease. Most of the studies dealing with orbital decompressions have indicated that this type of surgery is associated with lessening of the subjective perception of retro-ocular tension. In the early 1990s, Khan et al.\textsuperscript{53}, using the McGill pain questionnaire and visual analogue scales, specifically addressed this issue, and, although their study was not free of biases, it seemed to confirm that orbital discomfort significantly responded to orbital decompression.

4.3. Which Surgical Technique Should Be Preferred?

The raised intraorbital pressure and its consequences can be surgically addressed by expansion of the bony orbital boundary and/or by means of fat removal. For about one century, the two possibilities developed through parallel routes; only recently did it become clear that they should no longer be considered alternatives but complementary approaches concuring in tailoring the most adequate treatment to the specific patient’s needs (Figures 7, 8).\textsuperscript{54-56} Through the years, there have been many proposed techniques and variations. This has been largely due to the multifaceted nature of the disease, the different indications for decompression surgery, surgeon preferences and expertise, variations in orbital osteology, and patients’ expectations and attitude towards intervention. Furthermore, the constant attempt to implement the beneficial effects of this type of surgery while simultaneously decreasing the aesthetic impact of surgical scars, convalescence periods and
Chapter 1

Figure 5. A patient with moderately severe non-active GO. (a) The patient upon admittance for orbital decompression. (b) The patient at the end of the surgical rehabilitation which included bilateral transinferior conjunctival fornix inferomedial orbital decompression, upper lid lengthening by means of transconjunctival Müllerectomy, and upper lid blepharoplasty.

Figure 6. A patient affected with GO, and presenting a flat forehead, and a scarce anterior projection of the zygomatic eminence. The patient appears disfigured by exophthalmos although her exophthalmometric value is only 18 mm.

risks for iatrogenic complications in general, and consecutive strabismus in particular, has further extended the case scenario (Figures 8-12).

Every type of fat removal or osteotomy has been hypothesized to cause critical relief of pressure at the apex, which can be beneficial for optic nerve dysfunction. The current
Figure 7. Bone removal in course of transinferior conjunctival fornix inferomedial orbital decompression.

Figure 8. Orbital fat removal. Lpectomies can be performed alone or may precede or follow osteotomies in the course of the same intervention. Preventive fat removal can be sufficient to adequately reduce exophthalmos and can aid bone exposure, thus easing the possible osteotomies that may follow. Fat removal following bone decompressions aids to increase the reduction in exophthalmos. (a) Removal of fat from the inferior lateral orbital quadrant as part of a combined transinferior conjunctival fornix inferomedial bone/inferior lateral fat decompression procedure. (b) Removal of fat from the inferior medial orbital quadrant during an extensive three-wall/fat decompression procedure performed through a combined transinferior conjunctival fornix and coronal approach.

trend is, however, to directly relieve the apical pressure as much as possible by increasing the apical volume of the bony orbit. This is obtained by removing the medial orbital wall (Figure 10b).56 In particularly severe cases, preventive removal of the lateral wall including its rim can prove convenient (Figure 10 a). Forces exerted by retractors in an attempt to
achieve apex decompression along the medial orbital wall can increase the already high retro-bulbar pressure up to critical levels for optic nerve fibres and vasculature. The preventive removal of the lateral orbital wall permits surgeons to address the deepest orbit more smoothly, reducing the risk of adding an iatrogenic component to the pathologically high orbital pressure at the basis of the neuropathy. There are several possible options to remove the medial orbital wall, but transconjunctival routes (either transcaruncular or transinferior fornix), which leave no visible scars are currently preferred. The endoscopic transnasal approach, described first and relatively recently by Kennedy et al., addressing the orbital apex without any substantial increase in the intraorbital pressure can also be a valid alternative that can even be performed under local anesthesia.

During the last three decades, when the number of rehabilitative orbital decompressions started to rise, it became of primary importance to balance a given technique in terms of not only effectiveness in reducing exophthalmos, but also (and mostly) in terms of safety. In the early 1980s, the antral-ethmoidal decompression by a transantral approach, as described by Walsh and Ogura in 1957, was the mainstay technique. The major disadvantage reported with transantral surgery was a subsequent motility imbalance as high as 52%, and therefore alternative procedures were sought in an attempt to decrease the risk of decompression-induced diplopia. In cases of mild exophthalmos, trans-lid antral-ethmoidal decompression appeared to be a valid alternative, with a risk of iatrogenic diplopia in only 4.6% of patients. For more severe exophthalmos, infero-medial decompression was used in combination with lateral decompression. Such procedures were also related with a low incidence of consecutive diplopia. In 1989, Leone et al., in an attempt to further reduce post-decompression strabismus, proposed balancing the decompression by removing the medial and lateral orbital walls while sparing the floor. This technique, which theoretically should have minimised the risk of iatrogenic diplopia, later appeared to be associated with a higher risk of such a complication compared with removal of the lateral orbital wall alone, or with inferomedial and three-wall surgeries.

At present the medial wall, the orbital floor and the lateral wall continue to be addressed during bony decompression surgery (Figure 10), while orbital roof removal has been abandoned due to the fact that its contribution to orbital expansion is minimal and associated with potential complications and side effects. Although orbital floor removal in
the course of orbital decompression is currently not favoured in North America, a recent prospective survey of the European Group on Graves’ Orbitopathy (EUGOGO) showed that inferomedial bone decompression is still a widely used procedure in Europe. Depending on the severity of exophthalmos, the effect of inferomedial decompression can be implemented by adding lateral wall decompression and/or removal of the fat, usually of the inferior lateral orbital quadrant (Figures 8, 11). In view of reducing postoperative diplopia, an opposite sequence which involves firstly the removal of the lateral wall, associated or not to fat excision, and secondly, if necessary, the removal of the medial and inferior walls has been suggested. This strategy represents a significant conceptual departure from the traditional approach, which began with inferomedial decompression, and suggests regarding the lateral orbital wall and in particular its deep portion as being the region of first choice for orbital decompression in the case of rehabilitative surgery (Figure 10a). Removal of the lateral orbital wall - which appears to be connected with a low risk of consecutive diplopia or severe complications, such as cerebrospinal fluid leak - perfectly fits the needs of the increasingly demanding patient population. It was recently reported that removal of the deep lateral wall as part of a rehabilitative coronal-approach 3-wall decompression gives a 32% enhancement in exophthalmos reduction without increasing the risk of consecutive diplopia as compared with traditional more conservative 3-wall decompression. The same study, however, confirmed the known high interindividual variability in the volume of the deep lateral wall. In light of this, the deep lateral wall is to be considered an effective although not always available zone of possible orbital volume expansion when dealing with rehabilitative decompression surgery. The effect of pure lateral wall decompression on exophthalmos reduction may be modest if not associated with medial wall removal, but in this case the risk of consecutive diplopia arises, while the result of lateral wall decompression can be augmented by intraconal fat removal without substantially increasing the risk of iatrogenic strabismus. On the contrary, removal of the lateral orbital wall and intraconal fat was beneficial in reducing preoperative primary gaze diplopia.
Figure 9. Common surgical incisions for orbital decompression: (1) coronal; (2) ‘Lynch’; (3) upper skin crease; (4) lateral canthus; (5) sub-ciliary; (6) inferior fornix; (7) direct translower lid; (8) transcaruncular; (9) transnasal; (10) transoral; (4+6) swinging eyelid.

Figure 10. Common zones of bone removal for orbital decompression. (a) Axial projection of an orbital CT scan which highlights possible lateral wall osteotomies: conservative anterior (red), deep (green), extended (red + green), total (blue). (b) Coronal projection of an orbital CT scan which highlights possible osteotomies: inferior (yellow), medial (red), inferomedial (yellow + red).
Figure 11. Schematic representation of sites for orbital lipectomies reachable (yellow) or not (blue) through hidden transconjunctival incisions (red line) superimposed on a periorbital region photograph of a patient with GO (a) and on a coronal projection of an orbital magnetic resonance scan taken at the level of the middle orbit in a patient with GO (b). The fat compartment of the superior lateral quadrant (blue) can be exposed only through transcutaneous incisions; however, it is not used as an elective site for lipectomy because it hosts delicate structures and its removal gives a minimal contribution to fat decompression surgery.

Figure 12. A patient with moderate non-active GO and documentation of his intervention. (a) The patient upon admission for orbital decompression. Exophthalmos, hypoglobus, and lower lid displacement right side were present. (b) The patient 3 months after superomedial transcutaneous-septal fat decompression performed through an upper skin crease approach. Exophthalmos, hypoglobus, and lower lid displacement were adequately treated. (c) Surgical site. The skin and the orbicularis oculi muscle are retracted. An aperture through the orbital septum (white arrow heads), which is kept open with a cotton tip applicator following partial removal of the superomedial extraconal fat, shows (from left to right): medial margin of the levator palpebrae superioris muscle aponeurosis (blue arrow), anterior margin of the superior oblique muscle tendon (white arrow), intracanal fat (yellow arrow), and belly of the medial rectus muscle (red arrow). (d) Fat removed from the superomedial orbital quadrant at the end of surgery.
Rehabilitative decompression surgery aimed at addressing the tiresome retroocular tension that may characterise the postinflammatory stage of GO\textsuperscript{53} can be performed with minimally invasive techniques leading to minimal, if any, impact on extraocular motility or complications in general.\textsuperscript{74}

Pure orbital fat decompression was first described by Moore in 1920.\textsuperscript{75} From the 1980s, Olivari has used and popularized fat decompression.\textsuperscript{39, 76-78} After a publication (in German) reporting on a small series of 9 patients\textsuperscript{76}, he presented a larger series of 75 patients (147 orbits) and reported a mean exophthalmos reduction of 5.9 mm, an improvement in all the operated patients presenting with preoperative diplopia, and a complete resolution of diplopia in 55\%.\textsuperscript{77} In such a series, new-onset permanent strabismus was observed in 14.3\%, and an additional 57\% of patients not presenting with pre-decompression diplopia experienced transient double vision up to 6 months after surgery.\textsuperscript{77} The same results have not been fully confirmed by other authors. With fat removal orbital decompression, Trokel \textit{et al.}\textsuperscript{79} (in a series of 81 patients, 158 orbits) did not have any cases of permanent induced diplopia and on average restrictions in extraocular eye motility ameliorated; however, only a modest reduction in exophthalmos could be attained. It was on the order of 1.8 mm, and rose to 3.3 mm only in patients with preoperative Hertel measurements of >25 mm.\textsuperscript{79} In terms of exophthalmos reduction, better results than those were reported by Adenis \textit{et al.}\textsuperscript{80} who obtained an average reduction in exophthalmos of 4.7 mm, with complications limited to extraocular eye motility disturbances, but the incidence of new-onset diplopia of this series rose to 22.2\%. In 2003, the same author\textsuperscript{81} found even a higher incidence of new-onset diplopia (32\%), in a study specifically aimed at evaluating the occurrence of such a complication after fat removal orbital decompression performed by using a similar technique to the one proposed by Olivari. Based on such results, Adenis \textit{et al.}\textsuperscript{81} concluded that the risk of new-onset diplopia after fat removal orbital decompression was similar to the average risk reported for bone decompression surgery.

A more recent series of 222 Asian orbits treated by means of fat removal orbital decompression through a swinging eyelid approach, however, showed promising results in terms of effect on extraocular eye motility with an incidence of new-onset diplopia of only 2\% and cure of double vision in 20\% of the patients affected by that before surgery.\textsuperscript{82} The authors explained these results and a lower mean exophthalmos reduction (3.6 mm), as
compared with the series of Adenies et al.\textsuperscript{81}, on the basis of differences in surgical techniques used and in anatomy between the Asian and Caucasian orbits.\textsuperscript{82}

Simultaneously with the Asian series, the group of Olivari reported on their 20-year experience with trans-palpebral fat decompression by presenting a monumental series of 2,697 operations.\textsuperscript{78} Although the mean exophthalmos reduction remained similar to the earliest study of the mentor of this group\textsuperscript{77}, persistent new-onset diplopia requiring surgical or prismatic correction later than 6 months after surgery rose to 22.2\%.\textsuperscript{78}

Despite the discrepancy in the amount of exophthalmos reduction and effects on extraocular eye motility, overall fat removal orbital decompression has proven to be a safe procedure through the years, and its positive effects also include improvement in visual function and reduction in intraocular tension when elevated secondary to raised intraorbital pressure.\textsuperscript{39, 58, 83} It appears to be an effective procedure mostly indicated in moderate-to-severe cases of lipogenic exophthalmos and periocular disfigurement due to fat prolapse and venous congestion, although it has also been used as a standard approach to any type of functional or rehabilitative orbital decompression (Figures 12, 13).\textsuperscript{39, 76-83}

During recent years, the combination of bone decompression associated with fat removal (Figure 8) has been gaining popularity in view of its reported safety and increased effectiveness as compared with bone or fat decompression alone.\textsuperscript{54-56}

Beveled osteotomies and onlay alloplastic periorbital implants - although sporadically used to camouflage more than to reduce exophthalmos - remain of uncertain effectiveness\textsuperscript{84-86}, and their edges, not infrequently visible, may devalue the final rehabilitative cosmetic result.

Most of the techniques currently used seem to be effective either in restoring impaired vision, and eye position or reversing congestive symptomatology and disfigurement of the periorbital region. An unbiased analysis of the current literature in terms of effectiveness versus safety, however, is extremely difficult because of the great heterogeneity of the patients included in the published studies; differences in definitions and methodologies used to study patients before decompression and to assess results after surgery; variations applied to surgical techniques that while falling under the same general definition may be completely different concerning surgical route, modality, location, and amount of removed bone or fat. Furthermore, it should be noted that the evidence of the literature concerning
rehabilitative decompression surgery is modest, and mostly based on retrospective case series.

As a result, most of the current speculations regarding the reliability and effectiveness of different techniques for decompression surgery are lacking conclusive proof. In an attempt to estimate the effectiveness of various surgical techniques, a prospective comparison of different treatment modalities along with different decompression surgeries - using a powerful tool, such as the Graves’ orbitopathy quality of life questionnaire (GO-QoL) - was advocated, and recently carried out by the EUGOGO consortium. The study showed that, except in rare cases where a tailored approach was offered to the patients, the choice of surgical technique continues to be based on the surgeon’s personal experience and local tradition. With such an attitude, exophthalmos reduction, complications, side effects, and patient satisfaction were largely comparable, and independent of the chosen technique. In light of this, if one technique fits all, and the surgeon’s experience and local tradition are the factors which regulate the choice of technique in decompression surgery, there is no doubt that minimally invasive approaches are to be preferred.
Although the average results may be largely comparable regardless of the surgical technique used, forcing patients into standardised surgical frames is suboptimal as a standardised approach may produce unsuitable results for the single patient. Ideally, the planning of decompression surgery should comply with the patient’s expectations and needs, and should be matched to the patient’s anatomical and pathological substrates and possible previous surgeries. In clinical practice, this desirable approach to orbital decompression, which may involve the use of several different surgical techniques, is possible only in centres where adequate referral and a long-lasting tradition in orbital surgery favour transmission of expertise and warrant adequate back-up, whilst offering the possibility to develop new techniques or to master ongoing variations of others. As this cannot be the case in most of the centres dealing with GO, the use of a standardised versatile approach is to be regarded as an acceptable although suboptimal alternative.

The swinging eyelid approach described first by McCord in the early 1980s - with the conjunctival incision that can be extended medially as much as necessary, offering an adequate access to the bony orbit and to the orbital fat compartments - is a versatile technique that can be used for the majority of patients needing decompression surgery. As an alternative, inferior and medial conjunctival fornix and upper skin crease incisions can be used separately or in combination (Figures 9-12).

In 2003, Cruz and Leme questioned whether the coronal approach continues to have a role in orbital decompression and concluded that there is little, if any, need for this technique. Although the study design and the results of their paper could not offer strong support to their conclusions, it is easy to share their doubts about using an invasive approach, such as the coronal incision, as a standard route for orbital decompression.

Minimally invasive approaches and hidden periorbital incisions are currently preferred (Figures 5, 9, 11-13); nevertheless, the coronal incision is not to be abandoned as it can be an additional tool in surgeons’ hands when dealing with patients who can benefit more from a tailored approach than a standardised one. There are many circumstances in which this may happen. These include the presence of remarkable periorbital swelling or conjunctival chemosis, the necessity of minimising the number of periorbital incisions, or the necessity of extensive manipulation of the lateral wall (including its rim). Through
a coronal incision, brow lift, and correction of frontal/glabellar rhytids, which are often necessary in patients with GO, can be performed simultaneously with orbital decompression; thus, favourably speeding-up the timing of rehabilitative surgery.\textsuperscript{89, 92}

4.4. What Are the Possible Complications of Orbital Decompression?
Orbital fat decompression has never reached the popularity of bone decompression due to the theoretical (more than real) complications that may potentially be connected with this approach and which encompass damages to oculomotor ciliary and lacrimal nerves, orbital vasculature, extraocular eye muscles, optic nerve and the eyeball itself.\textsuperscript{80} Also, in the case of bone orbital decompression, in spite of theoretical expectations, severe complications are rare in clinical practice. Common complications of this surgical approach are consecutive strabismus, infraorbital hypoesthesia and sinusitis\textsuperscript{93}, lower lid entropion\textsuperscript{94}, and eyeball dystopia\textsuperscript{95}, while leakage of cerebrospinal fluid, infections involving the central nervous system, damage to the eye and optic nerve or their vasculature, cerebral vasospasm, ischaemia and infarction are severe but rare events.\textsuperscript{42, 96} Reactivation of GO after rehabilitative bony orbital decompression is another rare complication very recently described in 3 of 239 patients not treated with perioperative glucocorticoids. The phenomenon consisted of the onset of typical signs and symptoms of active GO with radiologic evidence of extraocular muscle enlargement a few weeks after surgery and following a normal convalescence period. Based on its clinical characteristics, the observation was named delayed decompression-related reactivation (DDRR). The incidence of DDRR appeared to be in the order of 1.3\% and could be controlled with systemic immunosuppression or retrobulbar irradiation.\textsuperscript{97}

In addition to complications common to orbital decompressions in general, different surgical approaches and routes may carry the risk of specific complications. The second branch of the trigeminal nerve may be damaged in the course of orbital floor removal decompression. This may potentially induce the formation of traumatic or amputation neuromas. Such lesions, although rare, should be included in the potential complications of decompressions when counselling patients about to undergo this type of surgery, as they are difficult to treat and may cause persistent and disabling pain.\textsuperscript{98}
into the nasal cavity and scarring of the nasal mucosa with meatal and sinus obstruction, mucocele and sinusitis can occur with endoscopic endonasal approaches.\textsuperscript{99, 100}

The coronal approach leaving the eyelid undisturbed is less likely than periorbital incisions to create complications which may potentially be harmful to the eye. Periorbital scarring with iatrogenic lid retraction and cicatrical lagophthalmos, eyelid margin malpositions and ptosis (although rare) are more likely to occur with periorbital incisions. On the other hand, temporal bossing, damage to the frontalis nerve, scarring and alopecia at the site of the scalp incision, or effects upon ischemic areas of the frontal flap after healing by secondary intention may complicate the coronal approach.\textsuperscript{89}

The coronal approach should not be considered a more hazardous technique as compared with the less invasive periorbital incisions. The more serious complications connected with the coronal approach have been reported in small series where less than 3 patients per year were operated upon.\textsuperscript{90, 101}

### 4.5. Can Complications Be Predicted or Prevented?

Most of the possible complications cannot be predicted and their prevention is based on recommendations which are not specific in nature, and which include careful manipulation of the orbital content, accurate dissection of the orbital fat, and avoidance of expandable haemostatic agents and/or extensive use of diathermy within the orbit.

Other complications with known pathogenesis such as sinusitis can be simply prevented by taking care to create an adequate sinus aeration as a part of the surgical procedure at the time of bone decompression.

The occurrence of other complications, namely infraorbital hypoesthesia or pain, eyeball dystopia leakage of cerebrospinal fluid and possible consecutive infectious involvement of the central nervous system, can be reduced by means of accurate evaluation of preoperative imaging, adequate planning of surgical intervention and the use of prophylactic antibiotics.

Strict observance of this methodology helps detecting patients at an increased risk of possible complications. A low lamina cribrosa for instance should be regarded as a possible source of cerebrospinal fluid leakage for those patients planned for medial wall decompression. Late-onset enophthalmos and hypoglobus can be prevented simply by avoiding inferomedial decompression when dealing with patients recognised to be at higher risk due to their anatomical substrate. The complication had in fact been described as
dependent on prolapse of orbital fat into the ethmoidal infundibulum in the presence of a predisposing anatomy which includes septal deviation to the affected side and eventual abnormal middle turbinate whose inferior part, directed laterally, also crowds the maxillary infundibulum.95

Diplopia has a considerable impact on the quality of life of patients with GO, and is a feared complication that often prevents patients and physicians from undertaking decompression rehabilitative surgery. In light of the current literature, strabismus subsequent to decompression surgery has been linked to mechanical and neurological implications connected with the ‘lipogenic or myopathic’ types of GO50, the surgical route, the extension and location of the osteotomy, and the preservation of structures such as the maxillary ethmoidal strut or the anterior periorbit. Differing types of motor and/or sensory capacities for compensation of induced muscle imbalances may also play a role.33 A better understanding of all of the possible factors involved in the pathogenesis of diplopia consecutive to decompression surgery may help its prevention.
Outline and Aims of this Thesis

In 1999 the European Group on Graves Orbitopathy (EUGOGO) was established in Amsterdam in an attempt to contribute to a better understanding of the immunopathogenesis of Graves’ orbitopathy and to improve the frequently unsatisfactory outcomes in patients affected by this disease. This was followed by years of preparation and extensive internal discussions before any multicentric clinical studies could be started. Since the beginning, as ophthalmic delegate from one of the involved centres (University of Amsterdam) and founding member of the Group, I had the privilege to participate in the debates. The limitations in methodology and the scarce evidence of the available literature concerning the ophthalmic surgical management emerged frequently during that period, and were later confirmed in published reviews on the subject. “Time honoured axioms” and misleading statements also appeared in this same literature.

The studies which are included in this thesis were designed and conducted with the purpose of highlighting and possibly amending some limitations, flaws, or unproven concepts in the accepted literature within the field of decompression surgery (chapters 2-4); to critically evaluate and review its current trends regarding osteotomies and approaches (chapters 5, 6); to analyse the abnormal “situations” affecting GO patients about to undergo or who have undergone decompression surgery and whose investigations might have contributed to a better understanding (chapters 7, 8) and management (chapters 9-10) of this debilitating orbital disease.

This latter purpose was specifically included into the present thesis to show that the value of orbital surgery can go beyond its practical results and most importantly as a tribute to the far-sightedness of Professor Leo Koornneef, the mentor of Dutch orbital surgery, to whom this thesis is dedicated. Long ago, he recognised the value of multidisciplinarity, which continues to inspire the work of the EUGOGO consortium and to motivate initiatives such as the Amsterdam declaration. In his words: “The pathogenesis of Graves’ orbitopathy is still poorly understood. Through research into the normal and abnormal situations, approached by different disciplines, might elucidate the problems and enable better management to prevent this disfiguring disease.”
Chapter 2 discusses the effect of early versus late intervention on the outcomes of rehabilitative decompression surgery. The study aimed at investigating whether a group of patients with long standing disease and possible subsequent fibrosis of the soft orbital tissues had different surgical outcomes as compared with a group of patients decompressed by means of the same surgical technique and with similar baseline characteristics except for having received earlier decompression surgery.

Chapter 3 is concerned with the effect of pre-decompression administered orbital radiotherapy on the outcome of rehabilitative decompression surgery. The study aimed at investigating whether a group of patients who received pre-decompression radiotherapy (which could have been a possible cause of subsequent fibrosis of the soft orbital tissues) had different surgical outcomes as compared with two other groups of patients decompressed by the same surgical technique and with similar baseline characteristics except for having received systemic glucocorticoids or a combination of orbital radiotherapy and systemic glucocorticoids in the active phase of the disease preceding rehabilitative decompression surgery.

In chapter 4, a prospective observational case series is presented regarding a novel evaluation for the outcome of a graded bone removal of the infero-medial orbital wall in patients with GO. Outcomes of the novel appraisal were also compared with the results which could have been detected in the same cohort using a traditional methodology. The novel evaluation method consisted in scoring whether the targets (amount of desired exophthalmos reduction, improvement of retroocular tension, reduction of peri-orbital swelling / oedema, resolution of lagophthalmos) established before surgery were indeed achieved; in characterizing the cohort of included orbits and patients, and their sub-groups with indices which could readily identify: a) invasiveness of surgery to which they were exposed, b) score in target achievement, c) influence of surgery on central binocular vision; in performing comparisons after stratification of the included orbits for amount of desired exophthalmos reduction and invasiveness of surgery. Traditional methodology examined the entire series as a single homogeneous cohort which underwent rehabilitative surgery with infero-medial decompression independently of the different invasiveness of surgery.
In chapter 5, a case control study is presented on the contribution of the popular deep lateral wall orbital osteotomy on rehabilitative exophthalmos reduction in GO and the influence of such a procedure on the onset of consecutive diplopia.

In chapter 6, a review is presented on the indications, advantages, disadvantages, reported complications and their possible causes, of small versus coronal incisions in orbital decompression surgery. Practical implications associated with the choice of a standardized surgical approach as opposed to customized one are also discussed.

In chapter 7, an observational case series and retrospective follow-up study is presented on the incidence, clinical presentation, clinical course and treatment of previously unreported decompression induced reactivation of GO. Eventual pathogenetic hypothesis of this phenomenon are discussed and correlated to those of GO.

In chapter 8, the case of a patient who was a possible candidate for orbital decompression is presented. He was affected by X-linked childhood cerebral adrenoleukodystrophy and developed Graves’ hyperthyroidism and GO after a whole bone marrow transplantation from his sister. She was not affected by Graves’ hyperthyroidism at the time of bone marrow transplantation, but developed the condition thereafter. As in the preceding chapter, pathogenetic hypotheses are discussed and correlated to those of GO.

In chapter 9, the case of a patient affected by GO, and presenting with a CT and biopsy proven presence of a supernumerary extraocular muscle enlarged because of the orbitopathy and co-determinant of restrictive strabismus, is presented underscoring the importance of an accurate preoperative assessment to avoid diagnostic and surgical mistakes.

In chapter 10, the case of a patient affected by GO who developed a traumatic neuroma of the infraorbital nerve subsequent to inferomedial orbital decompression is presented. The causative mechanism of traumatic neuromas are discussed and, the relevance to mention
Chapter 1

this previously unreported cause of trigeminal neuralgia when counselling patients about to undergo inferomedial decompression is stressed.

In chapter 11, a historical perspective, associated with an overview on the most recent technical innovations in the field of orbital decompressions, and an analysis of the current possibilities of implementation for this type of surgery, are used as a framework for the discussion of the previous chapters. Their contribution to patient care, research and new perspectives in the field of orbital decompression surgery, along with their input towards a basic science approach to GO are critically reviewed.
REFERENCES

1. Ljunggren JG. Who was the man behind the syndrome: Ismail al-Jurjani, Testa, Flagani, Parry, Graves or Basedow? Use the term hyperthyreosis instead. Lakartidningen 1983;80:2902.


8. www.eugogo.eu

9. www.thyroideyedisease.org


42. Rose GE. Postural visual obscurations in patients with inactive thyroid eye disease; a variant of “hydraulic” disease. Eye 2006;20:1178-85.


Chapter 2
Early versus Late Orbital Decompression in Graves' Orbitopathy
A Retrospective Study in 125 Patients

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Ophthalmology 2006;113:874-8
Chapter 2

Early versus Late Orbital Decompression in Graves’ Orbitopathy
A Retrospective Study in 125 Patients

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Abstract

Purpose: To determine if early rehabilitative orbital decompression in Graves’ orbitopathy (GO) leads to a more effective postoperative outcome than the same intervention performed at a later, more likely, fibrotic stage.

Design: Retrospective comparative case series.

Participants: The medical records of all GO patients treated with a 3-wall orbital decompression at our institution between 1990 and 2000 were reviewed retrospectively. Only patients operated bilaterally for aesthetic rehabilitation, without preoperative diplopia, were included. They were divided into group 1 (duration of GO < 4 years) and group 2 (duration ≥ 4 years).

Methods and Main Outcome Measures: The 2 groups were compared for demographics, smoking habits, preoperative characteristics (immunosuppressive treatments, Hertel values, score in NOSPECS [no signs or symptoms, only signs, soft tissue involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight involvement] class 2, degree of extraocular muscle enlargement), and surgical outcome (mean reduction of exophthalmos, symmetry of exophthalmos reduction, reduction in upper and lower lid retraction, any persistent periorbital swelling requiring cosmetic eyelid surgery, postdecompression diplopia).

Results: The medical records of 125 of 376 patients were selected for this study. There were no differences between group 1 (n = 70) mean GO duration (2.2±0.8 years) and group 2 (n = 55) mean GO duration (9.0±5.4 years) with respect to demographics, smoking habits, and preoperative characteristics except for the degree of extraocular muscle enlargement, which was significantly greater in group 1 (P = 0.039). There was no difference in surgical outcomes between the 2 groups, with the exception of postdecompression diplopia, which was significantly more frequent in group 1 than in group 2 (29% vs. 13%, P = 0.033).

Conclusions: In GO, early rehabilitative orbital decompression does not improve surgical outcome and is associated with a higher risk of postdecompression diplopia.
Introduction

Graves’ orbitopathy (GO) is an inflammatory disorder characterized by autoimmune activity against orbital fibroblasts and adipocytes.\textsuperscript{1-3} The increased volume of the extraocular muscles, orbital connective tissues, and adipose tissues that develops leads to a mass effect, and may cause venous obstruction and congestion. Orbital fibrosis, which characterizes the final stage of GO\textsuperscript{4-7}, is a consequence of the long-lasting inflammatory and congestive involvement of the soft orbital tissues.

Prompt restoration of euthyroidism and, when necessary, immunosuppression represent the front line in the management of GO.\textsuperscript{1,8} Unfortunately, medical therapy alone is insufficient for many patients, and surgical intervention may be required for psychosocial rehabilitation and/or functional reasons. Rehabilitative surgery mostly consists of minor eyelid procedures, but in more severely affected patients, orbital decompression has to be considered.

Orbital compliance, which refers to the distensibility and plasticity of the orbital tissues, is reduced by orbital fibrosis in patients with GO.\textsuperscript{9} Reduced orbital compliance more likely occurs in the later stages of GO and may diminish the effectiveness of orbital expansion surgery due to the fact that orbital soft tissues can fail to prolapse maximally into the newly created spaces.\textsuperscript{10} The relationship between duration of GO at time of surgery and results of decompressive procedures, although incidentally mentioned\textsuperscript{11,12}, has never been specifically studied.

This study aimed to determine whether early orbital decompression is associated with a better postoperative outcome in terms of reduction of exophthalmos, symmetry in reduction of exophthalmos, reduction of periorbital swelling, reduction of eyelid retraction, and occurrence of the most frequent complication—namely, postdecompression diplopia.

Patients and Methods

Our study is a retrospective comparative case series. The medical records of all the patients affected by GO and treated with a 3-wall orbital decompression performed via a coronal approach at the Orbital Centre, Department of Ophthalmology, University of Amsterdam between January 1990 and December 2000 were evaluated retrospectively. Institutional review board approval was not required for this study.
Chapter 2

Inclusion Criteria
We included all patients (1) who were operated bilaterally for aesthetic rehabilitation and (2) who did not present with preoperative diplopia within 20° of the central position of gaze.

Exclusion Criteria
We excluded patients (1) who were operated unilaterally; (2) who were decompressed for optic neuropathy or exposure keratopathy; (3) who presented with preoperative diplopia; (4) who had been treated with iodine 131 in the 6 months preceding decompression or in the 6 months preceding postoperative evaluation; and (5) whose records did not clearly state (a) duration of GO at decompression, (b) smoking habits at surgery, (c) use of predecompression immunosuppressive treatments such as systemic corticosteroids and/or orbital radiotherapy, (d) results of an immediate preoperative clinical examination, including standard ophthalmological evaluation, NOSPECS (no signs or symptoms, only signs, soft tissue involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight involvement) classification, Hertel exophthalmometry, measurements of eyelid fissure, and the respective upper and lower eyelid positions, (e) results of at least one postoperative clinical examination performed ≥ 6 months after surgery, and (f) results of preoperative and postoperative orthoptic evaluations performed respectively not earlier than 6 months before decompression and between 3 and 6 months after surgery.

The following data were retrieved: (1) gender, (2) age at surgery, (3) duration of GO at decompression, (4) smoking habits at surgery, (5) use of predecompression immunosuppressive treatments, (6) preoperative Hertel values, (7) preoperative score in NOSPECS class 2, and (8) preoperative presence of upper and/or lower lid retraction with measurements of eyelid fissure and the respective upper and lower eyelid position. In addition to these, the degree of preoperative extraocular muscle enlargement was evaluated on coronal projections of orbital computed tomography scans, when available, and scored by a panel of 3 independent observers using a semiquantitative scale as absent, minimal, moderate, or severe. In case of discrepancy, the highest score was considered.

We considered as smokers those patients who were smokers on admission to the hospital at the time of surgery. The rationale for this choice is that in our center the clinical workup preceding rehabilitative orbital decompression consists of several ophthalmologic and
endocrinologic examinations. At all times, patients who smoke are strongly invited to give up smoking. We assume that those patients who maintain their habits up to the time of decompression despite multiple health warnings will not refrain from smoking after surgery.

The postoperative data that we used to assess the surgical outcome were (1) reduction of exophthalmos, (2) symmetry of exophthalmos reduction, (3) occurrence of reduction of upper and/or lower lid retraction when these signs were present before surgery, (4) persistence of periorbital swelling requiring cosmetic eyelid surgery, and (5) occurrence of postdecompression diplopia.

Based on the duration of the orbitopathy before decompression, the included patients were divided into 2 groups. Patients were included in group 1 when the duration of the orbitopathy before decompression was < 4 years and in group 2 when it was ≥ 4 years. The 4-year duration was chosen arbitrarily as a cutoff point because, in our view, such an interval may represent a reasonable border between the dynamic inflammatory phase and the static fibrotic stage of GO.

Demographics, smoking habits, and preoperative and postoperative data were compared between the groups by means of a database created in SPSS 11.5.2 Statistics UK (SPSS Inc., Chicago, IL). Right and left sides were not evaluated separately. Preoperative Hertel readings, NOSPECS class 2 score, and preoperative eyelid positions were the values measured at hospitalization for orbital decompression.

We considered as postoperative Hertel readings and postoperative eyelid positions the values measured at the first clinical examination carried out ≥ 6 months after surgery. For those patients presenting with a predecompression score ≥ a (mild) in NOSPECS class 2, persistence of periorbital swelling, implying the necessity for postdecompression cosmetic surgery, was defined as evidence in the medical record of upper or lower lid blepharoplasty proposed or performed at any time after orbital decompression. The presence of postoperative diplopia was assessed from the first orthoptic examination performed between 3 and 6 months after surgery.
CHAPTER 2

Statistical analysis
For univariate comparisons, Student’s t test was used to compare continuous variables. In case of ordinal or non-normally distributed variables, the Mann-Whitney U test was used. Categorical preoperative and postoperative data were investigated using the $\chi^2$ test.

Surgical Technique
All the patients included in this study underwent standardized 3-wall decompression via a coronal approach, as is performed traditionally at our institution. A coronal incision was made with a no. 10 blade from ear to ear, 3 to 4 cm behind the hairline. In the central portion of the skull, a subperiosteal plane was created by blunt dissection, and laterally, a surgical plane was developed bluntly between the deep and superficial temporalis fasciae. The forehead flap thus created was then turned down to expose the superior and lateral orbital rims. The supraorbital nerve was set free by chiseling its bony foramen, when present, and the periorbita, including the trochlea, was dissected off the orbital bones. After this, the temporalis muscle was dissected from its anterior origin with a no. 10 blade and periosteal elevators, leaving sufficient tissue for suturing at the end of surgery. In this way, the lateral orbital wall was exposed. A small osteotomy was chiseled behind the lateral orbital rim, and bone-nibbling rongeurs were used to remove the middle portion of the lateral orbital wall. After this, a Frazier suction tip was used to fracture the delicate bone of the medial orbital wall and the floor, and Blakesley forceps nos. 1 and 2 were used to remove bony fragments and sinuses’ mucosa. The bulla ethmoidalis beneath the frontoethmoidal suture was opened towards the orbit from the posterior lacrimal crest up to the orbital apex, and then the orbital floor medial to the infraorbital canal was removed from 0.5 cm behind the inferior orbital rim up to the posterior wall of the maxillary sinus. The posterior two thirds of the maxillary ethmoidal strut was removed, creating a wide antrostomy, whereas the anterior one third of the strut was left intact to prevent globe displacement and the possibility of medial entropion or hypoglobus.
Finally, the periorbita was incised to promote maximal prolapsed of the orbital tissues into the newly created spaces, the temporalis muscle was sutured back into position with 4 to 5 interrupted 2/0 Mersilene sutures (Ethicon, Inc., Somerville, NJ), and after the insertion of a 3.3-mm-diameter end-perforated wound drain into each temporalis fossa, the scalp incision was closed with iron staples.
Results

Medical records of 125 of 376 patients were selected for this study; 251 were excluded because they did not meet the inclusion criteria or the necessary data were not recorded.

Demographics, Smoking Habits, and Preoperative Characteristics

There were no differences between group 1 (n = 70) and group 2 (n = 55) with respect to demographics, smoking habits, or preoperative characteristics, except for the degree of extraocular muscle enlargement, which was significantly greater in group 1 (P = 0.039) (Table 1).

Table 1. Demographics, Smoking Habits, and Preoperative Characteristics in Group 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>&lt;4 yrs (n=70)</th>
<th>≥4 yrs (n=55)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>93%</td>
<td>93%</td>
<td>P = 0.978</td>
</tr>
<tr>
<td>Age at surgery (yrs ± SD)</td>
<td>40.0 (9.2)</td>
<td>40.4 (10.9)</td>
<td>P = 0.836</td>
</tr>
<tr>
<td>Duration of GO at surgery (yrs ± SD)</td>
<td>2.2 (0.8)</td>
<td>9.0 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>56%</td>
<td>54%</td>
<td>P = 0.471</td>
</tr>
<tr>
<td>Preoperative immunosuppression:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>14%</td>
<td>11%</td>
<td>P = 0.301</td>
</tr>
<tr>
<td>Orbital radiotherapy</td>
<td>27%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids and orbital radiotherapy</td>
<td>16%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Neither corticosteroids nor orbital radiotherapy</td>
<td>43%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Hertel values (mm) (± SD)</td>
<td>21.8 (2.5)</td>
<td>22.5 (2.5)</td>
<td>P = 0.415</td>
</tr>
<tr>
<td>Score in NOSPECS class 2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6%</td>
<td>15%</td>
<td>P = 0.312</td>
</tr>
<tr>
<td>a</td>
<td>63%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>30%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>1%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Degree of extraocular muscle enlargement:†</td>
<td></td>
<td></td>
<td>P = 0.039</td>
</tr>
<tr>
<td>absent</td>
<td>54%</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>minimal</td>
<td>27%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>16%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>3%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

GO = Graves' orbitopathy; NOSPECS = no signs or symptoms (class 0); only signs (class 1); soft tissue involvement with symptoms and signs (class 2); proptosis (class 3), extraocular muscle involvement (class 4), corneal involvement (class 5), sight involvement (class 6); SD = standard deviation.

*On the basis of a semiquantitative scale (0, absent; a, mild; b, moderate; c, severe).
†Only when coronal projections of orbital CT scan were available: <4yrs (n=56); ≥4yrs (n=39).

Surgical Outcome

There were no statistically significant differences in mean reduction of exophthalmos and symmetry of exophthalmos reduction between the 2 groups. When the predecompression score in NOSPECS class 2 was ≥ a, there were no statistically significant differences
between the 2 groups in persistence of postdecompression periorbital swelling requiring upper or lower lid blepharoplasty. The occurrence of reduction of upper and lower lid retraction also did not differ statistically when these signs were present before surgery. In contrast, the occurrence of postdecompression diplopia was significantly (\( P = 0.033 \)) more frequent in group 1 (Table 2), the relative risk and risk difference for decompressioninduced diplopia being 2.3 and 18.1%, respectively.

### Table 2. Postoperative Outcome

<table>
<thead>
<tr>
<th></th>
<th>&lt;4 yrs ((n=70))</th>
<th>≥4 yrs ((n=55))</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exophthalmos reduction (mm ± SD)</td>
<td>4.5 (1.8)</td>
<td>4.2 (1.9)</td>
<td>( P = 0.456 )</td>
</tr>
<tr>
<td>Symmetry in exophthalmos reduction</td>
<td>≤1mm (87%)</td>
<td>≤1mm (89%)</td>
<td>( P = 0.739 )</td>
</tr>
<tr>
<td></td>
<td>&gt;1mm (13%)</td>
<td>&gt;1mm (11%)</td>
<td>( P = 0.502 )</td>
</tr>
<tr>
<td>Occurrence of reduction of upper lid retraction *</td>
<td>58%</td>
<td>50%</td>
<td>( P = 0.771 )</td>
</tr>
<tr>
<td>Occurrence of reduction of lower lid retraction †</td>
<td>65%</td>
<td>62%</td>
<td>( P = 0.911 )</td>
</tr>
<tr>
<td>Persistence of post-decompression periorbital swelling requiring cosmetic surgery ‡</td>
<td>50%</td>
<td>49%</td>
<td>( P = 0.033 )</td>
</tr>
<tr>
<td>Post-decompression diplopia</td>
<td>29%</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>

* Only patients who presented with this sign before surgery: <4yrs \((n=48)\); ≥4yrs \((n=24)\).
† Only patients who presented with this sign before surgery: <4yrs \((n=48)\); ≥4yrs \((n=47)\).
‡ Only patients who presented with predecompression score in NOSPECS (no signs or symptoms, only signs, soft tissue involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight involvement) Class 2 ≥ a: <4yrs \((n=66)\); ≥4yrs \((n=47)\).

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**Discussion**

To the authors’ knowledge, the literature that evaluates the relationship between results of decompressive procedures and duration of the orbitopathy at surgery is scarce. At present, the assumption that links early intervention with more attractive results is hypothetical, often mentioned at meetings, and based on the natural course of the orbital disease.

McCord\(^{14}\) quantified the result of aesthetic orbital decompression by measuring the retrodisplacement of the globe in 23 patients. They concluded that the amount of retrodisplacement varied and depended strictly on orbital fibrosis, but neither duration of the orbitopathy at surgery nor explanations of the method to determine orbital fibrosis were given. Härtling et al.\(^{11}\) advocated early intervention without providing data to support their preference. Kalmann et al.\(^{12}\) reported no significant relation between duration of GO and the amount of proptosis reduction after 3-wall orbital decompression in 250 orbits.
However, because that study was not carried out specifically to evaluate this particular aspect, patient characteristics according to duration of the orbitopathy were not given, and the mean duration of the orbital disease was only 4.35 years. Male gender, old age, and heavy smoking habits are patient characteristics that are known to be associated with a more severe orbital disease\textsuperscript{15-17}, whereas preoperative Hertel values have been regarded as a factor influencing the amount of exophthalmos reduction.\textsuperscript{12}

The 2 groups compared in this survey did not differ with respect to gender, mean age at surgery, or smoking habits. Because other predecompression characteristics, such as Hertel values, NOSPECS class 2 score, and use of immunosuppressive treatments also did not differ, it is conceivable that the 2 groups were not dissimilar in either severity of GO at surgery or its activity during the active phase of the disease. In addition, based on our inclusion criteria, only patients decompressed for aesthetic reasons and not presenting with diplopia within 20° of the central position of gaze were included. Therefore, groups 1 and 2 can be considered to be composed of a homogeneous population of Graves’ patients, only differing in duration of the orbitopathy at decompression. The observed difference in preoperative volume of the extraocular muscles is, in fact, just the tomographic representation of the different pathophysiological periods that characterize the 2 groups. Therefore, it should be regarded as a consequence of the duration of the orbitopathy in group 1 and 2, rather than a self-standing characteristic of the groups.

Our retrospective observations did not show any statistically significant correlation between duration of the orbitopathy at decompression and (1) reduction of exophthalmos, (2) symmetry of exophthalmos reduction, (3) persistence of postdecompression periorbital swelling requiring postdecompression cosmetic surgery, and (4) amelioration of upper or lower lid retraction, whereas in our series patients decompressed within 4 years from the onset of the orbitopathy seemed to run a higher relative risk of postdecompression diplopia than patients decompressed later than 4 years.

The higher frequency of postdecompression diplopia in group 1 can be explained by the greater preoperative enlargement of the extraocular muscles in this group as compared with group 2, despite similar preoperative Hertel values in the 2 groups. This implies a more consistent contribution of the extraocular muscle mass to exophthalmos in group 1. Therefore, it is feasible to deduce from the similar reduction of exophthalmos that was achieved in the 2 groups that, for group 1, there was a more consistent shift of extraocular muscles.
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muscles into the spaces newly created by decompression surgery. This could have led to a
greater decompensation of extraocular muscle balance in group 1. Differing motor and/or
sensory capacities for compensation of induced muscle imbalance between the 2 groups
also may have played a role. Further investigations are required to clarify this.
In conclusion, in contrast to the assumption that early intervention is related to a more
desirable surgical outcome, our observation links early intervention with a higher risk of
postdecompression diplopia. Our results, however, are far from conclusive, because the
study might have been biased by systemic corticosteroid use, orbital radiotherapy, and
relatively low preoperative Hertel values. The immunosuppressive effect of corticosteroids
and/or radiotherapy has influenced the pathophysiological course of the disease and might
have reduced the final orbital fibrosis in about half of our patients. On the other hand, the
toxicity of radiation therapy to soft tissues, which includes fibrotic sequelae, might have
reduced the distensibility and plasticity of the soft orbital tissues, decreasing the effect of
decompression surgery. In addition, the low mean preoperative Hertel values in the 2
groups can be regarded as the epiphenomenon of a minimally to moderately increased
intraorbital pressure, which reasonably induced only mild congestion, leading to scarce
final fibrosis.
We acknowledge that, to overcome the shortcomings of our retrospective analysis, a
prospective clinical trial would be needed, with some design difficulties. If only patients
who did not require treatment with systemic corticosteroids or orbital radiotherapy were
included, the study would enroll only those patients with milder disease who, presumably,
are less prone to develop late fibrosis. On the other hand, it would be ethically questionable
to design a study in which immunosuppression is not administrated to reduce biases, and
patients are randomized to early or late decompression.
Patients with GO who do not have prompt access to diagnosis and medical treatment and
who finally present to the orbital surgeon with advanced disease could offer an adequate
population for a prospective study aimed to validate our major conclusions.
Chapter 2

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We acknowledge that, to overcome the shortcomings of our retrospective analysis, a prospective clinical trial would be needed, with some design difficulties. If only patients who did not require treatment with systemic corticosteroids or orbital radiotherapy were included, the study would enroll only those patients with milder disease who, presumably, are less prone to develop late fibrosis. On the other hand, it would be ethically questionable to design a study in which immunosuppression is not administrated to reduce biases, and patients are randomized to early or late decompression.

Patients with GO who do not have prompt access to diagnosis and medical treatment and who finally present to the orbital surgeon with advanced disease could offer an adequate population for a prospective study aimed to validate our major conclusions.

References

Chapter 3

The Influence of Previous Orbital Irradiation on the Outcome of Rehabilitative Decompression Surgery in Graves' Orbitopathy

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Chapter 3

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2 Department of Radiotherapy, University of Amsterdam, Amsterdam, The Netherlands.
3 Department of Endocrinology, University of Amsterdam, Amsterdam, The Netherlands.

Abstract

**Purpose:** To investigate whether orbital irradiation influences the outcome of decompression surgery in Graves’ orbitopathy.

**Design:** Retrospective, comparative case series.

**Methods:** The medical records of all the patients with Graves’ orbitopathy treated with a three-wall orbital decompression through a coronal approach at our institution between January 1, 1990 and December 31, 2000 were reviewed. Only patients who underwent bilateral surgery for aesthetic rehabilitation, without preoperative diplopia, and who, in the active phase of the disease, had received orbital radiotherapy alone (20 Grays (Gy) in 10 daily fractions of two Gy over a period of two weeks; group R), systemic glucocorticoids alone (daily administration for more than three months independently from the dosage; group G), or both radiotherapy and glucocorticoids (group RG) were selected. Groups were compared for demographics, smoking habits, predecompression characteristics, and surgical outcome (mean reduction of exophthalmos, reduction of lid retraction, persistence of periorbital swelling requiring cosmetic eyelid surgery, onset of diplopia within 20 degrees of the central position of gaze, and variations in the peripheral field of diplopia).

**Results:** Sixty-one of 376 patients were selected for this study. There were no differences between group R (n = 29), group G (n = 15), and group RG (n = 17) with respect to demographics or predecompression characteristics, whereas the number of smokers was significantly greater in group RG ($P = 0.019$). We could not find differences in surgical outcome by comparing the three groups.

**Conclusions:** The total radiation dose, fraction size, and irradiated volume commonly used to treat active Graves’ orbitopathy do not adversely interfere with the outcome of rehabilitative decompression surgery.
Introduction

Since 1913, external beam irradiation therapy has been used for the treatment of Graves’ orbitopathy. Initially, when exophthalmos was thought to be the result of dysfunction of the hypothalamus and the pituitary gland, radiotherapy was aimed at these structures. It later became clear that only those patients with iatrogenic orbital irradiation resulting from poorly collimated radiation delivery systems improved. Radiotherapy subsequently was directed to the orbital tissues behind the globe.2

Although its efficacy was questioned recently3, orbital radiotherapy continues to represent a mainstay in the management of active Graves’ orbitopathy. This is largely the result of its superiority of optimal tolerance and almost no short-term side effects, as opposed to the alternative of systemic immunosuppression with glucocorticoids.4 Issues of concern with radiotherapy in benign diseases are the long-term adverse effects of ionizing radiation to tissue, which in the case of Graves’ orbitopathy may lead to an increased risk of malignancy in the head and neck region, retinopathy, cataract formation, and diffuse fibrosis of the retroocular soft tissues. So far, no secondary tumors have been observed in long-term follow-up studies, and ocular complications, such as retinopathy or cataract, do not seem to represent real aftermaths of orbital irradiation for Graves' orbitopathy.5 Fibrosis of the orbital soft tissues secondary to radiation therapy may influence the results of later surgical procedures such as squint or decompression surgery. Preoperative radiotherapy was demonstrated not to affect squint surgery adversely6, but its effect on orbital decompressions remains undetermined. Although this issue has been mentioned incidentally in the literature7,8 and is a source of debate at meetings, we are unaware of previous reports that link orbital radiotherapy to the effects of decompression surgery in patients with Graves’ orbitopathy, and a computerized search using MEDLINE failed to reveal any references. This study sought to determine whether orbital irradiation in Graves’ orbitopathy influences the outcome of rehabilitative decompression surgery.
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Patients and Methods

Our study was a retrospective, comparative case series. The medical records of all the patients with Graves’ orbitopathy who underwent three-wall orbital decompression performed via a coronal approach at the Orbital Center, Department of Ophthalmology, University of Amsterdam, between January 1, 1990 and December 31, 2000 were evaluated retrospectively.

Inclusion Criteria

We included all patients who: 1) had undergone bilateral surgery for aesthetic rehabilitation, 2) did not have preoperative diplopia within 20 degrees of the central position of gaze, and 3) had been treated, in the active phase of Graves’ orbitopathy, with bilateral orbital radiotherapy alone (total dose of 20 Grays (Gy) in 10 daily fractions of two Gy over a period of two weeks), systemic glucocorticoids alone (for a period of at least three consecutive months independently from dosage regimens), or with both retrobulbar radiotherapy and systemic glucocorticoids.

Exclusion Criteria

We excluded patients who: 1) had undergone unilateral surgery; 2) were decompressed for optic neuropathy or exposure keratopathy; 3) did not receive bilateral orbital radiotherapy, systemic glucocorticoids or both the treatments in the active phase of Graves’ orbitopathy or did not receive these treatments as specified in the inclusion criteria; 4) had preoperative diplopia; 5) had been treated with thyroidectomy or iodine 131 in the six months preceding decompression or in the six months preceding postoperative evaluation; 6) had concurrent orbital or periorbital diseases, injuries, or surgeries (except for postdecompression blepharoplasty) within six months after decompression; and 7) whose records did not clearly state the duration of Graves’ orbitopathy at decompression; smoking habits at surgery; the date and method of administration of predecompression orbital radiotherapy or systemic corticosteroids; the results of an immediate preoperative clinical examination, including standard ophthalmologic evaluation, NOSPECS (no signs or symptoms, only signs, soft tissues involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight involvement) classification,9 Hertel exophthalmometry, measurements of eyelid fissure and respective upper and lower eyelid positions; the results of at least one postoperative clinical examination performed six months or more after surgery; the results of preoperative and postoperative orthoptic
evaluations performed, respectively, not earlier than six months before decompression and between three and six months after surgery.

The following data were retrieved: 1) gender; 2) age at surgery; 3) duration of Graves’ orbitopathy at decompression; 4) smoking habits at surgery; 5) type of immunosuppression used in the active phase of Graves’ orbitopathy; 6) interval between end of immunosuppression by steroids or radiation and time of decompression (in the case of treatment with radiotherapy and glucocorticoids, such an interval was calculated based on the last of the two administered treatments); 7) predecompression thyroidectomy or use of iodine 131; and 8) predecompression Hertel readings, score in NOSPECS class 2, presence of upper or lower lid retraction, or both, with measurements of eyelid fissure and the respective upper and lower eyelid position. Predecompression Hertel readings, score in NOSPECS class 2, and preoperative eyelid positions were those measured at hospitalization for orbital decompression. Data concerning the activity of Graves’ orbitopathy according to the seven-point clinical activity score (CAS) at baseline also were retrieved or were calculated retrospectively based on recorded signs of inflammation. We considered baseline to be the last ophthalmologic evaluation preceding the immunosuppressive treatment (the first immunosuppressive treatment when both orbital radiotherapy and systemic glucocorticoids had been administered).

We considered smokers to be those patients who were smokers on admission to the hospital at the time of surgery. In our center, the clinical work-up preceding rehabilitative orbital decompression consists of several ophthalmologic and endocrinologic examinations. Patients who smoke are strongly encouraged to give up smoking at all times. We assume that those patients who maintain their habit up to the time of decompression, despite multiple health warnings, will not refrain from smoking after surgery.

The postoperative data we used to assess the surgical outcome were: 1) reduction of exophthalmos; 2) reduction of upper or lower lid retraction, or both, when these signs were present before surgery; 3) persistence of periorbital swelling requiring cosmetic eyelid surgery; 4) occurrence of postdecompression diplopia within 20 degrees of the central position of gaze; and 5) variations in the peripheral field of diplopia. Postoperative Hertel readings and postoperative eyelid positions were those measured at the first clinical examination carried out six months or more after surgery.
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The included patients were divided into three groups based on the immunosuppression treatments administered in the active phase of Graves’ orbitopathy: those who had received orbital radiotherapy alone were included in group R, those who had received systemic glucocorticoids alone were included in group G, and those who had received both orbital radiotherapy and systemic glucocorticoids were included in group RG. Patients in group R were compared with those of groups G and RG for demographics, smoking habits, and preoperative and postoperative data by means of a database created using version 11.5.2 of the SPSS statistical analysis software package (SPSS, Inc, Chicago, Illinois, USA.). Right and left sides were not evaluated separately except for reduction of upper and lower lid retraction. For those patients presenting with a predecompression score $\geq a$ in NOSPECS class 2, persistence of periorbital swelling implying the necessity for postdecompression cosmetic surgery was defined as evidence in the medical record of upper or lower lid blepharoplasty proposed or performed at any time after orbital decompression. Postoperative orthoptic data were based on the first orthoptic examination performed between three and six months after decompression.

Statistical Analysis
Univariate comparisons were carried out using a one-way analysis of variance to compare continuous variables. In case of ordinal or non normally distributed variables, the Mann-Whitney $U$ test was used. Categorical preoperative and postoperative data were investigated using the $\chi^2$ test.

Orbital Radiotherapy
Orbital irradiation was delivered with a 5- or 6-mV accelerator in 10 daily fractions of two Gy over a period of two weeks. Localization and verification films with lead markers on the lateral canthus of each eye were performed for each patient on a simulator. The dose was calculated at the midline and given by two three degree anterior angled lateral portals of $5 \times 5$ cm, with the patient’s head fixed by an individual full-head shell.

Surgical Technique
All the patients included in this study underwent a standardized three-wall decompression via a coronal approach as is traditionally performed at our institution. A coronal incision was made with a no. 10 blade from ear to ear, 3 to 4 cm behind the hairline. In the central portion of the cranium, a subperiosteal plane was created by blunt dissection, and laterally, a surgical plane was developed bluntly between the deep and the superficial temporalis
fascia. The forehead flap thus created was then turned down to expose the superior and lateral orbital rims. The supraorbital nerve was set free by chiselling its bony foramen when present and the periorbitala, including the trochlea, was dissected off the orbital bones. The temporalis muscle then was dissected from its anterior origin with a no. 10 blade and periosteal elevators, leaving sufficient tissue for suturing at the end of surgery. In this way, the lateral orbital wall was exposed. A small osteotomy was chiselled behind the lateral orbital rim, and bone-nibbling rongeurs were used to remove the mid portion of the lateral orbital wall. A Frazier suction tip was used to fracture the delicate bone of the medial orbital wall and the floor, and Blakesley forceps nos. 1 and 2 were used to remove bony fragments and mucosa of the sinuses. The bulla ethmoidalis beneath the frontoethmoidal suture was opened toward the orbit from the posterior lacrimal crest up to the orbital apex, and then the orbital floor medial to the infraorbital canal was removed from 0.5 cm behind the inferior orbital rim up to the posterior wall of the maxillary sinus. The posterior two-thirds of the maxillary ethmoidal strut were removed creating a wide antrostomy, whereas the anterior one-third of the strut was left intact to prevent globe displacement and the possibility of medial entropion or hypoglobus. Finally, the periorbita was incised extensively to promote maximal prolapse of the orbital tissues into the newly created spaces. The temporalis muscle was sutured back into position with four to five interrupted 2-0 Mersilene sutures and, after the insertion of a 3.3-mm diameter end-perforated wound drain into each temporalis fossa, the scalp incision was closed with steel staples.

Results
The medical records of 61 of 376 patients were selected for this study, whereas 315 were excluded because they did not meet the inclusion criteria or the necessary data were not recorded.

Demographics, Smoking Habits, and Preoperative Characteristics
There were no differences between group R (n = 29), group G (n = 15), and group RG (n = 17) with respect to demographics or preoperative characteristics, whereas the number of smokers was significantly greater in group RG ($P = 0.019$). It was not possible to compare group RG with the other two groups with regard to CAS at baseline because we could not retrieve enough data from the medical records of the patients included in this group (Table 1).
**Table 1.** Demographics, Smoking Habits and Predecompression Characteristics in Three Groups of Patients Affected by Graves’ Orbitopathy Who Had Been Treated with Different Immunosuppressive Strategies during the Active Phase of the Disease

<table>
<thead>
<tr>
<th></th>
<th>Group R* (n=29)</th>
<th>Group G* (n=15)</th>
<th>Group RG* (n=17)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>86%</td>
<td>93%</td>
<td>100%</td>
<td>P = 0.250</td>
</tr>
<tr>
<td>Age at surgery (yrs ± SD) (95% CI)</td>
<td>41.8 (8.5) (38.5-45.0)</td>
<td>43.0 (9.6) (37.6-48.5)</td>
<td>46.3 (10.0) (41.1-51.4)</td>
<td>P = 0.292</td>
</tr>
<tr>
<td>Duration of Graves’ orbitopathy at surgery (yrs ± SD) (95% CI)</td>
<td>3.6 (2.7) (2.6-4.7)</td>
<td>4.9 (4.4) (2.5-7.4)</td>
<td>5.1 (3.9) (3.0-7.0)</td>
<td>P = 0.321</td>
</tr>
<tr>
<td>Interval end immunosuppression by steroids or radiation, and time of decompression (mts ± SD) (95% CI)</td>
<td>15.1 (14.7) (9.5-20.7)</td>
<td>28.5 (28.4) (11.3-45.6)</td>
<td>15.9 (10.3) (10.7-21.2)</td>
<td>P = 0.070</td>
</tr>
<tr>
<td>Smokers</td>
<td>43%</td>
<td>31%</td>
<td>80%</td>
<td>P = 0.019</td>
</tr>
<tr>
<td>Radioactive Iodine</td>
<td>21%</td>
<td>40%</td>
<td>41%</td>
<td>P = 0.244</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>7%</td>
<td>13%</td>
<td>29%</td>
<td>P = 0.114</td>
</tr>
<tr>
<td>Hertel values (mm ± SD) (95% CI)</td>
<td>23.3 (2.3) (22.4-24.2)</td>
<td>23.1 (2.5) (21.7-24.5)</td>
<td>21.9 (2.3) (20.7-23.0)</td>
<td>P = 0.130</td>
</tr>
<tr>
<td><strong>Upper lid retraction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monolateral</td>
<td>7%</td>
<td>20%</td>
<td>6%</td>
<td>P = 0.860</td>
</tr>
<tr>
<td>Bilateral</td>
<td>65%</td>
<td>40%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>28%</td>
<td>40%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td><strong>Lower lid retraction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monolateral</td>
<td>7%</td>
<td>0%</td>
<td>12%</td>
<td>P = 0.750</td>
</tr>
<tr>
<td>Bilateral</td>
<td>69%</td>
<td>80%</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>24%</td>
<td>20%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td><strong>Score in NOSPECS class 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7%</td>
<td>13.3%</td>
<td>6%</td>
<td>P = 0.372</td>
</tr>
<tr>
<td>a</td>
<td>52%</td>
<td>33.3%</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>38%</td>
<td>53.4%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>C.A.S. (+/7 ± SD) at the last examination preceding immunosuppression</strong></td>
<td>3.6 (1.5)</td>
<td>3.44 (1.4)</td>
<td>§</td>
<td>P = 0.817</td>
</tr>
</tbody>
</table>

C.A.S = clinical activity score; CI = confidence interval; SD = standard deviation; a = mild; b = moderate; c = severe; NOSPECS (classification of eye changes in Graves’ orbitopathy) = class 0, no signs or symptoms; class 1, only signs; class 2, soft tissue involvement with symptoms and signs; class 3, proptosis; class 4, extraocular muscle involvement; class 5, corneal involvement; class 6, sight involvement.

*Group R = patients in whom immunosuppression was obtained by means of orbital radiotherapy; Group G = patients in whom immunosuppression was obtained by means of systemic glucocorticoids; Group RG = patients in whom immunosuppression was obtained by means of orbital radiotherapy and glucocorticoids.

†Interval calculated based on the last of the two immunosuppressive treatments that was administrated.

‡CAS, expressed as one point positive for each of seven signs of activity taken into consideration, namely: 1-retroocular pain at rest; 2-retroocular pain induced by eye movements; 3-redness of the eyelids; 4-redness of the conjunctiva; 5-conjunctival chemosis; 6-swelling of the caruncle; 7-swelling of the eyelids. Group R (n = 24); Group G (n = 15).

Surgical outcome

There were no statistically significant differences regarding mean reduction of exophthalmos, occurrence of diplopia consecutive to orbital decompression within 20 degrees around primary position of gaze, or variation in the peripheral field of diplopia among the groups. When the predecompression score in NOSPECS class 2 was ≥ a, there were no statistically significant differences among the groups with regard to persistence of postdecompression periorbital swelling requiring upper or lower lid blepharoplasty. The
reduction of upper and lower lid retraction also was not statistically different among groups when these signs were present before surgery (Table 2).

Table 2. Outcome of Three-Wall Rehabilitative Orbital Decompression Through a Coronal Approach in Three Groups of Patients Affected by Graves’ Orbitopathy Who Had Been Treated with Different Immunosuppressive Strategies during the Active Phase of the Disease

<table>
<thead>
<tr>
<th></th>
<th>Group R*</th>
<th>Group G**</th>
<th>Group RG***</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=29)</td>
<td>(n=15)</td>
<td>(n=17)</td>
<td></td>
</tr>
<tr>
<td>Mean exophthalmos reduction (\pm SD, \text{mm (95% CI)})</td>
<td>4.9 (1.8) (4.2-) 5.6</td>
<td>4.6 (1.9) (3.5-) 5.7</td>
<td>5.3 (1.9) (4.3-) 6.2</td>
<td>(P = 0.598)</td>
</tr>
<tr>
<td>Reduction of upper lid retraction right/left†</td>
<td>52% / 47%</td>
<td>50% / 33%</td>
<td>36% / 40%</td>
<td>(P = 0.683/P = 0.772)</td>
</tr>
<tr>
<td>Reduction of lower lid retraction right/left‡</td>
<td>62% / 52%</td>
<td>67% / 67%</td>
<td>67% / 60%</td>
<td>(P = 0.946/P = 0.719)</td>
</tr>
<tr>
<td>Persistence of postdecompression peri-orbital swelling requiring cosmetic surgery§</td>
<td>48%</td>
<td>46%</td>
<td>31%</td>
<td>(P = 0.536)</td>
</tr>
<tr>
<td>Onset of diplopia consecutive to decompression within 20° around primary position of gaze</td>
<td>28%</td>
<td>40%</td>
<td>41%</td>
<td>(P = 0.563)</td>
</tr>
</tbody>
</table>

Field of diplopia beyond 20° from primary position of gaze:
- Increased | 50% | 72% | 25% | \(P = 0.494\)
- Decreased | 17% | 14% | 25% |
- Unchanged | 33% | 14% | 50% |

CI = confidence interval; SD = standard deviation.
*Group R = patients in whom immunosuppression was obtained by means of orbital radiotherapy; Group G = patients in whom immunosuppression was obtained by means of systemic glucocorticoids; Group RG = patients in whom immunosuppression was obtained by means of orbital radiotherapy and glucocorticoids.
†Only patients with upper lid retraction before surgery: Group R, 21 right 19 left; Group G, six right nine left; Group RG, 11 right 10 left.
‡Only patients with lower lid retraction before surgery: Group R, 21 right 21 left; Group G, 12 right 12 left; Group RG, 12 right 12 left.
§Only patients with predecompression score in NOSPECS class 2 – a: Group R, 27; Group G, 13; Group RG, 16.
¶| Only patients who did have postdecompression diplopia within 20 degrees around the primary position of gaze: Group R, 18; Group G, 7; Group RG, 8.

Discussion

Orbital irradiation is a common method of treatment of Graves’ orbitopathy in its early, inflammatory, active phase. It seems to be effective on soft tissue inflammatory changes, recent extraocular muscle involvement, and optic neuropathy by inactivating orbital lymphocytes and fibroblasts, which are, respectively, the mediators and the effectors of the inflammatory reaction in the orbit. Ionizing radiation, however, may not be without negligible side effects even when low doses are used. Histopathologic radiation-induced alterations mainly occur in a repetitive form in different structures, namely, epithelia and parenchymatous tissues, stroma, and blood vessels. Some alterations are characteristic of particular organs. All of them are delayed radiation injuries
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that appear months to years after exposure to ionizing radiation. Acute radiation injury is rare.

Fibrosis, one of the most common delayed injuries of stroma, may affect soft orbital tissues, especially the fat and, in turn, may have an adverse effect on bone removal orbital rehabilitative decompression surgery. Fibrosis occurs in practically all tissues and organs exposed to ionizing irradiation, but the extent and severity vary from site to site and are dependent on the total radiation dose, fraction size, and treated volume. The typical radiation-induced fibrosis is inhomogeneous: some areas have very dense, acellular collagen, whereas next to them, other areas have only a few fibrous bands. The fibrous areas are within the irradiated field but do not fill it entirely. Such alterations are typical of irradiated adipose tissue. Classic theories of radiation effects not only indicate deoxyribonucleic acid double-strand breaks as the early lethal event, but also assert that tissues that are prone to late radiation fibrosis have slow reproductive rates that delay cell death and result in late reactions. Adipose tissue perfectly fits such characteristics.

Eventual late radiation toxicity to orbital fat in Graves’ orbitopathy is not likely to be solely the result of delayed cell death and slow cell turnover. Orbital irradiation is administered in the active, inflammatory phase of Graves’ orbitopathy, and it has long been observed that inflammation worsens delayed radiation fibrosis. Inflammation is mediated largely by proinflammatory cytokines, including tumor necrosis factor α, which in injured tissue has been shown to be involved in the recruitment and activation of macrophages with the release of downstream fibrogenic cytokines. These cytokines include fibroblast growth factor 2 (FGF2) and transforming growth factor β 1 (TGFβ1). FGF2 is chemotactic and mitotic for fibroblasts, and TGFβ1 stimulates fibroblast proliferation and premature end differentiation, leading to excessive extracellular matrix glycoprotein production. Thus, irradiation dramatically alters the ability of macrophages to stimulate normal fibroblast populations, and fibrosis induced by radiation is a multicellular event in which the macrophage and fibroblast cell systems interact through intracellular communication mediated by specific growth factors such as FGF2 and TGFβ1.

Orbital compliance, which refers to the distensibility and plasticity of the orbital tissues, may be reduced by fibrosis of the orbital soft tissues and reduced orbital compliance may
diminish the effectiveness of orbital expansion surgery because orbital soft tissues can fail to prolapse maximally into the spaces newly created by surgery. In view of this possibility, orbital radiotherapy may be expected to have a negative effect on decompression surgery in patients with Graves’ orbitopathy.

Because of the extreme heterogeneity of patients with Graves’ orbitopathy who need rehabilitative decompression surgery, the variation applied to surgical techniques, and the use of perioperative glucocorticoids, it may prove difficult to verify whether this affects the results of orbital surgery. The paucity of data available in literature seems to be in line with this viewpoint, which our results confirm further. In our retrospective survey, conducted in a tertiary referral center with an established tradition for the treatment of Graves’ orbitopathy and encompassing a period of 11 years, among 376 patients decompressed using the same technique, we could recruit only 61, meeting the criteria that we regarded as essential for a comparative case series.

Male gender, older age, and heavy smoking habits are patient characteristics that are known to be associated with more severe orbital disease, whereas extension and location of the osteotomy performed during decompression surgery, differences in aperture of the periorbit, and preoperative Hertel values have been regarded as factors influencing the amount of exophthalmos reduction. In addition, the timing for assessment of surgical outcome can be an additional source of bias when evaluating the results of decompression surgery. As a consequence, any meaningful comparison of the results of rehabilitative decompression surgery in different cohorts of patients with Graves’ orbitopathy necessitates a careful evaluation of their baseline characteristics and a careful control of confounding factors by means of the methodology of investigation. We therefore compared the groups for baseline characteristics and we tried to control confounding factors and bias by means of our strict inclusion and exclusion criteria, timing for assessment of the results, and clear definitions for important symptoms such as diplopia or signs such as persistence of postdecompression periorbital swelling.

The three groups of patients included in our study were basically homogeneous at baseline, although smoking was a most common habit among the patients in the RG group.

Considering the well-known negative influence of smoking on the course of Graves orbitopathy and its capacity to impair the response of Graves orbitopathy to radiotherapy and glucocorticoids, it was not unexpected that group RG required the most intensive
immunosuppression regimen. By comparing the results of rehabilitative decompression surgery of the three groups, we did not find that patients treated with retrobulbar irradiation in the active phase of Graves’ orbitopathy had a different outcome than those treated with systemic glucocorticoids alone or with both retrobulbar irradiation and systemic glucocorticoids in the same phase of the disease.

We acknowledge that the results of our study should be weighed in light of its retrospective nature and its limitations. Our survey was a retrospective comparative case series, and the results of this type of study need to be confirmed by investigations with stronger study designs. The number of patients included was relatively small, the mean interval between retrobulbar irradiation and orbital decompression was relatively short, and patients were not allocated randomly to either of the three treatment groups. Despite these shortcomings, our results seem to suggest that the total radiation dose, fraction size, and irradiated volume commonly used to treat active Graves’ orbitopathy do not adversely interfere with the outcome of rehabilitative decompression surgery.
Chapter 3

References


Chapter 4

A Novel Method for Measuring Outcome of Orbital Decompression in Graves’ Orbitopathy by Evaluating an Infero-medial Decompression Technique

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Manuscript in preparation
Chapter 4

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Manuscript in preparation
Abstract

**Purpose:** To evaluate outcome of a graded bone removal infero-medial orbital decompression in Graves’ orbitopathy (GO) by means of a novel stratified appraisal (NSA) versus a traditional group analysis (TGA).

**Design:** Prospective observational case series.

**Participants:** All the orbits decompressed at our institution, for rehabilitative reasons by one surgeon (L.B.), using the technique under evaluation, between June 1999 and December 2005.

**Methods and main outcome measures:** NSA assessed or quantified: (1) the invasiveness of surgery from minimally (25%) to maximally (100%) invasive, allowing to calculate a mean index of invasiveness per orbit (MIIO) and per patient (MIIP) (25%≤values≤100%); (2) at ≥ 6 months postoperatively the surgical targets recorded prior to surgery (amount of desired exophthalmos reduction, improvement of retroocular tension, reduction of periorbital swelling / aedema, resolution of lagophthalmos) were scored allowing to calculate a mean index of targets achieved per orbit (MITAO) and per patient (MITAP) (0≤values≤1); (3) an index of diplopia (ID) (ratio of central 20° of gaze decompression-induced / cured diplopia) was calculated based on orthoptics at ≥ 3 months postoperatively and before any strabismus surgery; (4) demographics and preoperative characteristics were compared after stratification of the included orbits for surgical target; surgical outcomes were assessed after stratification for amount of desired exophthalmos reduction and invasiveness of surgery.

TGA examined the entire series as a single homogeneous cohort independently of the different targets and invasiveness of surgery.

NSA and TGA were compared and complications noted.

**Results:** 151 orbits of 84 patients (78% female, mean age 45.5±9.7 years) were included. The NSA detected differences among groups within the studied cohort, the overall achievement of surgical targets was very high, indices precisely quantified the extent of applied surgery and surgical results, at variance with those obtained with TGA. A negligible complication rate was recorded.

**Conclusions:** The NSA may represent a step forward towards a more comprehensive and accurate evaluation of decompression surgery outcomes.
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Conclusions:
The NSA may represent a step forward towards a more comprehensive and accurate evaluation of decompression surgery outcomes.

Introduction
For roughly a century decompression surgery has been used to treat Graves’ orbitopathy (GO).\textsuperscript{1} Initially it was utilized to address sight threatening conditions such as optic neuropathy, or exposure keratopathy. More recently the indications for orbital decompression were extended to the treatment of the typical disfigurement, and symptoms caused by the disease, which include globe and eyelid displacement, periorbital swelling, and raised retroocular tension. At present, it is also used as a preliminary step before squint surgery when space is required for recession of enlarged extraocular muscles, and functional indications of orbital decompression have been further expanded for the treatment of globe subluxation, postural visual obscuration in patients with congestive inactive GO\textsuperscript{2} and choroidal folds of recent onset due to globe indentation by enlarged extraocular muscles.\textsuperscript{3, 4}

Despite the multiple indications for rehabilitative decompression surgery, mean exophthalmos reduction and incidence of new onset diplopia have been the main outcome measures reported in most of the published series. Through the years most authors have linked effectiveness and reliability of the reported techniques to the highest extent of exophthalmos reduction and the lowest incidence of induced diplopia.

We perceive this perspective as suboptimal since the data which have been generated/ reported are incomplete, often imprecise and most likely misleading.

Data are incomplete because most of the effects of decompression surgery other than those on exophthalmos and binocular single vision have remained unmeasured.

Data are also often imprecise because many series inappropriately mix patients decompressed for disfigurement, with those presenting with compressive dysthyroid optic neuropathy, in whom the reduction of exophthalmos was not the reason to undertake decompression surgery and in whom the true incidence of decompression induced diplopia could have been confounded by the low pre-decompression visual acuity.

Data are most likely misleading because it is assumed that decompression surgery is always performed to obtain the maximal possible exophthalmos reduction when in reality any decompression technique can be used with different extent of osteotomies, fat removal or periorbita manipulation to achieve any degree of desired reduction of exophthalmos in the single orbit. In addition, high exophthalmos reduction is not an index of effectiveness as any excessive exophthalmos reduction is to be regarded as a complication of
decompression surgery. Similarly the incidence of decompression induced diplopia is not itself most appropriate to describe surgical outcome because it does not take into account the cases of preoperative diplopia that are cured by decompression.

Based on these considerations it appears evident that the results of decompression surgery deserve a more adequate, comprehensive and reliable evaluation. We tried to make a move towards this goal by evaluating the outcome of a graded, bone inferomedial rehabilitative decompression technique performed through a minimally invasive suture-less trans inferior fornix approach, under a novel perspective which possibly overcomes the existing “time honoured” limitations.

**Patients and methods**

Our survey is a prospective observational case series. The study was carried out following the tenets of the Declaration of Helsinki and of the “CODE of CONDUCT” of the Dutch Federation of Biomedical Scientific Societies (http://www.federa.org/) as recommended by the Review Board of the Academic Medical Center University of Amsterdam. The same Review Board ruled that for this type of study its permission need not to be requested, nor was patients’ informed consent necessary if data are collected anonymously from the medical records used by the authors in their every day practice.

**Inclusion criteria:**

We included all the patients decompressed mono or bilaterally for rehabilitative reasons, who were clinically and biochemically euthyroid for at least 3 months, and who had undergone a graded bone inferomedial rehabilitative decompression performed through a minimally invasive suture less trans inferior fornix approach by one surgeon (L.B.), between June 1999 and December 2005.

**Exclusion criteria:**

We excluded all the patients 1) who had been treated with thyroidectomy or $^{131}$I in the 6 months preceding decompression or in the 6 months preceding postoperative evaluation; 2) who had concurrent orbital or periorbital diseases, injuries or surgeries (except for postdecompression blepharoplasties) within 6 months after decompression; 3) whose surgical targets were not listed in the respective medical files and whose pre and post operative notes were not filled out by means of the GO case record form in use in our clinic at the time of the study. It included all the necessary information for an adequate
clinical assessment of patients with GO, and was very similar to the EUGOGO case record form⁵ being one of its precursors.

**Surgical technique**

In bilateral cases, surgery was always initially performed on the more protruding eye if any. After the exposure of the inferior fornix by mean of a Desmarres’ retractor and a malleable orbital retractor, both electrically insulated, the conjunctiva and lower lid retractor complex were severed en-bloc with a Colorado needle and the inferior orbital rim was exposed. The periorbita was incised at this level and the medial and inferior orbital walls exposed by developing a subperiosteal plane. In order to obtain the best possible exposure of the medial wall, the bone insertion of the inferior oblique muscle was partially detached, and the conjunctival incision extended up to the caruncle.

Once the medial orbital wall and the orbital floor were exposed a Frazier suction tip was used to fracture the delicate bone of the medial orbital wall and of the floor and Blakesley forceps were used to remove bony fragments and mucosa of the sinuses. If necessary bone-nibbling rongeurs were also used. The bulla ethmoidalis underneath the fronto-ethmoidal suture was opened towards the orbit from the posterior lacrimal crest up to the orbital apex, and then the orbital floor medial to the infra-orbital canal was removed from about 1 cm behind the inferior orbital rim up to the posterior wall of the maxillary sinus.

Starting from this point, on the basis of intra operative estimations of eye position and resistance to retropropulsion of the globe, and considering the targets to be pursued in the single orbit, surgery was graded to the specific patient’s needs. Clear surgical notes were prepared so that 4 progressively invasive surgical classes could be defined in the single orbit (A = minimally invasive to D maximally invasive, with an attributed index of invasiveness orbit (IIO) ranging from 25% for class A to 100% for class D).

- **Surgical class A**: Osteotomies were terminated at this stage, and the periorbita left intact.
- **Surgical class B**: The periorbita was opened inferiorly and medially sparing the anterior portion of its inferior and medial surfaces for roughly 1.5 cm behind the arcus marginalis.
- **Surgical class C**: The bony infraorbital canal and the orbital floor lateral to it were completely removed, the periorbita was addressed as for class B.
- **Surgical class D**: The posterior two thirds of the maxillary ethmoidal strut were removed creating a wide antrostomy between the maxillary sinus and the nasal cavity. The bony infraorbital canal, the orbital floor lateral to it, and periorbita were addressed as for class C.
At all times possible sources of bleeding were controlled with cautious bipolar diathermy. In all cases, at the end of surgery the fornix incision was not sutured and a pressure bandage was applied on the operated eye, after absence of bleeding was assessed.

Immediate post operative care:
Pupil reflexes, visual function, ductions and versions were checked when the patient was awake postoperatively, then daily up until the morning of post operative day 2 when patients were discharged from the hospital. Pressure bandages were removed and reapplied daily after clinical examination up until discharge. At surgery, post operative day 1 and 2 intravenous ceftriaxone (1 g/day) was administered; patients left hospital without medications except for artificial tears.

Evaluated data
The following data were evaluated: 1) gender; 2) age at surgery; 3) duration of GO at decompression; 4) smoking habits at surgery; 5) possible administration of systemic immunosuppressive treatments, and/or or orbital radiotherapy before decompression; possible treatments with I131 or thyroidectomy before and after decompression; 8) pre and post operative best corrected visual acuity, exophthalmometric values, measure of possible lagophthalmos, NOSPECS, and CAS scores; 9) expected targets of infero medial decompression surgery; 10) information useful for defining IIO; 11) pre and postoperative orthoptic evaluations including information on central diplopia defined as double vision within 20° of the central position of gaze, field of peripheral diplopia, namely extension of diplopia beyond 20 degrees of the central position of gaze, measures of ductions in degrees performed with a modified perimeter; 12) any information concerning intraoperative, perioperative or medium term complications other than strabismus.

Clinical pre operative data were those of the last ophthalmic examination before decompression, while post operative data and scoring of the single targets as achieved or not achieved referred to the first ophthalmic examination performed 6 or more months after surgery. In the case of post decompression blepharoplasties performed earlier than post decompression month 6 the achievement of the target “reduction of periorbital oedema” referred to the last ophthalmic examination preceding blepharoplasty.

Pre and postoperative data concerning eye motility were those collected at the orthoptic evaluations performed respectively not earlier than 6 months before decompression and not earlier than 3 months, but before any strabismus surgery.
Chapter 4

Methodology
Predecompression characteristics and outcome by a novel stratified appraisal (NSA) were weighed against that of a traditional group analysis (TGA).

Novel Stratified Appraisal
Before surgery the targets to be achieved by the graded inferomedial decompression technique in the single orbit, were discussed with the patients and listed in their medical records.

Orbital targets were scored as achieved as desired or not, and were: (1) amount of desired exophthalmos reduction specified as a) none to minimal, i.e. \( \leq 2 \) mm; b) moderate to maximal, i.e. \( \geq 3 \) mm without causing enophthalmos and/or hypoglobus namely excessive reduction of exophthalmos, and/or eyeball dystopia for which surgical correction was advised or performed; (2) resolution of retroocular tension, defined as patient’s subjective perception of disappearance of such a symptom after decompression; (3) reduction of periorbital swelling oedema, defined as decrease of at least 1 point in NOSPECS class 2 after decompression; (4) cure of lagophthalmos, defined as disappearance or reduction of \( \geq 3 \) mm of preoperative lagophthalmos.

In addition symmetry in exophthalmos reduction was considered as a constant patient target to be pursued. We considered symmetry as achieved when post operative Hertel readings were right = left \( \pm 1 \) mm.

In order to characterize different groups according to the invasiveness of surgery a mean IIO, named mean index of invasiveness orbit (MIIO) was calculated, as well as a mean index of invasiveness patient (MIIP) which was based on the formula \( 0.5 \times \sum \text{IIO} / \text{number of patients included into the group} \) (the coefficient 0.5 in the formula was chosen because in a patient the contribution of each orbit to invasiveness is 50%). IIO, MIIO, and MIIP express invasiveness in percentages from 25-100%.

For measuring in different groups the average amount of achievement of the desired surgical targets, a mean index of targets achieved orbit (MITAO) and a mean index of targets achievement patient (MITAP) were calculated, respectively based on the formulas: \( \sum 1 \) or 0 point for each target respectively achieved as desired or not in the single orbit / overall number of desired targets in a group of orbits; \( \sum 1 \) or 0 point for each target respectively achieved as desired or not for targets concerning only one of the two orbits, and for target symmetry (constant) + \( \sum 0.5 \) or 0 points for each target respectively achieved.
as desired or not for targets concerning both the orbits / overall number of desired targets in a group of patients (0.5 points for targets desirable in both orbits was chosen because in a patient the contribution of each orbit to the achievement of that target is 50%). MITAO and MITAP are numbers between 0 and 1; MITAO=1 and MITAP=1 when all the targets are achieved in a group of orbits or in a group of patients respectively.

Based on the ratio frequency decompression induced diplopia / frequency decompression cured diplopia, an index of diplopia (ID) was calculated. ID is =1 when the frequency of induced diplopia is the same as that of cured, is > 1 when the frequency of induced diplopia is higher than that of cured, is < 1 vice versa.

Orbits grouped for target “amount of desired exophthalmos reduction” and stratified for class of surgical invasiveness (IIO) were compared within groups and within classes in respect to mean exophthalmos reduction, mean decompression induced change in ductions.

Central and peripheral fields of diplopia were assessed in patients in whom preoperative binocular vision was present and who did not have anomalous retinal correspondence.

Patients stratified for decompression induced or cured central diplopia were compared.

*Traditional Group Analysis*

Surgical outcomes (mean post operative exophthalmos, mean exophthalmos reduction, decompression induced change in duction) of the entire cohort of orbits were evaluated as a whole in the TGA. Incidence of decompression induced diplopia was evaluated in the same cohort of patients as for NSA.

*Statistical analysis*

Pre and post operative data were inserted in a data base created in SPSS 16.0 Statistics UK and analysed.

Univariate comparisons: one-way ANOVA and Student's t test were used to compare continuous variables. In case of ordinal or not normally distributed variables the Mann-Whitney U test was used. Categorical preoperative and post-operative data were investigated using $\chi^2$ test. Significance was assumed if $P \leq 0.05$.

Multiple regression analysis was used to assess the independent influence of preoperative Hertel values and IIO on exophthalmos reduction, and decompression induced mean changes in ductions.
Results
Eighty-four patients (151 orbits) out of 295 patients decompressed within the study period were selected for this survey, 210 patients were excluded because they did not meet the inclusion criteria or the necessary data were not recorded. One patient, previously reported, was excluded because of delayed decompression related reactivation (DDRR)\(^9\), requiring high dose oral glucocorticoids starting from 1 month after surgery.

Preoperative characteristics
The 151 orbits had the following characteristics: 77.5% were feminine, mean age ± SD at decompression was 45.5±9.7 years, mean duration of GO ± SD at decompression 45.7±44.6 months; 51.3% were smokers, and 34.2% had received \(^{131}\)I and 11.6% thyroidectomy. Steroids, orbital radiotherapy, or combined steroids and orbital radiotherapy had been administered in 12.2%, 17.6%, and 10.1% respectively.

The NSA disclosed the following differences among orbits stratified for surgical target:
The orbits that required “moderate to maximal exophthalmos reduction” were younger and had higher mean preoperative Hertel values than those that required “no to minimal exophthalmos reduction” (mean± SD age at decompression (44.4±9.6 vs 52.3±7.6 years, \(P = 0.000\)) (mean± SD preoperative Hertel 21.6±2.2 vs 19.6±1.5 mm, \(P = 0.000\)). In addition the orbits whose target was “no to minimal exophthalmos reduction” had received orbital radiotherapy less frequently than those whose target was “moderate to maximal exophthalmos reduction” (9.5% vs 30.7% \(P = 0.001\)). The orbits that required treatment of lagophthalmos had received combined radiotherapy and glucocorticoids less frequently (0%) as compared with those who did not (12%) (\(P = 0.000\)). The duration of GO ± SD at decompression was longer in those orbits that did not require reduction of the periorbital oedema (70.3±67.5 months) as compared with those who required it (40.7±36.8 months) (\(P = 0.003\)).

Surgical outcome
After decompression surgery there was no clinically relevant change in visual acuity in any patient.
The achievement of the desired targets in the operated orbits are outlined in table 1. Calculated MITAO and MITAP were 0.95±0.16 and 0.94±0.15 respectively, attained by
Chapter 4

Table 1. Achievement of the Surgical Target in the Operated Orbit

<table>
<thead>
<tr>
<th>Surgical targets</th>
<th>Operated orbits out of the whole series (n=151) in which the achievement of the surgical target was desired</th>
<th>Achievement of the surgical target as desired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exophthalmos reduction:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderate to maximal (≥ 3mm, &lt;enophthalmos/hypoglobus*)</td>
<td>130 (86.1%)</td>
<td>Yes = 127/130 (97.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No = 3/130 (2.3%)</td>
</tr>
<tr>
<td>none to minimal (≤ 2mm)</td>
<td>21 (13.9%)</td>
<td>Yes = 21/21 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No = 0/21 (0%)</td>
</tr>
<tr>
<td>Reduction of retroocular tension</td>
<td>100 (66.2%)</td>
<td>Yes = 100/100 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No = 0/100 (0%)</td>
</tr>
<tr>
<td>Reduction of periorbital aedema</td>
<td>122 (80.8%)</td>
<td>Yes = 110/122 (90.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No = 12/122 (9.8%)</td>
</tr>
<tr>
<td>Reduction of lagophthalmos</td>
<td>24 (15.9%)</td>
<td>Yes = 24/24 (100%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No = 0/24 (0%)</td>
</tr>
</tbody>
</table>

*enophthalmos / hypoglobus = excessive reduction of exophthalmos or eye globe dystopia for which surgical correction was advised or performed.

One patient operated bilaterally had monolateral enophthalmos / hypoglobus, another had bilateral hypocorrection.

MIIO and MIIP of 86.4±21.9% and 78.2±26.1% respectively. Symmetry in exophthalmos reduction was achieved in 78 (94%) of 83 patients, with post decompression Hertel values right side = left in 56.4%; asymmetry in exophthalmos reduction resulted in 5 (6%) of 83 patients with post decompression Hertel values right = left ± 2 mm and ± 3 mm in 40% and in 60% respectively. In one of the 84 patients symmetry in exophthalmos reduction could not be assessed nor MITAP calculated. Prior to decompression, he had been enucleated on one side without orbital implant, and he was not wearing any eye prosthesis or willing to do that at the time of decompression.

The number of other targets to be achieved were not different between groups in which the desired exophthalmos reduction was ≤ 2 mm or ≥ 3 mm.

Surgical outcome measures of the orbits grouped for target “amount of desired exophthalmos reduction” are given in table 2.

TGA mean decompression induced changes in abduction, adduction, elevation and depression (degrees ± SD, increase in negative numbers) were 3.8±7.8; -0.05±6.6; 5.6±7.7; -0.03±10.6 with significant decrease of abduction (P = 0.000) and elevation (P = 0.000), could be calculated on 93 orbits for which pre- and postoperative orthoptic evaluations...
were available and were attained with a MIO of 85±23.4%. The same measures stratified for target “amount of desired exophthalmos reduction” are given in table 3.

In table 4 orbits are grouped for target “amount of desired exophthalmos reduction” and, stratified for class of surgical invasiveness. Within and between group comparisons are specified for exophthalmos reduction, and decompression induced changes in ductions. Multiple linear regression analysis demonstrated that the amount of exophthalmos reduction was proportional to mean preoperative Hertel readings and IIO for the entire cohort of orbits (P = 0.000 and P = 0.000) and for those whose target was “moderate to maximal exophthalmos reduction” (P = 0.000 and P = 0.002), but not for those where “no to conservative exophthalmos reduction” was desired.

Multiple linear regression analysis demonstrated that decompression induced changes in abduction, elevation and depression were proportional to IIO (P = 0.022; P = 0.047; P = 0.001) for those orbits where “moderate to maximal exophthalmos reduction” was desired but not for those whose target was “no to conservative exophthalmos reduction”.

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Table 2. Invasiveness of Applied Decompression Surgery and Its Effect on Exophthalmos and Overall Achievement of Surgical Targets in a Cohort of 151 Orbits Grouped for Target “Amount of Desired Exophthalmos Reduction”

<table>
<thead>
<tr>
<th>Orbits which required moderate to maximal exophthalmos reduction:</th>
<th>Orbits which required none to minimal exophthalmos reduction:</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(≥3mm,&lt;enophthalmos/hypoglobus*) (n=130/151)</td>
<td>(≤ 2mm) (n=21/151)</td>
<td></td>
</tr>
<tr>
<td>Mean index of invasiveness orbits (MIO) ± SD, %**</td>
<td>91.3±15.8</td>
<td>P = 0.000</td>
</tr>
<tr>
<td>Mean index target achievement orbit (MITAO) ± SD</td>
<td>55.9±29.4</td>
<td></td>
</tr>
<tr>
<td>Mean post decompression</td>
<td>0.96±0.15</td>
<td>P = 0.075</td>
</tr>
<tr>
<td>Hertel values ± SD, mm</td>
<td>0.90±0.17</td>
<td></td>
</tr>
<tr>
<td>Mean exophthalmos reduction ± SD, mm</td>
<td>16.5±2.3</td>
<td>P = 0.002</td>
</tr>
<tr>
<td></td>
<td>18.1±1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.0±1.9</td>
<td>P = 0.000</td>
</tr>
<tr>
<td></td>
<td>1.5±0.6</td>
<td></td>
</tr>
</tbody>
</table>

*enophthalmos / hypoglobus = excessive reduction of exophthalmos or eye globe dystopia for which surgical correction was advised or performed.

**Four progressively invasive surgical classes were defined in the single orbit (A = minimally invasive to D maximally invasive, with an attributed index of invasiveness orbit (IIO) ranging from 25% for class A to 100% for class D), MIO is the mean index of invasiveness for the orbits of a given group.

The mean index of targets achievement orbit (MITAO) is the average amount of achievement of the desired surgical targets for the orbits of a group. It was calculated based on the formula: Σ 1 or 0 point for each target respectively achieved as desired or not in the single orbit / overall number of desired targets for the orbits of a group.

Calculated excluding in this group the 3 orbits in which the target was no achieved (in one because of exophthalmos, in the other two because of hypo-correction) and which were considered failed surgeries in respect to desired exophthalmos reduction.
Effects on central and peripheral fields of diplopia

The effect of decompression surgery on binocular vision was assessed based on retrievable information from medical records of 75 out of the 84 included patients. Nine patients were excluded because functional or anatomical monocularity, suppression, or anomalous retinal correspondence.

A MIIP of 78.33\pm25.5\% was associated with a ID of 0.59: diplopia was induced by decompression in 8 (13.8\%) of the 58 patients who had no preoperative central diplopia, and disappeared in 4 (23.5\%) of the 17 patients who had preoperative central diplopia. In the other patients of this latter group, central diplopia improved in 2 (11.9\%), worsened in 3 (17.6\%) and remained unchanged in 8 (47.0\%). Of the 50 patients without pre- or post-decompression central diplopia, 2 (4.0\%) and 5 (10.0\%) had decreased and increased extension of the field of peripheral diplopia after surgery.

The NSA did not disclose differences between patients with preoperative diplopia who were cured by decompression and those who were not and between those who developed post decompression diplopia and those who did not with respect to preoperative characteristics, MIIP and symmetry of surgery. The same results were found also by

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**Table 3. Invasiveness of Applied Decompression Surgery and Its Effect on Ductions for Orbits Grouped for Target “Amount of Desired Exophthalmos Reduction”**

<table>
<thead>
<tr>
<th>Stabilization</th>
<th>Orbits which required moderate to maximal exophthalmos reduction (≥3 mm, &lt;enophthalmos / hypoglobus*), (n=82)</th>
<th>Orbits which required none to minimal exophthalmos reduction (≤ 2mm) (n=11)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Index of invasiveness orbit (MIIO) ± SD, %**</td>
<td>90.4±16.0</td>
<td>45.4±31.3</td>
<td><em>P = 0.000</em></td>
</tr>
<tr>
<td>Mean decompression-induced variations in ductions ± SD, degrees**</td>
<td>4.0±8.2</td>
<td>2.6±5.0</td>
<td>P = 0.598</td>
</tr>
<tr>
<td>Abduction</td>
<td>-0.3±6.7</td>
<td>1.4±6.1</td>
<td>P = 0.426</td>
</tr>
<tr>
<td>Adduction</td>
<td>5.5±8.0</td>
<td>6.3±5.1</td>
<td>P = 0.722</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.2±10.7</td>
<td>1.7±10.4</td>
<td>P = 0.566</td>
</tr>
</tbody>
</table>

\* exophthalmos / hypoglobus = excessive reduction of exophthalmos or eye globe dystopia for which surgical correction was advised or performed.

** Four progressively invasive surgical classes were defined in the single orbit (A = minimally invasive to D maximally invasive, with an attributed index of invasiveness orbit (IIO) ranging from 25\% for class A to 100\% for class D), MIIO is the mean index of invasiveness for the orbits of a given group.

** Mean decompression-induced variations in ductions was defined as the average difference between pre- and post-operative ductions measured in degrees by mean of a perimeter. Calculations were performed when pre- and post-decompression orthoptic data were available: orbits requiring “moderate to maximal exophthalmos reduction” = 82/130; orbits requiring “none to minimal exophthalmos reduction” = 11/21.

Increased ductions are negative numbers, bold text when t test for paired data indicated a significant (P<0.05) variation in ductions after decompression.
Table 4. Orbits Grouped for Target "Amount of Desired Exophthalmos Reduction" and Stratified for Classes of Surgical Invasiveness Are Compared for the Effect of Surgery on Exophthalmos Reduction and Decompression Induced Changes in Ductions

<table>
<thead>
<tr>
<th>Class of surgical invasiveness</th>
<th>Class of surgical invasiveness</th>
<th>Class of surgical invasiveness</th>
<th>Class of surgical invasiveness</th>
<th>Significance**</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (IIO*=25%)</td>
<td>B (IIO*=50%)</td>
<td>C (IIO*=75%)</td>
<td>D (IIO*=100%)</td>
<td></td>
</tr>
<tr>
<td>Mean exophthalmos reduction ± SD, mm:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>orbits which required moderate to maximal exophthalmos reduction (n=127/151)**</td>
<td>3.4±0.5</td>
<td>4.2±1.2</td>
<td>5.4±2.0</td>
<td>(P = 0.000)</td>
</tr>
<tr>
<td>orbits which required none to minimal exophthalmos reduction (n=21/151)</td>
<td>1.5±0.5</td>
<td>1.5±0.6</td>
<td>1.8±0.4</td>
<td>(P = 0.627)</td>
</tr>
</tbody>
</table>

| Significance*** | \(P = 0.000\) | \(P = 0.000\) | \(P = 0.000\) |

| Mean decompression-induced variations in ductions ± SD, degrees\(^2\): | | | | |
| orbits which required moderate to maximal exophthalmos reduction (n=82) | | | | |
| Abduction | Adduction | Elevation | Depression |
| -3.1±10.3 | 2.1±6.8 | 5.4±7.8 | \(P = 0.017\) |
| -7.4±6.8 | 3.0±8.1 | -0.3±5.6 | \(P = 0.002\) |
| 2.1±9.6 | 3.4±6.9 | 6.5±8.0 | \(P = 0.199\) |
| -16.7±16.8 | -1.6±9.5 | 2.2±8.2 | \(P = 0.000\) |

| orbits which required none to minimal exophthalmos reduction (n=11) | | | | |
| Abduction | Adduction | Elevation | Depression |
| 4.6±4.6 | 4.0 | -8.0 | 0.5±3.5 | \(P = 0.084\) |
| 1.9±6.6 | 1.0 | 5.0 | -1.5±9.2 | \(P = 0.886\) |
| 3.3±9.1 | 0.0 | 6.0 | -5.0±21.2 | \(P = 0.813\) |

| Significance*** | \(P = 0.541\) | \(P = 0.165\) | \(P = 0.387\) |
| \(P = 0.291\) | \(P = 0.813\) | \(P = 0.779\) |
| \(P = 0.420\) | \(P = 0.740\) | \(P = 0.998\) |
| \(P = 0.390\) | \(P = 0.609\) | \(P = 0.251\) |

\* Four progressively invasive surgical classes were defined in the single orbit (A = minimally invasive to D maximally invasive, with an attributed index of invasiveness orbit (IIO) ranging from 25% for class A to 100% for class D)

\**Significance refers to comparisons among different classes of invasiveness, within 2 groups of orbits which required exophthalmos reduction "moderate to maximal" (≥ 3 mm) or "none to minimal" (≤ 2 mm).

\***Significance refers to comparisons between 2 groups of orbits which required exophthalmos reduction "moderate to maximal" (≥ 3 mm) or "none to minimal" (≤ 2 mm), within different classes of invasiveness.

\(^2\)Mean decompression-induced variations in ductions was defined as the average difference between pre- and postoperative ductions measured in degrees by mean of a perimeter. Calculations were performed when pre- and post-decompression orthoptic data were available: orbits requiring "moderate to maximal exophthalmos reduction" = 82/130; orbits requiring "none to minimal exophthalmos reduction" = 112/21. Increased ductions are negative numbers, bold text when t test for paired data indicated a significant \(P<0.05\) variation in ductions after decompression.

Comparing patients affected by preoperative diplopia and cured by decompression with those who presented decompression induced diplopia (Table 5).
Table 5. Preoperative Characteristics, Surgical Outcomes and Surgical Invasiveness in Patients Whose Preoperative Diplopia Was or Was not Cured by Decompression Surgery, and in Patients with or without Decompression Induced Diplopia

<table>
<thead>
<tr>
<th>Patients whose preoperative central diplopia was cured by decompression (n. 4/17)</th>
<th>Patients whose preoperative central diplopia was not cured by decompression (n. 13/17)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at decompression ± SD, yrs*</td>
<td>51.7±17.9</td>
<td>52.1±7.5</td>
</tr>
<tr>
<td>Mean duration of the orbitopathy at decompression ± SD, mts**</td>
<td>43.5±24.9</td>
<td>25.5±11.0</td>
</tr>
<tr>
<td>Mean pre decompression Hertel values ± SD, mm</td>
<td>20.1±1.8</td>
<td>20.1±2.1</td>
</tr>
<tr>
<td>Mean exophthalmos reduction ± SD, mm</td>
<td>5.1±4.3</td>
<td>3.5±2.0</td>
</tr>
<tr>
<td>IIO symmetry Symmetric</td>
<td>50%</td>
<td>Symmetric 30.7%</td>
</tr>
<tr>
<td>MIIP[^2]</td>
<td>68.7±36.1</td>
<td>68.3±28.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients who developed diplopia subsequent to decompression surgery (n. 8/58)</th>
<th>Patients who did not develop diplopia subsequent to decompression surgery (n. 50/58)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at decompression ± SD, yrs*</td>
<td>43.6±6.7</td>
<td>44.0±9.7</td>
</tr>
<tr>
<td>Mean duration of the orbitopathy at decompression ± SD, mts**</td>
<td>44.3±29.6</td>
<td>50.4±51.5</td>
</tr>
<tr>
<td>Mean pre decompression Hertel values ± SD, mm</td>
<td>20.0±1.4</td>
<td>21.3±2.2</td>
</tr>
<tr>
<td>Mean exophthalmos reduction ± SD, mm</td>
<td>4.3±1.4</td>
<td>4.1±2.0</td>
</tr>
<tr>
<td>IIO symmetry Symmetric</td>
<td>75%</td>
<td>Symmetric 66%</td>
</tr>
<tr>
<td>MIIP[^2]</td>
<td>90.6±18.6</td>
<td>80.7±24.0</td>
</tr>
</tbody>
</table>

*yrs=years
**mts=months
[^2] Four progressively invasive surgical classes were defined in the single orbit (A = minimally invasive to D maximally invasive, with an attributed index of invasiveness orbit (IIO) ranging from 25% for class A to 100% for class D). Symmetric IIO was when IIO right side = left; asymmetric IIO when IIO right side ≠ left or in any monolateral decompression.
[^3] In order to characterize different groups of patients for invasiveness of decompression surgery, a mean index of invasivety patient (MIIP) was calculated based on the formula 0.5 x Σ IIO / number of patients included into the group (the coefficient 0.5 in the formula was chosen because in a patient the contribution of each orbit to invasiveness is 50%).

Complications

No patients had relevant intraoperative or perioperative complications. One patient had an excessive correction of exophthalmos and developed 3 mm enophthalmos and 2 mm hypoglobus of the left side necessitating surgical correction (Figure 1). Another patient developed a posttraumatic neuroma of the infraorbital nerve, and has been previously reported.10
Discussion

Different techniques are used for decompression surgery in GO and each of them can be personalized at patient’s and surgeon’s convenience for invasiveness and technical variations. Most of the study up until now provide a careful description of the surgical procedures, but invasiveness and technical variations have been left undetermined. In this study, the uniform execution of surgery secured by selecting patients operated by one surgeon, and indices such IIO, MIIO and MIIP were aimed at a better classification of applied decompression surgery for the benefit of study comparisons.

There are multiple indications for decompression surgery in GO. Hence the evaluation of its results should be inseparable from the assessment of the achievement of the targets, for which it has been performed. Only a precise, quantitative assessment of target achievement can allow meaningful and straightforward comparisons of the effectiveness of decompression surgery within and among studies. Our input to this goal was represented by clear definitions of targets, scoring of target achievement and corresponding MITAO and MITAP indices. The NSA which includes descriptive figures (Table 1) and easily interpretable quantitative indices is specific for decompression surgery and can be regarded as a further step in defining the overall response to treatment as proposed by EUGOGO.

Figure 1. The patient who developed left enophthalmos subsequent to inferomedial orbital decompression. (Top) The patient at first ophthalmologic evaluation. (Bottom) The patient after bilateral orbital decompression, correction of strabismus, and correction of left hypoglobus and enophthalmos. Left lower lid retraction was still present and amenable of possible surgical correction.
In the NSA, all targets chosen for the assessment of rehabilitative surgery outcomes are direct consequences of decompression induced decrease of intra-orbital pressure and globe displacement; decompression allows to reach these goals based on intraoperative estimations of resistance to retropropulsion of the globe, eye position and aspect of the periorbital region. Decompressions may influence eyelid positions and lid fissure width modifying vertical ductions, eyeball position, or as a consequence of eyelid scarring. Lid fissure width is therefore not controllable during decompression surgery and for this reason we did not consider it as a target in our study. Conversely dysthyroid lagophthalmos is a static consequence of eyelid retractions or of the relative eyelid shortening due to the presence of a protruding eye; its reduction can be assessed based on intraoperative estimations. The minimally invasive transinferior conjunctival fornix approach that we used in the present series, by minimally disrupting tissues, ease intraoperative estimations. Similar exophthalmometric values can cause different degrees of disfigurement when anthropomorphic characteristics like gender, ethnicity, shell and face conformation are considered. This has implications on the extent of required exophthalmos reduction; hence it is within the context of the targets to be achieved, and not, as it was previously done, on the basis of preoperative Hertel values per se, that traditionally used measures such as the amount of exophthalmos reduction assumes a specific means. High values of mean exophthalmos reduction, which for decades has been linked to effectiveness of decompression surgery, may, on the contrary, represent a complication when excessive or not desired.

Data concerning the potential of a given approach for exophthalmos reduction can be relevant when counseling patients, but are of less interest to those patients about to be operated for other targets. The latter patients in fact might be more interested in opposite informations, or rather the possibilities to use a particular type of decompression avoiding the induction of unwanted reduction of Hertel values, while still taking advantage of its other possible beneficial effects.

A similar perspective applies to the effects of decompressions on extraocular eye motility. Till now the incidence of decompression induced diplopia was considered a good safety marker. Although extremely valuable when counseling patients unaffected by diplopia prior to surgery it is unhelpful to patients who already have diplopia, and who would be more interested about the potential benefits of decompression to their double vision. The
ID, which merges in one single number information concerning frequency of decompression induced and cured diplopia, represents an easy means to describe diplopia-related intervals. This can have distinct advantages for comparisons within and among studies.

Decompression induced changes in ductions, which quantify the influences of surgery on extra-ocular monocular movements, are very valuable measures not only for study comparisons but also for counseling purposes. With respect to induced changes in ductions, the NSA is specific for decompression surgery and consistent with EUGOGO suggestion for clinical trials.

The above considerations were the rationale behind the NSA. Most of the novel observations are liable to speculative interpretations and might be cues for future studies.

We found that orbits for which “no to conservative exophthalmos reduction” was desired, had the lowest preoperative Hertel reading and belonged to the oldest patients, but did not have a longer duration of GO. This suggests a particular sub set of GO developing at older age. Additionally we showed that when combined steroids and radiotherapy were administered before decompression, orbits were less likely to need reduction of lagophthalmos. Reduction of periorbital oedema was needed less frequently in orbits with a longer duration of GO. This suggests that the use of medical options may reduce the need of surgical treatment of lagophthalmos, and that simply “tincture of time” may reduce the necessity of surgery for periorbital oedema.

Overall the inferomedial decompression approach with graded degree of invasiveness described in this paper resulted in a rather high degree of achievement of desired targets, with negligible occurrence of complications. In about 10% of the cases orbital decompression was not effective in reducing preoperative periorbital oedema, and indeed this target was achieved less frequently than the other.

When “no to conservative exophthalmos reduction” was desired, the observed MIIO was the lowest, and exophthalmos reduction was not related to the degree of surgical invasiveness. This latter finding is a substantial departure from the traditional concept that more extensive osteotomies result in higher mean exophthalmos reduction. Explanation of our finding can only be speculative; it can be linked (as observed at surgery) to the distinct lack of compliance of the soft tissues in many of the orbits included in the group whose target was “no to conservative exophthalmos reduction”. The statistically
significant less frequent administration of predecompression radiotherapy could have contributed to the stiffness of the soft orbital tissue observed in this group. Its differences in IIO were not relevant to decompression induced changes in ductions. Interestingly unlike for orbits whose target was exophthalmos reduction ≥ 3mm, a maximal surgical invasiveness of 100% was not associated with any change ductions. The explanation of this is again speculative and in line with the previous one. In this group of orbits, despite maximally sized osteotomies, reduced compliance of the soft orbital tissue might have resulted in minimal if any displacement (and scarring) of the soft orbital tissues, including extraocular muscles. In line with this perspective, a lower surgical invasiveness of 25% which was presumably associated with better compliance of soft orbital tissues, was related to reduction of preoperative abduction and elevation.

In all groups, independent of the amount of desired exophthalmos reduction, IIO 75% was neutral to ductions, while invasiveness 50% (which is a commonly used pattern of osteotomies for the treatment of disfiguring exophthalmos either through a trans cutaneous, or a swinging eyelid approach) was beneficial to altered adduction and depression.

Apart from the observed novel figures the main value of the NSA is that of providing a more comprehensive outlook. Although the NSA may appear more complete, precise and reliable than the TGA, the NSA it is far from being ideal. Variations in morphology of the orbital cavity and in orbital osteology might significantly influence the degree of exophthalmos reduction which can be obtained by standardized decompression procedures.\(^\text{14}\) In our study, the influence of different osteotomies weighed for invasiveness of applied surgery on outcomes of decompression surgery remains unexplored. Additionally in our analysis the lipogenic or myopathic nature of the orbital disease was not taken into account, nor was the orbital compliance which is not directly measurable before decompression. For these reasons the figures given by our method cannot be considered absolute when counseling patients about to undergo surgery. Depending on the soft tissue response to surgery, the invasiveness of the planned approach, if not the surgical technique itself, may need to be changed during surgery. Nevertheless when counseling patients, the observations generated by our novel approach can be offered to them as a possible case scenario. The same observation are also invaluable to the surgeon faced with intraoperative decision making for balancing risk benefits of his / her eventual choices.
Finally the time frame that we chose to study the outcome of decompression surgery was relatively short and therefore suboptimal for assessing long-term complications such as permanent dysesthesias of the infraorbital nerve or sinus obstructions. We however regard our choice as justifiable because it was aimed at reducing the influence of confounding factors linked to further post decompression rehabilitative procedures. Despite its shortcomings the value of this study lies in its innovative perspectives and in having pioneered a new path linking specific needs, and background characteristics of the patients to a detailed graded surgical approach. This therefore has the potential to be a step towards the final goal of a desirable, and as much as possible, evidence based customized approach to orbital decompression.
References


5. www.eugogo.eu


Chapter 5

The Removal of the Deep Lateral Wall in Orbital Decompression: Its Contribution to Exophthalmos Reduction and Influence on Consecutive Diplopia

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Abstract

Purpose: To evaluate the contribution of maximal removal of the deep lateral wall of the orbit to exophthalmos reduction in Graves’ orbitopathy and its influence on the onset of consecutive diplopia.

Design: Case-control study.

Methods: The medical records of two cohorts of patients affected by Graves’ orbitopathy with exophthalmos >23 mm, without preoperative diplopia, were retrieved at random from the pool of patients decompressed for rehabilitative reasons at our institution (01/1990 to 12/2003), and retrospectively reviewed. They had been treated with an extended (cases, group 1, n = 15) or conservative (controls, group 2, n = 15) 3-wall orbital decompression performed through a coronal approach. The deep portion of the lateral wall had been removed in the extended decompression group while preserved in the conservative decompression group. Demographics, preoperative characteristics, and surgical outcome were compared. The difference in mean exophthalmos reduction between groups 1 and 2 was considered to be the contribution of the deep lateral wall to reduction of exophthalmos.

Results: Groups 1 and 2 were drawn from a pool of 37 and 335 patients, respectively. Demographics and preoperative characteristics of the two groups were not significantly different. The mean contribution of the deep lateral wall to exophthalmos reduction was 2.3 mm. The onset of consecutive diplopia was not significantly different between the two groups (case n = 2/15, controls n = 5/15; P = 0.203). Diplopia resolved spontaneously in all the patients of group 1, while all the patients of group 2 required surgery.

Conclusions: Removal of the deep lateral orbital wall as part of a coronal-approach, 3-wall decompression, enhances the degree of exophthalmos reduction without increasing the risk of consecutive diplopia.
Chapter 5

Introduction

The natural history of Graves’ orbitopathy has been known for many years and yet, the etiopathogenesis of this autoimmune disease remains unknown and consequently no specific medical therapy currently exists. Corticosteroids or radiotherapy may modulate the initial inflammatory dynamic phase by reducing its duration and by reducing the tendency to progression towards more severe signs and symptoms. Nevertheless, a considerable proportion of patients require decompression surgery either for functional reasons or for esthetic rehabilitation.

The history of orbital decompression surgery can be dated back to 1911 when Dollinger first proposed orbital enlargement by removing the lateral wall for the cure of exophthalmos. Since then, various osteotomies involving one or more of the other orbital walls have been proposed, and recently the lateral wall, and in particular its deeper portion, has been described as an elective zone of possible orbital volume expansion. The potential volume for soft orbital tissue expansion after the removal of the lateral wall or its deeper part has been measured and in terms of exophthalmos reduction, the possible advantage of the strategic location of the deeper portion, just behind the globe, has been emphasized. Additionally, in contrast to medial or inferior orbital decompression, deep lateral wall osteotomy is not at the mercy of potential limitations imposed by coexisting pathology of the paranasal sinuses.

The contribution of any osteotomy to clinical decompression is not only dependent on its volume and location: many patient-related characteristics such as the stage of the orbitopathy at the time of surgery, orbital compliance, and preoperative Hertel readings can play a role in the final reduction of the exophthalmos. Consequently, controlled studies are necessary to validate and quantify the actual effect of any given bone removal and although deep lateral wall osteotomy has been described in several clinical studies, its contribution to exophthalmos reduction remains undetermined. We, therefore, found it interesting to measure the contribution of the deep lateral wall to exophthalmos reduction and secondarily to evaluate its influence on the onset of consecutive diplopia.
Patients and Methods

The medical records of a cohort of 15 patients randomly chosen from the pool of patients with Graves’ orbitopathy decompressed at the Orbital Center, Department of Ophthalmology, University of Amsterdam between January 1990 and December 2003, who had the deep portion of the lateral wall extensively removed during a 3-wall orbital decompression performed by a coronal approach (cases, group 1) were retrospectively reviewed.

Demographics (gender and age at surgery), preoperative characteristics (duration of the orbitopathy at surgery, immunosuppressive treatments, Hertel values), and surgical outcome (reduction of exophthalmos, frequency, and time course of postdecompression diplopia) were compared with the same data obtained by reviewing the medical records of another cohort of 15 patients (controls, group 2), also selected at random from the pool of patients treated, in the same time interval, with a 3-wall orbital decompression performed by the same route, but who had a more conservative removal of the lateral orbital wall which, as previously described and is traditional for our center, was limited to its anterior portion. The mean difference in exophthalmos reduction between the two groups was considered to be attributable to the contribution of the deep lateral wall to exophthalmos reduction.

All complications other than consecutive diplopia were recorded. Postoperative Hertel values were considered those measured at the first ophthalmologic examination performed at least 6 months after decompression. Right and left sides were not evaluated separately.

Selection of cases and controls was performed with a random number table.

Inclusion Criteria

We included patients: (1) who presented with moderate/severe exophthalmos, defined as eye protrusion ≥ 23 mm on the less affected side; (2) who were operated on bilaterally for rehabilitative reasons; and (3) who did not have preoperative diplopia, defined as double vision within 20 degrees around the primary position of gaze.

Exclusion criteria

We excluded patients: (1) who presented with preoperative exophthalmos < 23 mm on the less affected side; (2) who underwent surgery on only one side; (3) who underwent decompression for optic neuropathy or exposure keratopathy; (4) who had preoperative diplopia as defined above; and (5) who had a postoperative follow-up period ≤ 6 months.
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Statistical analysis

The analysis was conducted by means of a database created using version 11.5 of the SPSS statistical analysis software package (http://www.spss.com). Student t test was used to compare continuous variables showing no marked deviations from the normal distribution. For other continuous variables or ordinal variables, the Mann-Whitney U-test was used. Categorical preoperative and postoperative data were investigated using the $\chi^2$ test.

Surgical technique

The surgical approach to orbital decompression was the same for cases and controls: a coronal incision was made with a no. 10 blade from ear to ear, 3 to 4 cm behind the hairline. The incision extended down to the periosteum of the parietal bones centrally, and to the deep temporalis fascia laterally. Bleeding from the wound edges was controlled with Raney scalp clips. In the central portion of the skull, a subperiosteal plane was created by blunt dissection and laterally a surgical plane was bluntly developed between the deep and the superficial temporalis fascia. Laterally and inferiorly, where the deep temporalis fascia divides into a deeper and a more superficial layer to enclose Yasargil’s superficial temporal fat pad, the surgical dissection was carried out directly against the deeper division of the fascia.

The forehead flap thus created was then turned down to expose the superior and lateral orbital rims. The supraorbital nerve was set free by chiselling its bony foramen when present, and the periorbita, including the trochlea, was dissected off the orbital bones and the temporalis muscle was dissected from its anterior origin with a no. 10 blade and periosteal elevators, exposing the lateral orbital wall while leaving sufficient tissue for suturing at the end of surgery.

In group 2, only the anterior portion of the lateral orbital wall behind the orbital rim (which was left intact) was removed, “allowing a fingertip to pass through”12,18 (Figure 1). In group 1, the osteotomy of the lateral wall was started as for patients of group 2 but was then extended inferiorly up to the inferior orbital fissure with bone punches and posteriorly up to the dura of the middle cranial fossa by mean of bone punches and a surgical high-speed drill equipped with a cutting-burr or a diamond-burr tip (Figure 2). While removing the lateral orbital wall, the soft orbital tissues and the temporalis muscle were retracted and protected with malleable orbital retractors.
Bone removal was discontinued when small spots of dura were exposed through the thin inner cortical bone of the greater wing of the sphenoid, as any further removal might have increased the risk of complications without substantially contributing to creating space (Figure 2, bottom).

In each group, the removal of the medial wall and the floor of the orbit was the same: after having retracted the soft orbital tissues with malleable orbital retractors, a Fraizer suction tip was used to fracture the delicate bone of the medial orbital wall and the floor, and Blakesly forceps no. 1 and no. 2 were used to remove bony fragments and mucosa of the sinuses. The bulla ethmoidalis beneath the fronto-ethmoidal suture was opened towards the orbit from the posterior lacrimal crest up to the orbital apex, and the orbital floor medial to the infra-orbital canal was then removed from 0.5 cm behind the inferior orbital rim up to the posterior wall of the maxillary sinus. The posterior two thirds of the maxillary ethmoidal strut were removed, creating a wide antrostomy, while the anterior one third of the strut was left intact to reduce the risk of globe displacement and the possibility of medial entropion.

Finally, the periorbita was incised to promote maximal prolapse of the orbital tissues into the newly created spaces, the temporalis muscle was sutured back in to position with four to five interrupted 2/0 mersilene sutures and after the insertion of one Redon drain catheter into each temporalis fossa the scalp incision was closed with iron staples.
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Figure 1. Conservative lateral wall osteotomy as part of a 3-wall orbital decompression in a patient with Graves’ orbitopathy. Postoperative computer tomography scan showing the removal of the lateral orbital wall in a patient of group 2. The osteotomy was limited to the anterior portion of the lateral wall. Bone removal was discontinued when small spots of dura were exposed through the thin inner cortical bone of the greater wing of the sphenoid, as any further removal might have increased the risk of complications without substantially contributing to creating space (Figure 2, bottom).

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Figure 2. Extended lateral wall osteotomy as part of a 3-wall orbital decompression in a patient with Graves’ orbitopathy. (Top) Postoperative computer tomography scan showing the removal of the lateral orbital wall in a patient of group 1. The osteotomy was extended to the more posterior portion of the lateral wall. (Bottom) Intraoperative photo showing the removal of the deep lateral orbital wall by a coronal approach. A spot of exposed dura is evident (arrow).

Figure 3. A patient of group 1. (Top) The patient at admittance for orbital decompression. (Bottom) The patient 4 months after surgery. An adequate decompression had been achieved, esophoria, and deficit of accommodation which were present soon after surgery were disappeared, a mild anisocoria persisted.
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Results
Patients in group 1 were drawn from a pool of 37, while patients in group 2 were drawn from a pool of 335. The patients’ demographics and preoperative characteristics are summarized in the table.

The mean reduction of exophthalmos was 7.2 mm (SD = 2.3) in group 1 and 4.9 mm (SD = 1.1) in group 2 and the mean reduction of exophthalmos in group 1 was significantly higher than in group 2 ($P = 0.001$). The contribution of the deep lateral wall to exophthalmos reduction was 2.3 mm, giving the patients of group 1, on average, a 32.0% greater degree of exophthalmos reduction. Decompression-induced diplopia arose in two (13.3%) of the 15 patients of group 1 and in five (33.3%) of the 15 patients of group 2, although the difference in onset of decompression-induced diplopia between the two groups was not statistically significant ($P = 0.203$). Both of the patients of group 1 with postoperative diplopia presented with an esotropia and a deficit of abduction that resolved spontaneously 4 to 6 months after surgery, while all five patients of group 2 with postoperative diplopia presented with esotropia and in two cases there was associated vertical strabismus: all of these patients required subsequent surgical correction once the squint angle became stable. One of the two patients of group 1 with postoperative diplopia presented with mild persistent anisocoria and a transient deficit of accommodation of the left eye (Figure 3).

Discussion
In the 1980s, when the number of orbital decompression procedures being performed started to rise as surgery was being undertaken not only for functional reasons, but also for the esthetic/psychosocial rehabilitation of patients with Graves’ orbitopathy, the antral-ethmoidal decompression by a transantral approach, as described by Walsh and Ogura in 1957, was the mainstay technique. The major disadvantage reported with transantral surgery was subsequent motility imbalance as high as 52% and, therefore, alternative procedures were sought in an attempt to decrease the risk of decompression-induced diplopia. In cases of mild exophthalmos, trans-lid antral-ethmoidal decompression appeared to be a valid alternative, with a risk of iatrogenic diplopia in only 4.6% of patients and for more severe exophthalmos, inferomedial decompression was used in combination with lateral decompression. Such procedures, whether performed with separate periorbital incisions or through a coronal approach, were also related with a low incidence of
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Recently, the lateral orbital wall has been promoted as being the region of first choice for orbital decompression. Its removal, which is connected with a low risk of consecutive diplopia or severe complications such as cerebrospinal fluid leak, perfectly fits the needs of the increasingly demanding patient population. The lateral wall of the orbit is the thickest orbital wall and is composed of the zygomatic bone anteriorly and the greater wing of the sphenoid posteriorly. The thinnest part of the lateral wall is at the zygomaticosphenoid suture, approximately 1 cm behind the orbital rim, and approximately 1 cm behind the

**Table.** Demographics and Preoperative Characteristics in Patients Treated With Extended (Cases, Group 1) or Conservative (Controls, Group 2) Removal of the Lateral Orbital Wall as Part of a Coronal-approach, 3-wall Decompression

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=15)</th>
<th>Controls (n=15)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>80%</td>
<td>86.66%</td>
<td>$P = 0.624$</td>
</tr>
<tr>
<td>Age at surgery (yrs, ± SD)</td>
<td>40.9 (9.7)</td>
<td>40.1 (12.4)</td>
<td>$P = 0.852$</td>
</tr>
<tr>
<td>Duration of Graves’ orbitopathy at surgery (yrs, ± SD)</td>
<td>5.43 (5.8)</td>
<td>3.78 (2.1)</td>
<td>$P = 0.314$</td>
</tr>
<tr>
<td>Preop. immunosuppressive therapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) corticosteroids</td>
<td>20%</td>
<td>13%</td>
<td>$P = 0.500$</td>
</tr>
<tr>
<td>b) orbital radiotherapy</td>
<td>27%</td>
<td>47%</td>
<td>$P = 0.225$</td>
</tr>
<tr>
<td>c) corticosteroids and orbital radiotherapy</td>
<td>13%</td>
<td>7%</td>
<td>$P = 0.500$</td>
</tr>
<tr>
<td>d) neither corticosteroids nor orbital radiotherapy</td>
<td>40%</td>
<td>33%</td>
<td>$P = 0.500$</td>
</tr>
<tr>
<td>Preoperative Hertel values (mm, ± SD)</td>
<td>26.3 (2.4)</td>
<td>25.0 (1.4)</td>
<td>$P = 0.123$</td>
</tr>
</tbody>
</table>
zygomaticosphenoid suture the sphenoid bone thickens where it divides to form the anterior corner of the middle cranial fossa.22 Here compact bone passes into thick cancellous bone to form a trigonus, nicknamed the “door-jamb” by Goldberg who, more than any other author, has stressed the importance of this zone of possible orbital expansion.9,10 Experimental studies on the basis of dry skulls and clinical radiologic surveys have quantified the absolute volume expected from the lateral orbital wall to clinical decompressions.8,9 Although there is considerable interindividual variability, the doorjamb represents a mean volume of 2.9 cm³ and because of its anatomical position located directly behind the globe, an almost millimeter-for-millimeter relationship between door-jamb removal and exophthalmos reduction was hypothesized.9,10 However, even by the use of a coronal approach where excellent access to the deep lateral wall can be obtained, thus permitting the possibility of performing the widest possible osteotomy, the volume of the doorjamb should be regarded as an idealized measurement that is impossible to be used fully for clinical decompressions.9 In addition to the volume and location of a given orbital wall, several disease-dependent variables can, in clinical practice, influence the possible reduction of exophthalmos. The stage of the orbitopathy at the time of surgery, the distensibility and plasticity of the soft orbital tissues and the degree of preoperative exophthalmos have all been highlighted as possible factors determining the final outcome of decompression surgery.11-13

Although removal of the deep lateral wall has been reported in several clinical trials9, 10, 14-17, its contribution to exophthalmos reduction has never been specifically studied. Additionally, the extreme heterogeneity of the patients included in each series and the variation of applied surgical techniques do not permit any attempt of its quantification on the basis of the data already available in the literature. In our study, the calculated contribution of the deep lateral wall to exophthalmos reduction can be regarded as maximal and on the basis of a homogeneous population of patients with Graves’ orbitopathy. We selected patients operated by the coronal approach, which permitted maximal removal of the deep lateral wall in the group 1 patients, and we chose to consider the reduction of exophthalmos later than 6 months after decompression as exophthalmos reduction is expected to be maximal in most of the decompressed patients by this time.18 Furthermore,
in our study, surgical access and inclusion and exclusion criteria were identical for the two groups, and we found no difference in the demographics or preoperative characteristics between groups 1 and 2.

We found that removal of the deep lateral wall contributed a mean of 2.3 mm to exophthalmos reduction. Interestingly, the standard deviation of the exophthalmos reduction in group 1 was approximately twice that of group 2 and we interpret this finding as a manifestation of the known interindividual variability of the volume of the deep lateral wall.

Removal of the deep lateral wall during 3-wall orbital decompression was not found to be associated with an increased risk of consecutive diplopia when compared with the more conservative 3-wall orbital decompression applied in group 2. Furthermore, both patients in group 1 who presented with consecutive esotropia and deficit of abduction after removal of the deep lateral wall experienced a spontaneous resolution of their strabismus 4 to 6 months after surgery. Transient strabismus after deep lateral wall removal has previously been reported. Deep mechanical contusions of the soft orbital tissues associated with the wide exposure that is necessary to accomplish the osteotomy with a cutting-burr can be regarded as a possible cause of this transient strabismus that most probably has a paralytic, rather than a restrictive, etiology and this hypothesis is supported by the simultaneous, mild anisocoria, and transient deficit of accommodation demonstrated by one of our patients.

Given the multifaceted nature of Graves’ orbitopathy, the numerous indications for decompression surgery and the many variations in surgical techniques, an ideal attempt to quantify the contribution of a specific osteotomy to exophthalmos reduction and consecutive diplopia must take the influence of these variables into account. We attempted to do this by selecting patients at random from a homogeneous group of patients with Graves’ orbitopathy undergoing surgery for the same indication and by utilizing a consistent surgical approach in each group. Nevertheless, we wish to acknowledge the limitations of our study. Our observations are retrospective, and patients were not randomly allocated to either of the two treatment groups. Additionally, our findings are only applicable to the specific population of patients with Graves’ orbitopathy as selected in this study, although our population, which was composed of individuals affected by moderate/severe exophthalmos, with no preoperative diplopia and treated exclusively for esthetic reasons, may be considered to be representative of a numerically significant and,
for obvious reasons, demanding subpopulation of patients with Graves’ orbitopathy. We, therefore, believe that our findings are of practical relevance when planning decompression surgery.

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Small Versus Coronal Incision Orbital Decompression In Graves’ Orbitopathy

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*Orbit 2010;29:177-82*
Abstract
Ideally the planning of decompression surgery should be adequate to the severity of the orbitopathy, its possible “lipogenic” or “myopathic” variants, the patient’s specific orbital osteology and possible previous surgeries. Due to surgeon’s experience and local traditions, however, a standardized rather than a tailored approach is often offered to the patient.
An inferior fornix incision can be used for infero medial bony decompression and/or for removing fat from the medial and lateral inferior orbital quadrants. Through the same route a lateral osteotomy can also be performed although an upper skin crease incision offers a wider access to the lateral orbital wall. As an alternative the swinging eyelid technique, offering an adequate access to the bony orbit and to the orbital fat compartments is a versatile technique that can virtually be used as a standard approach for the greatest majority of patients needing decompression surgery.
Orbital decompression by coronal incision is an invasive technique and for this not to be used as a standard approach to orbital decompression. Nevertheless, it is not to be abandoned as it can be an additional tool in surgeons’ hands when dealing with patients who can better benefit out of a particular, tailored rather than a standardised approach. Many are the circumstances in which this may happen.
Major complications associated with the coronal approach have been mainly described in small series, where only a few patients per year were operated. In this respect it is therefore unavoidable to emphasize that each technique has its own learning curve and it may be difficult to differentiate the effects of each technique from the experience of the surgeon.
For almost one century decompression surgery has been used to treat Graves’ orbitopathy (GO), and through the years it has been subjected to a paradigm shift in respect to indications, approaches, and surgical routes. This has been largely due to a better understanding of the multifaceted nature of the disease, a constant attempt to implement the beneficial effects of this type of surgery simultaneously decreasing the aesthetic impact of surgical scars, hospitalisation time, reconvalescence periods and risks for iatrogenic complications in general, and consecutive strabismus in particular. Patients’ increased expectations and a more critical attitude towards surgical interventions are also not negligible aspects that have driven the shift of orbital decompression surgery.

Orbital decompression was first used only to address sight threatening conditions, such as optic neuropathy refractory to medical therapy, or exposure keratopathy unresponsive to local measures and/or to minor eyelid surgeries. More recently the indications for orbital decompression were extended to the treatment of disfiguring exophthalmos and symptoms. Eyeball subluxation, which may be a possible cause of acute optic neuropathy and exposure keratopathy, postural visual obscuration in patients with congestive inactive GO and choroidal folds due to eyeball indentation by enlarged extraocular muscles represent other, more recently recognised functional indications for decompression surgery.¹

Expansion of the bony orbital boundary and fat removal had been the surgical methods to reduce the raised intra-orbital pressure. The two approaches, which developed through parallel routes up until recently, are no longer to be considered alternatives, but complementary possibilities concurring in tailoring the most adequate treatment to the specific patient’s needs.²

As indications and approaches also surgical routes to orbital decompression have been changed through the years. In the 1950s, when decompression surgery started to be used routinely for functional purposes or rehabilitation of patients with GO, transbuccal incisions were preferred to former visible and more invasive periorbital trans-cutaneous incisions. The coronal approach to orbital decompression introduced by Tessier (1969)³, used by Krastinova and Rodallec (1985)⁴ and later popularized by Leo Koornneef and his fellows beginning in the 1980s⁵-⁸, although virtually invisible in patients who do not present baldness, is a rather invasive access to the orbit. It is a common incision for plastic, maxillofacial and neurosurgical procedures, which gives a wide access to the bony orbit, but in general is not the surgical access to the orbit preferred by ophthalmologists, who are
more accustomed to microsurgery. There is no doubt that the coronal incision is a technique that requires more surgical skills and anatomical knowledge and a longer learning curve as compared with less invasive periorbital surgeries. However, once the technique is mastered the bicornual flap dissection, the exposure of the orbital walls, the completing of the osteotomies, and the closure of the surgical site are usually rapid and the duration of surgery is comparable with that required for decompressions through periorbital incisions. In males with prominent upper orbital frame, the elevation of the periostium can prove difficult, in fact slightly prolonging the surgical time.

With the coronal approach the exposure of the lateral orbital wall and the possibility of its manipulation are superior to any other orbitotomy. The medial wall is addressed from above in a centrifuge fashion in respect to the lamina cribrosa, virtually reducing the risk to damage the latter and to induce leakage of cerebrospinal fluid. On the other hand, the access to the orbital floor through a coronal approach can be sub-optimal depending on orbital osteology and compliance of the soft orbital tissue (Figure 1).

**Figure 1.** Coronal projections taken at the level of the middle orbit in two patients with Graves’ orbitopathy. Differences in osteology are highlighted. To approach the orbital floor by a coronal incision in a patient with an obtuse angle between the medial wall and the floor (top) may be less difficult than in a patient with an almost square angle at the same level (bottom). This concept may apply also within the same orbit as, in general, such an angle becomes more obtuse the deepest is the orbit.
The coronal incision continues to be used as the standard approach for orbital decompression in some centres, while only for selected patients in others.9 Because of its invasiveness and technical difficulties, not rarely, issues of concern are raised at meetings on whether or not this technique is to be abandoned, and if it can be fully replaced by other less invasive, but equally effective approaches. Based on the current literature, it is difficult to establish if the coronal approach continues to have a place in modern decompression surgery. My opinion can neither aim at increasing the level of evidence on the argument nor, due to my education as a fellow of Leo Koorneef, may it be a totally unbiased overview on the issue. Thus acknowledging these shortcomings, I hope that my experience with the coronal approach orbital decompression may result useful to highlight its possible advantages and limitations. The literature regarding the use of the coronal route to orbital decompression is limited, and only a few papers compare the coronal approach to other less invasive incisions.9-12 In addition, the evidence of the current literature on decompression surgery is impaired by its retrospective nature, the heterogeneity of the patient populations included in the published case series, the inhomogeneous perioperative medical regimens, which may or may not include glucocorticoids, the use of various surgical techniques which, thus falling under a given definition, (e.g., coronal incision) are virtually different concerning planes of dissection and, therefore, potentially connected with a different morbidity.7-9, 12, 13 As a result, most of the speculations available in the current literature regarding reliability and effectiveness of different techniques for decompression surgery are not proven conclusively.

In an attempt to estimate the effectiveness of various surgical techniques, a prospective comparison of different treatment modalities along with different decompression surgeries, using a powerful tool, such as the Graves’ orbitopathy quality-of-life questionnaire (GO-QoL)14, has been advocated15, and recently published by the EUGOGO consortium.9 The study showed that, except in rare cases where a tailored approach was offered to the patients, the choice of surgical technique continues to be based on personal experience and local tradition.

With such an attitude, exophthalmos reduction, complications, side effects, and patient satisfaction resulted grossly comparable and independent from the chosen technique. In light of this, if one technique should fit all, and personal experience and local tradition are the factors which regulate the choice of technique in decompression surgery, there is no
doubt that minimally invasive approaches are to be preferred to more invasive ones. However, to force patients into standardised surgical frames is suboptimal. Although on average results may be grossly comparable despite the used surgical technique, a standardised approach may be inadequate to the specific needs, and to the anatomic and pathologic substrate of the single patient. Ideally the planning of decompression surgery should be adequate to the severity of the orbitopathy, its possible “lipogenic” or “myopathic” variants, the patient’s specific orbital osteology, and possible previous surgeries.2

In clinical practice, this desirable approach to orbital decompression, which may imply the use of several different surgical techniques, is possible only in centres where adequate referral and a long-lasting tradition in orbital surgery favour transmission of expertise, warrant adequate back-up whilst giving the possibility to develop new techniques or to master ongoing variations of others. As this cannot be the case in most of the centres dealing with GO, the use of a standardised versatile approach is to be regarded as an acceptable although suboptimal alternative.

The swinging eyelid technique described first by McCord in the early 1980s16, with the conjunctival incision that can be extended medially as much as necessary, offering an adequate access to the bony orbit and to the orbital fat compartments is a versatile technique that can virtually be used for the vast majority of patients needing decompression surgery, independently from the orbital osteology and the compliance of the orbital soft tissues. As an alternative inferior fornix and upper skin crease incisions can be used separately or in association.

Sasim and co-authors in their retrospective survey of 200512 showed that the use of the swinging eyelid technique in 28 patients or coronal incision in 46 as a standardised approach for rehabilitative three wall orbital decompression could produce similar effects in terms of reduction of exophthalmos, induction of new onset diplopia and patient satisfaction. In a preceding series the incidence of diplopia following coronal and trans-lid orbital decompression was also not different.11

In 2003 Cruz and Leme had questioned if coronal approach continues to have a role in orbital decompression and concluded that there is little, if any need for this technique.10 Although the study design and the results of this paper could not offer a strong support to its conclusions, it is conceivable to share with Cruz and Leme their doubts with respect to
using an invasive approach, such as the coronal incision, as a standard route for orbital decompression. Nevertheless the coronal incision is not to be abandoned as it can be an additional tool in surgeons’ hands when dealing with patients who can better benefit out of a particular, tailored rather than a standardised approach. Many are the circumstances in which this may happen.

The coronal incision can be easily performed also in those GO patients presenting remarkable periorbital swelling or conjunctival chemosis in whom periorbital routes, including the swinging eyelid, may result inconvenient (Figure 2). The same applies to those patients in whom previous surgery might have adversely interfered with the periorbital lymphatic drainage. Possible scarring at the outer canthus, as it can occur with the swinging eyelid technique, can cause a complete impairment of the lymphatic drainage of the lower lid if a previously performed direct excision of lower lid bags, had already interrupted the lymphatic drainage towards the submandibular lymph nodes (Figure 3).

The coronal incision may be useful to minimise the number of periorbital incisions which may be necessary to accomplish a full rehabilitation in those patients, whose initial severe clinical picture suggests the necessity of multiple surgeries. This may result particularly advantageous in young or black patients who are more prone to develop evident scars. Through a coronal incision frontal lift, correction of glabellar rhytids or brow plasty, which are often necessary in patients with GO, can be performed simultaneously with orbital decompression and thus contribute to earlier surgical rehabilitation. Another elective use of the coronal incision is when extensive manipulation of the lateral wall is necessary or when the lateral wall including the lateral orbital rim is completely removed. The coronal approach implies the elevation of a periorbital subperiosteal plane which, different than with any direct periorbital incision, does not disrupt, full-thickness, the anatomical planes of the region. Consequently, depressed disfiguring iatrogenic scars due to adhesions between deep and more superficial layers, which are possible with periorbital incisions (Figure 4), are prevented by the use of a coronal approach (Figure 5).
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Figure 2. Preoperative (top) and postoperative (bottom) aspect of a patient affected by dysthyroid optic neuropathy, with remarkable periorbital swelling and conjunctival chemosis treated with a three wall orbital decompression by a coronal approach.

Figure 3. A patient presenting with scarring at the lateral canthus, left side after a three wall orbital decompression by swinging eyelid approach. The patient who had bilateral direct excision of lower lids bags eighteen months prior to decompression, continued to present persistent lower eyelid oedema, eight months after decompression, as a result of the interruption of residual lymphatic drainage to the preauricular lymph nodes.

Figure 4. A patient with Graves’ orbitopathy, who visited our clinic after being treated elsewhere with a complete lateral wall removal orbital decompression by a direct periorbital incision. The iatrogenic deformity caused to the lateral orbital rim is evident.

Figure 5. Preoperative (top) and postoperative (bottom) aspect of a patient affected by dysthyroid optic neuropathy, treated with an extensive 3-wall orbital decompression by a coronal approach, which included the total removal of the lateral orbital wall. No deformities of the lateral canthus or of the lateral orbital rim are evident in spite of the fact that the bony lateral frame was removed.
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Figure 5. Preoperative (top) and postoperative (bottom) aspect of a patient affected by dysthyroid optic neuropathy, treated with an extensive 3-wall orbital decompression by a coronal approach, which included the total removal of the lateral orbital wall. No deformities of the lateral canthus or of the lateral orbital rim are evident in spite of the fact that the bony lateral frame was removed.
The complete removal of the lateral orbital wall including the lateral orbital rim is an extreme procedure that may become necessary for functional (Figure 5) or more rarely for rehabilitative decompressions. In the case of severe infiltrative orbitopathy with elevated intraorbital pressure, the forces exerted by retractors in an attempt to reach and remove the deepest part of the medial orbital wall can increase the already high retrobulbar pressure up to critical levels for the optic nerve fibres and vasculature. The preventive removal of the lateral orbital wall permits to address more smoothly the orbital apex, reducing in fact, the risk to add an iatrogenic component to the pathologically high orbital pressure.

For obvious reasons, this approach may be extremely convenient when decompression has to be performed on an urgent basis for dysthyroid optic neuropathy or for severe corneal exposure if a descemetocele with impending risk for eyeball perforation is present. The endoscopic transnasal approach as first proposed by Kennedy et al., addressing the orbital apex without any substantial increase of the intraorbital pressure can be a valid alternative, although offering an inferior decompression effect if not associated with additional transcutaneous surgery which, in most of the cases, implies a multidisciplinary approach.

Finally, in course of rehabilitative orbital decompression, the presence of a shallow orbit, a small anterior orbital aperture, a myopic eyeball, a prolapsed lacrimal gland surrounded by a consistent amount of orbital fat also prolapsed (exorbitism), a partial dislocation of the eyeball in front of the lateral orbital rim in the case of extreme degrees of exophthalmos, may be situations that singularly or in different combinations can benefit by a total removal of the lateral orbital wall including its rim for optimizing the decompression effect.

Independently from whatever approach was used, a given number of possible common complications have been reported to affect decompression surgery. In this regard, the largest series reporting on coronal approach do not grossly differ from those in which more conservative periorbital incisions are used. Regarding the surgical route itself the possible complications connected with the coronal approach are different from those that may be related to periorbital incisions. The coronal approach leaving the eyelid undisturbed less likely than periorbital incisions can create complications which may potentially be harmful to the eye. Periorbital scarring, eyelid margin malpositions, lid retraction and ptosis, although rare events, are more likely to occur in decompression surgery periorbital incisions (Figure 6). On the other hand, temporal bossing, damage to the frontalis nerve,
scarring and alopecia at the site of scalp incision, or affecting ischemic areas of the frontal flap after healing by secondary intention, may complicate the coronal approach (Figure 7). Major complications connected with the coronal approach have been mainly described in small series where three\textsuperscript{10} or less\textsuperscript{13} patients per year were operated. In this respect it is therefore unavoidable to emphasize that each technique has its own learning curve and it may be difficult to differentiate the effects of each technique from the experience of the surgeon.\textsuperscript{10}

Besides the patient’s determination to accept major surgeries, and surgeon’s skills to perform them, the possibility of aiming at attaining only partial results should always be weighed in light of patients’ characteristics such as age, general health conditions, profession, education and psychosocial environment. Often conservative surgery is of maximal benefit to the patient in spite of modest final results that may be unattractive to the surgeon.\textsuperscript{20}
Figure 6. A patient one month after insufficient orbital decompression by upper skin crease incision performed in a not ophthalmologic setting (top). Lagophthalmos and extensive corneal damages due to entrapment of the orbital septum into the surgical scar are evident (bottom).

Figure 7. A patient decompressed by coronal approach. One month after surgery, an extended area of the frontal flap is granulating after an escharotomy. Scarring and alopecia of the area are to be expected.
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Figure 7. A patient decompressed by coronal approach. One month after surgery, an extended area of the frontal flap is granulating after an escharotomy. Scarring and alopecia of the area are to be expected.

References
Chapter 7

Reactivation of Graves’ Orbitopathy after Rehabilitative Orbital Decompression

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Ophthalmology 2007;114:1395-402
Abstract

Objective: To present and discuss three cases of apparent reactivation of Graves’ orbitopathy (GO) after orbital decompression and to evaluate the incidence of this phenomenon.

Design: Observational case series and retrospective follow-up study.

Participants: A few weeks after surgery 2 patients with GO (patients 1 and 2), treated at our institution with rehabilitative bony orbital decompression during the static phase of the disease showed clinical and radiologic evidence of reactivated orbitopathy. After this observation, a sample of 249 patients who had consecutively undergone the same treatment for the same reason before the second of the 2 observed patients was selected for this study.

Methods: The records of the selected patients were retrospectively reviewed searching for cases presenting with clinical and radiologic evidence of GO reactivated as a consequence of any type of bony orbital decompression. Patients treated with perioperative systemic glucocorticoids or who had concurrent periorbital diseases, injuries, or surgeries, or who had immunocompromised conditions or a follow-up of \( \leq 2 \) months, were excluded.

Main Outcome Measures: Incidence of reactivation. Clinical history, clinical and radiologic characteristics, treatment modalities, and time course of the reactivation in patients presenting with this phenomenon.

Results: Decompression surgery took place between 1994 and 2000. Eleven patients were excluded for having been treated with perioperative glucocorticoids. Only 1 patient (patient 3) presented with reactivation. The incidence of the phenomenon that we regard as reactivation of GO after rehabilitative bony orbital decompression was therefore 1.3% (3/239). In all 3 patients, the reactivation took place a few weeks after surgery, after an early normal convalescence period and could be controlled with systemic immunosuppression or orbital radiotherapy. None of the patients we report developed further episodes of reactivation during the follow-up period (mean, 7.5 years).

Conclusions: Based on its clinical characteristics, we suggest naming our observation delayed decompression related reactivation and we propose using its acronym DDRR when referring to it. Although DDRR appears to be a rare event, it is important for physicians and patients to be aware of its possible occurrence with rehabilitative decompression surgery.
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Introduction

In Graves’ orbitopathy (GO), signs and symptoms progressively increase in severity during an early dynamic, active, inflammatory phase; later, they become milder and relatively stable during a consecutive inactive, postinflammatory static phase. Prompt restoration of stable euthyroidism and immunosuppression, when necessary, may decrease the duration of the dynamic phase and reverse the tendency to progress toward more severe symptomatology. During the dynamic active phase, patients with functional complications such as optic neuropathy or exposure keratopathy can benefit from surgical expansion of the bony orbit when medical therapy fails.

Bony orbital decompression is the mainstay therapy for the treatment of stable alterations such as exophthalmos, periorbital congestion, and retro-ocular tension that typify the inactive postinflammatory phase of the disease. Worsening of the disease after bony decompression surgery performed for functional reasons during the inflammatory phase has been described, but it is debatable whether the phenomenon should be considered the natural progression of the active phase despite surgical intervention or a direct consequence of surgery.

In this paper, we present and discuss clinical history, clinical and radiologic characteristics, treatment modalities, and time course of a few cases of apparent reactivation of GO after orbital decompression performed for aesthetic rehabilitation during the inactive phase of the disease. Because we are unaware of previous reports of this phenomenon and could not find references to it in a computerized search using MEDLINE, we chose to evaluate its incidence by means of a retrospective survey.

Patients and methods

Our survey is an observational case series and retrospective follow-up study. A few weeks after surgery 2 patients (patients 1 and 2) treated with bony orbital decompression surgery at our institution for aesthetic rehabilitation during the inactive, postinflammatory phase of GO started showing clinical signs and symptoms and computed tomography (CT) evidence of reactivated orbitopathy. A sample of 249 records of patients with GO who had consecutively undergone the same treatment for the same reason before the second of the 2 observed patients were retrospectively reviewed to assess the incidence and clinical characteristics of the phenomenon, which appeared subsequent to orbital decompression.
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Inclusion Criteria

All patients presenting with clinical signs and symptoms of reactivated orbitopathy together with CT or magnetic resonance imaging evidence of increased extraocular muscle volume soon after rehabilitative bony orbital decompression surgery, carried out through any approach, were included as patients presenting reactivation of the orbitopathy subsequent to orbital decompression.

All patients not presenting with such characteristics were included as patients who did not present reactivation subsequent to orbital decompression.

Exclusion Criteria

Patients treated with perioperative systemic glucocorticoids or who had concurrent periorbital diseases, injuries, or surgeries, or who had immunocompromised conditions or a follow-up of ≤ 2 months, were excluded.

For the second of the observed patients, a 5-year follow-up period was chosen to accommodate the variable active phase duration of GO and we decided to invite for a final examination any patient included in the retrospective study as having reactivation of the orbitopathy. The latter included 1) evaluation of severity and activity of the orbitopathy respectively by means of “no signs or symptoms, only signs, soft tissues involvement with symptoms and signs, proptosis, extraocular muscle involvement, corneal involvement, sight involvement” (NOSPECS) classification7, which in our clinic is applied scoring right and left sides separately, and clinical activity score (CAS)8, and 2) the following blood tests: triiodothyronine, thyroxine, free thyroxine, thyroid stimulating hormone, thyrotropin binding inhibiting immunoglobulins, and thyroid peroxidase autoantibodies.

Results

The cohort of patients that we studied underwent decompression between 1994 and 2000. Eleven treated with perioperative systemic glucocorticoids to prevent postoperative aedema at the surgical site were excluded. Only 1 patient (patient 3) could be included in this study together with patients 1 and 2 as presenting reactivation of the orbitopathy subsequent to rehabilitative decompression. There were 236 patients who did not present reactivation. The incidence of the phenomenon that we regard as reactivation of GO after rehabilitative bony decompression surgery was therefore 1.3% (3/239). Demographics and pre- and post-decompression prominent clinical characteristics of patients 1, 2, and 3 are summarized.
in table 1. The clinical history as well as characteristics and time course of the phenomenon presented by the 3 patients are reported below.
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Patient 1

A 48-year-old Caucasian female presented with hypothyroidism in 1984 when she was 32. In early 1997, she developed bilateral GO, left more severe than right, that was treated with oral glucocorticoids between May 1997 and March 1999 and with orbital irradiation (2 Gray × 10 sessions = 20 Gray) in July 1997.

The patient was first seen at our center in June 1999. In January 2000, she was admitted for left rehabilitative inferior orbital decompression. The operation was carried out via an anterior transinferior fornix approach.

From the first examination at our center, the patient was euthyroid on levothyroxine replacement therapy and had presented with stable inactive orbitopathy. On admission for decompression, eyelid aperture was normal bilaterally; Hertel values were 16 mm right, 20 mm left; best-corrected visual acuity (BCVA) (pin hole) was right 20/25, left 20/30; and according to NOSPECS classification, the severity of the orbitopathy was 2ab, 300, 4aa, 50b (class 6 could not be scored due to a known amblyopia left > right). Clinical activity score was 0+/7. Bilateral limitation of elevation and diplopia in up gaze above 22 degrees were recorded. Orbital CT scan showed enlargement of the extraocular muscles more in the left orbit than in the right (Figure 1, top).

The first postoperative review carried out 10 days after surgery was unremarkable with minimal left periorbital aedema and symmetric Hertel readings of 16 mm. Starting from the third postoperative week, the clinical picture began to deteriorate progressively and for this the patient attended our outpatient clinic 4 weeks after surgery. This time the typical signs and symptoms of active orbitopathy were unequivocally present. Eyelid aperture was 15 mm on both sides, Hertel readings were 22 mm right and 19 mm left, and BCVA was unchanged as compared with preoperative BCVA. According to NOSPECS classification, the severity of the orbitopathy was 2ab, 300, 4aa, 50b could not be scored for the aforementioned reason. Clinical activity score was 7+/10 with signs of activity being more evident on the right non decompressed side. A bilateral limitation of elevation and diplopia in up gaze above 10 degrees was present. In addition, the volume of the extraocular muscles was consistently increased when pre- and post-decompression CT scans were compared (Figure 1).

Oral glucocorticoids (prednisone, total dose of 2.59 g; initial dosage of 60 mg/day tapered down over 15 weeks) administered starting in early April 2000 inactivated the orbitopathy.

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Exophthalmos decreased on the left to 17 mm; the right side remained 22 mm. In March 2002, the patient underwent a right rehabilitative inferomedial orbital decompression through an inferior fornix approach. This time the postoperative course was uneventful and right exophthalmos decreased to 17 mm. Bilateral eyebrow ptosis correction and upper lid blepharoplasty followed in February and July 2003, respectively.

The orbitopathy remained stable without signs of reactivation up to the last examination performed in May 2006, 6.3 years after the phenomenon that we regard as reactivation subsequent to rehabilitative orbital decompression. The patient has been euthyroid with levothyroxine replacement therapy, and thyroid autoimmunity has been abnormal for the entire review period at our institution (Table 1).

**Patient 2**

A 71-year-old Caucasian female was diagnosed with hyperthyroidism in 1969 at the age of 43. In September 1972, a few weeks after subtotal thyroidectomy, she developed GO with optic neuropathy. For this she was first treated with oral glucocorticoids and then with lateral orbital decompression bilaterally.

She first presented to our center in December 1981 (at age 52) with a disfiguring clinically inactive orbitopathy. The severity of the orbitopathy scored as 2cc, 3bb, 4aa, 500, and 600 with NOSPECS classification. Eyelid aperture was 14 mm right, 16 mm left; Hertel readings were 26 mm right, 28 mm left; and BCVA was 20/20 both sides.

In July 1994, clinical signs of active orbitopathy became evident. Hertel values rose to 30 mm right and 31 mm left, and BCVA dropped to 20/30 bilaterally. For this she was treated with a bilateral inferomedial orbital decompression through a translid approach in August 1994.

In 1995, several functional and aesthetic eyelid surgical procedures were carried out. Thereafter, for some years, the orbitopathy remained stable. Her BCVA was 20/30 and Hertel values 28 mm bilaterally; CAS was 0+/7. The patient was euthyroid and disturbed by a retro-ocular pressure feeling and symptoms related to exposure keratopathy.

In an attempt to improve her symptoms in September 2000, it was decided to proceed with a third orbital decompression, as despite 2 previous decompression procedures, most of the medial and lateral bony orbit was still intact (Figure 2, top). The procedure was carried out bilaterally by means of a combined transcaruncular and upper skin-crease approach.
After surgery, periorbital edema did not subside as expected, and starting from the third postoperative week typical clinical signs of active orbitopathy were clearly evident (Figure 3). NOSPECS classification and CAS worsened to 2cc, 3cc, 4cc, 5bb, 6aa, and 7+/10 respectively. In addition, postoperative orbital CT scans showed an increased enlargement of extraocular muscles as compared with preoperative scans (Figure 2). Her BCVA did not worsen and Hertel values remained unchanged despite the extensive osteotomies. In April 2001, the patient underwent simultaneous treatment with IV and oral glucocorticoids (IV methylprednisolone, total dose 6 g, 1 g/day at days 1, 2, 3, 8, 9, and 10 followed by oral prednisone, total dose, 2.73 g, initial dosage of 40 mg/day, starting at day 15 and tapered down over 17 weeks) combined with orbital irradiation (2 Gray × 10 sessions).

By the end of 2001, her orbitopathy was inactive, Hertel values decreased to 22 mm right and 23 mm left, eyelid swelling was greatly reduced, and BCVA was 20/20 bilaterally. Ophthalmic signs and symptoms remained stable, and evidence of active orbitopathy has been absent through the last examination performed in May 2006, 5.7 years after the phenomenon that we regard as decompression-related reactivation. Since the time of the last decompression, the patient has remained biochemically euthyroid with levothyroxine replacement therapy and presented abnormal thyroid autoimmunity (Table 1).

**Patient 3**

A Caucasian female who was 51 years old at the time of our retrospective observation presented with hyperthyroidism and diffuse goiter in 1993 at the age of 48. She was initially treated with antithyroid drugs and later with block replacement therapy. In September 1994, the patient developed GO; she was treated with low-dose oral glucocorticoids until May 1995, when she was first seen at our institution. At that time, she presented with a moderately severe, inactive orbitopathy. Her NOSPECS classification was 2bb, 300, 400, 5aa, 600, and her CAS 0+/7. She presented an increased eyelid aperture (14 mm right, 17 mm left), Hertel readings were 21 mm right, 22 mm left, and BCVA was right 20/20, left 20/25. Ocular motility and the field of binocular vision were normal. The patient also presented a mild form of psoriasis. The clinical picture was unchanged when in December she was admitted for bilateral inferomedial orbital decompression. A coronal
approach was used and on postoperative day 10, exophthalmos was reduced to 19 mm bilaterally; no double vision was present.

Starting from postoperative week 3, the patient experienced increased retro-ocular pressure feeling, double vision in primary position of gaze, foreign body sensation, and profuse tearing; psoriasis worsened simultaneously. When she was examined 4 weeks after surgery NOSPECS classification was 2cc, 300, 4bb, 500, 600 and CAS 5+/10. Eye movements were reduced in every direction of gaze, Hertel readings were not worsened, and BCVA was unchanged as compared with preoperative acuity. The volume of extraocular muscles was increased on postoperative CT when compared with preoperative (Figure 4).

Orbital irradiation (2 Gray × 10 sessions) administered in May 1996 produced inactivation of the orbitopathy. In March 1997, the patient underwent successful horizontal squint surgery, and 1 month later she was treated with bilateral upper lid lengthening.

At the end of 1997, Hertel values of 14 mm right, 15 mm left, persistent bilateral upper lid lateral flare, and the presence of puffy eyelids were recorded. Despite the eyelid alterations, the patient refused any further rehabilitative surgical procedure.

Signs and symptoms of the orbitopathy remained stable, and evidence of reactivation has been absent through the last examination performed in June 2006, 10.6 years after the phenomenon that we regard as decompression-related reactivation.

From the first examination at our institution to April 1999, when she was treated with $^{131}$I, the patient had been euthyroid under antithyroid drugs and levothyroxine replacement therapy. After April 1999 and to the last examination, the patient remained metabolically stable with levothyroxine replacement therapy. The patient’s thyroid autoimmunity had never been investigated until the most recent follow-up, when it was found to be grossly abnormal (Table 1).
Figure 1. Coronal computer tomography scans of the orbits in patient 1. (Top) Predecompression scan. The left extraocular muscles were enlarged more than the right. (Bottom) Postdecompression scan 1 month after surgery. The right orbital floor was removed, and a consistent enlargement of the extraocular muscles was present bilaterally.

Figure 2. Coronal computer tomography scans of the orbits in patient 2. (Top) Scan before the third orbital decompression. The extraocular muscles were moderately enlarged, and the medial orbital wall and part of the lateral were intact bilaterally. (Bottom) Scan 3 weeks after the third decompression. The medial and the lateral orbital walls were removed, and the extraocular muscles were severely enlarged bilaterally.

Figure 3. Patient 2. (Top) The patient before the third orbital decompression. No signs of active orbitopathy were present. (Bottom) The patient 3 weeks after the third orbital decompression. Signs of active Graves’ orbitopathy were evident.

Figure 4. Coronal computed tomography scans of the orbits in patient 3. (Top) Predecompression scan. A moderate enlargement of the extraocular muscles was present bilaterally. (Bottom) Postdecompression scan 3 weeks after surgery. Right and left medial orbital wall, and right orbital floor osteotomies were evident; the extraocular muscles were severely enlarged bilaterally.
Chapter 7

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Discussion

Graves’ orbitopathy is a T-cell-mediated autoimmune disorder, closely associated with Graves’ disease. The immune mechanisms underlying the orbitopathy as well as the primary autoantigens involved in the disease are poorly characterized. A consensus has emerged that orbital fibroblasts are key to the pathophysiology of GO. Indeed, fibroblasts from patients with GO produce excess matrix glycosaminoglycans, including hyaluronan, are very proliferative, and can differentiate into fatlike adipocytes. Proliferation of orbital fibroblasts is dependent on proper activation of T helper (T_H) cells. These CD4⁺-expressing T lymphocytes are able to recognize (auto)antigens present in major histocompatibility complex (MHC) class II molecules by antigen presenting cells (APC). This initial trigger leads to the expression of T-cell surface receptors, such as CD40 ligand (CD40L), which can interact with CD40 expressed on the surface of APC. This CD40-CD40L signaling is a crucial step for efficient activation of T-cell effector functions.

Of special interest is the discovery that orbital fibroblasts express CD40 and MHC class II molecules, thus suggesting that proper T-cell activation can also be achieved through presentation of autoantigens by fibroblasts. The activated T lymphocytes then produce increased cytokines driving activation and proliferation of fibroblasts, thus leading to fibroblast-associated diseases like GO. In agreement, it has been shown that activation by the CD40-CD40L signaling induces orbital fibroblasts to synthesize excess hyaluronan and proinflammatory cytokines.

Proper activation of APC can be achieved not only by T_H cells but also by inflammatory stimuli, for example, lipopolysaccharide and proinflammatory cytokines like interferon-γ, which is produced during an infection/inflammatory process. In light of this, the inflammatory process induced by surgery may be a sufficient stimulus for proper activation of APC.

Interestingly, MHC class II molecules expressed by orbital fibroblasts can be upregulated by interferon-γ. The increased expression of MHC class II molecules together with the CD40-CD40L signaling would allow the fibroblasts to present autoantigens and fully activate the T cells.

Therefore, the exposure of soft orbital tissues to pathogen components / endogenous microbial flora as well as the surgical trauma may lead to proper activation of professional.
APC, and perhaps orbital fibroblasts. These events singularly, or in combination, might have induced the processing and presentation of normally sequestered self-antigens with possible reactivation of GO. In this respect, genetic factors may have also played a role.\textsuperscript{19} Clearly, more research is required to decipher the mechanisms underlying the phenomenon that we described as related to surgical decompression. Investigation of patients presenting this phenomenon may also be useful in uncovering valuable information regarding the etiology of GO itself.

We could directly or retrospectively observe reactivation of the disease after orbital bony decompression in a restricted number of patients. We described 3 of a sample of 239 Graves’ patients decompressed for rehabilitative reasons and not treated with perioperative systemic glucocorticoids. At the time of surgery, 2 of these patients had alteration of thyroid autoimmunity; information regarding the third patient was not available. In all of them, thyroid autoimmunity was altered at the time of the last evaluation.

The incidence of the complication that we described appears to be on the order of 1.3%. It is a rare event that in our series of patients could be controlled with systemic immunosuppression or orbital radiotherapy. None of the patients we reported developed further episodes of reactivation during the period of our observation. Our estimated incidence, however, could have been biased. Our calculation was based on patients referred to a tertiary center who can be expected to have a somewhat more problematic disease, resulting in an overestimation. We do not think that this was the case because the entire case scenario of patients affected by GO is referred to our institution. On the other hand, we excluded\textsuperscript{11} patients treated with perioperative glucocorticoids, which may have resulted in an underestimation; we cannot exclude that in some of them glucocorticoids could have prevented the trigger of the reactivation or jeopardized its clinical manifestations. This is unlikely, however, because all received glucocorticoids to prevent postoperative aedema and not to treat a disease suspected for reactivation. Besides these considerations, we found the exclusion of patients treated with perioperative glucocorticoids correct from a methodologic viewpoint. Our purpose was in fact to evaluate the incidence of reactivation in a cohort of patients as similar as possible to cases 1 and 2, who represented our prototypes of reactivation and who did not receive corticosteroids perioperatively.

The phenomenon that we described consists in the onset of the typical signs and symptoms of active GO with radiologic evidence of extraocular muscles enlargement after
rehabilitative orbital decompression and after a normal convalescence period of a few weeks soon after surgery. Based on its clinical characteristics, we propose naming our observation delayed decompression-related reactivation, or DDRR.

A similar phenomenon had been previously described by Wai et al.\textsuperscript{20} after cataract extraction. Severe reactivation of GO took place 3 weeks after surgery in a patient who had presented inactive orbitopathy for 24 years. The authors hypothesized that trauma and pressure in the retrobulbar space induced by retrobulbar anesthesia triggered local inflammatory and immune responses, which in turn caused progression of GO. That conclusion was in keeping with the concept of Rapoport et al.\textsuperscript{21} that trauma and/or pressure explains, at least in part, the distribution of the extrathyroidal manifestations of Graves’ disease.

Before this case, Hamed and Lingua\textsuperscript{22} reported previously unsuspected GO in 8 patients out of a series of 58 who developed dysthyroid strabismus after cataract extraction. If in some of these cases it appeared that the diplopia may have been masked before surgery by the impaired vision, in others there was a clear progression of GO in the following months, suggesting that the surgical procedure may have contributed to aggravating the disease.

To our knowledge, reactivation of GO after rehabilitative orbital decompression has not been reported. The findings we described present several similarities to those described as subsequent to cataract extraction, which is by far a more common ophthalmologic intervention. In our cases, as in Wai et al.’s and Hamed and Lingua’s, GO worsened a few weeks after surgical trauma, and the phenomenon was invariably bilateral despite unilateral cataract extraction in all their cases and despite unilateral orbital decompression in one of ours.

Although DDRR is a rare complication, we feel that it is an event which deserves to be known by physicians and to be mentioned to those patients with GO undertaking surgical rehabilitation by means of orbital decompression.
In our cases, as in Wai et al.,


delayed decompression-related reactivation


disease.


event which deserves to be


to be mentioned to those patients with GO undertaking surgical


References


Chapter 8

Graves’ Orbitopathy in a Patient with Adrenoleukodystrophy after Bone Marrow Transplantation

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European Journal of Endocrinology 2009;161:369-73
Abstract

Objective: For many years, the treatment of X-linked childhood cerebral adrenoleukodystrophy (XALD) consisted of hydrocortisone replacement and a mixture of short chain-fatty acids, known as ‘Lorenzo’s oil’. Recently, bone marrow transplantation (BMT) has also been used.

Case report: We report the case of a patient affected by XALD who developed Graves’ hyperthyroidism (GH) and Graves’ orbitopathy (GO) after BMT and who we could follow-up for 6.5 years afterwards.

Evidence synthesis: A boy affected by XALD was treated at the age of 6 years, with a whole BMT from his sister. One year after BMT, the transplanted patient presented TSH at the lower normal value and 3 years later he developed thyrotoxicosis. After a further 2 years, the patient developed GO, which showed clinical evidence of reactivation 5 years after its onset as a consequence of an attempt to treat thyrotoxicosis by means of I

Conclusions: This case illustrates that autoimmunity originating from a pre-symptomatic donor can be transferred into the host during allogeneic stem cell transplantation. In cases where autoimmune phenomena are recognized in the donor prior to donation, alternative donors or T-cell manipulation of the graft might be considered.
Chapter 8

Abstract

Objective: For many years, the treatment of X-linked childhood cerebral adrenoleukodystrophy (XALD) consisted of hydrocortisone replacement and a mixture of short chain-fatty acids, known as "Lorenzo’s oil". Recently, bone marrow transplantation (BMT) has also been used.

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Conclusions: This case illustrates that autoimmunity originating from a pre-symptomatic donor can be transferred into the host during allogeneic stem cell transplantation. In cases where autoimmune phenomena are recognized in the donor prior to donation, alternative donors or T-cell manipulation of the graft might be considered.

Introduction

X-linked childhood cerebral adrenoleukodystrophy (XALD) is a peroxisomal disorder involving defective β-oxidation of very long-chain fatty acids that accumulate in plasma, brain, and adrenal cortex.1 Clinical symptoms include adrenal insufficiency and motor-mental deterioration accompanied by visual and hearing impairment due to intracranial demyelination.1, 2 For many years treatment consisted of hydrocortisone replacement and administration of a mixture of short-chain fatty acids, known as “Lorenzo’s oil”.1 Recently, bone marrow transplantation (BMT) has been reported to decrease the elevated blood levels of very long-chain fatty acids, to reduce the intracranial demyelination, and in turn to ameliorate the neurologic symptoms of the disease.2-5 BMT can be regarded as an in vivo model of inducing autoimmune reactions, as in this procedure human leukocyte antigen (HLA) matched bone marrow cells are exposed to a new set of pre-existing antigens. Occasionally, BMT has been related to both transmission6-9 and cure10, 11 of autoimmune diseases, and relapse of Graves’ disease after BMT has also been described.11 Considering that only 30% of the patients with Graves’ hyperthyroidism (GH) may develop Graves’ orbitopathy (GO)13, it is not surprising that publications that link BMT to GO are scarce. We are aware of only one publication reporting concordant GH and GO after BMT14, and could not find any other by means of a computerized search using MEDLINE.

In this article, we present and discuss the case of a patient affected by XALD, who developed GH 4 years, and GO 6 years after BMT from his sister. Seven years after BMT, the donor also showed alteration of thyroid autoimmunity and 1 year thereafter she developed GH. Both patient and donor were followed up for 12 years after BMT.

Case report

A 12-year-old boy affected by XALD was referred to the Orbital Center, Department of Ophthalmology, University of Amsterdam with a 3 month history of bilateral signs and symptoms compatible with GO. The boy had been treated with supplementary ‘Lorenzo’s oil’ and hydrocortisone replacement therapy since when, 6 years prior to our observation,
his neurological deterioration imposed a whole BMT from his sister, which resulted in successful control of XALD. The transplant was HLA identical and at 2 years post-BMT full-donor chimerism was found. There was no evidence of acute or chronic graft-versus-host disease (GVHD).

BMT was preceded by cytoreductive conditioning protocol with chemotherapy (busulfan 4 mg/kg in four daily doses from day 9 till day 5 and cyclophosphamide 50 mg/kg in a single daily dose from day 5 till day 2 before BMT). After the transplant, standard cyclosporin A and a short-course methotrexate (10 mg/m² i.v. at days +1, +3, and +6) were administered to prevent acute GVHD. At the moment of BMT, the donor was 7 years old and free from thyroid diseases, but at the age of 14, 7 years after the BMT, she showed alterations of thyroid autoimmunity with raised anti-thyroidperoxidase autoantibodies (TPO-Ab; 80 kU/l), and 1 year thereafter she developed GH (TPO-Ab 280 kU/l, thyroxine (T4) 200 nmol/l, and tri-iodothyronine (T3) 295 nmol/l).

Before BMT, the transplanted patient had never presented hypo- or hyperthyroidism, and TSH had always been normal, as documented by several blood tests performed at our hospital, during the 3 years preceding BMT. Starting from the year following the BMT, TSH was found to be at the lower normal value and 2 years prior to our examination the transplanted patient had developed thyrotoxicosis (Table 1) that was corrected with block and replacement therapy (methimazole 30 mg/die and L-T4 25 mg/die).

At his ophthalmic baseline examination, in September 2002, the patient presented an eyelid aperture of 12 mm right and 15 mm left with respectively a 2 mm lower lid retraction right, a 2 mm upper, and 1 mm lower lid retraction left. Hertel values were bilaterally 17 mm, and a mild eyeball dystopia of 2 mm with left eye over right was present (Figure 1). The orbitopathy was not active and according with NOSPECS classification its severity was 2a, 30, 40, 50, and 60. Anterior segment, intraocular pressure, and fundus were normal. Natural visual acuity was bilaterally 20/20.

Direct and indirect pupil reflexes were normal and the patient could read all the Ishihara tables either with the left or the right eye. Orthoptic evaluation was unremarkable and computer tomography of the orbit showed a mild enlargement of the extraocular muscles. The diagnosis of inactive, mild GO was made.
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Table 1. Laboratory Findings in a Patient with Adrenoleukodystrophy, before and after Bone Marrow Transplantation that Took Place in 1996

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After block and replacement therapy had been suspended for a few months, the patient developed recurrent thyrotoxicosis. For this I\textsuperscript{131} (300 MBq) was administered in February 2007. About 6 weeks later, the patient, aged 17 years, presented a reactivation of the orbitopathy. The reactivation included worsening of the soft tissue signs, increasing of the exophthalmos up to 23 mm both sides, with rising of the clinical activity score\textsuperscript{16} from 0+/10 to 5+/10 (retroocular tension, conjunctival hyperemia, redness of the skin, periorbital edema, and increased exophthalmos). Visual function and extraocular eye motility remained normal. The symptoms could be controlled with oral glucocorticoids, and in a few months, by the end of the summer, the orbitopathy became inactive, all the soft tissue signs disappeared, while the increased exophthalmos persisted.

The ophthalmic picture remained stable up to the end of the summer 2008, despite a further treatment with I\textsuperscript{131} (350 MBq) that took place in April 2008. A few months after this further treatment with I\textsuperscript{131} the patient became euthyroid under L-T4 replacement therapy, thyrotropin-binding inhibitor immunoglobulin (TBII), and TPO-Ab remained elevated (4.1 E/l and > 3000 kU/l respectively).

The patient’s sister never showed clinical evidence of GO during the entire follow-up period, which lasted 5 years from her first alterations of thyroid autoimmunity.

**Discussion**

We report the case of a boy who was treated with whole BMT for XALD. This X-linked disorder has stabilized following treatment, but the patient developed GH and GO thereafter. Although the temporal relation among these events supports the role of BMT in
inducing GH and GO, other etiopathogenetic hypothesis cannot be neglected and should therefore be included into the possible case scenario.

Although Laureti et al.\textsuperscript{17} reported that two out of five patients with adult onset of XALD presented elevated titers of thyroid microsomal autoantibodies and one of them developed clinical hypothyroidism, GO has never been described as part of XALD, and at present there is no evidence that GH or GO and XALD are connected in one way or another. Nevertheless, immunomodulation might play a role in the pathomechanism of demyelination as well as in the development of GH or GO. The positive familiar history for alteration of thyroid autoimmunity presented by the transplanted patient that we report may itself be a factor connected with a higher risk for developing other autoimmune disorders such as autoimmune thyroid disease (ATD) or GO\textsuperscript{14, 18}, although he had never presented hypo- or hyperthyroidism or alterations of thyroid autoimmunity before BMT as is documented by several blood tests performed in the years preceding such a procedure (Table 1).

Occurrence and remission of GH after BMT have been reported.\textsuperscript{11, 12} Although thyroid dysfunction is a common long-term complication associated with total body irradiation given in the pre-BMT conditioning protocol, Slatter \textit{et al.}\textsuperscript{9} reported thyroid dysfunction also in patients who were given cytoreductive conditioning with chemotherapy, but without total body irradiation as was the case for the patient we report. They found that 10.8\% of their patients had clinical and/or biochemical thyroid dysfunction at 4 months to 4.5 years post-BMT, and 33\% of these patients had positive antithyroid microsomal antibodies.

Both thyroid stimulating and blocking autoantibodies were detected after BMT.\textsuperscript{10} According to Sherer’s and Shoenfeld’s hypothesis, the induction of autoimmune diseases post-BMT lays its foundations into the current understanding of GVHD\textsuperscript{19}, and it could fit to the case that we report, although the patient did not show typical evidences of GVHD. Graves’ disease is a multisystemic autoimmune disorder characterized in its complete form by alteration of thyroid metabolism, orbitopathy, dermopathy, and acropachy. It involves autoantigens common to the thyroid and other affected body districts. The autoimmune attack on the thyroid leads, in the majority of cases, to alteration of thyroid hormones homeostasis, and the autoimmune attack on the orbit causes the typical constellation of signs and symptoms that characterize the clinical picture of GO.
It has been shown that orbital tissue from patients with GO is infiltrated with B and T cells, and it has been reported that orbital fibroblasts from Graves’ patients can stimulate proliferation of autologous T cells and that autologous T cells from patients with GO can stimulate proliferation of orbital fibroblasts, thus providing a mechanism by which infiltration of orbital tissue by autoimmune lymphocytes can drive the pathogenic features of GO. Another evidence of the involvement of T lymphocytes in the pathogenesis of GO derives from the observation that newborns from mothers with GO can be hyperthyroid as a result of possible passage of thyroid-stimulating IgG through the placental barrier, but they never show GO at birth due to the placental barrier to T lymphocytes.

Here, we show that whole BMT, from a donor who was free from thyroid diseases at the time of BMT, but who developed GH thereafter, may be involved in the induction of GO 6 years later in the transplanted patient. It is likely that the disease process is primarily dependent upon altered function of the T lymphocyte. Although the immune mechanisms underlying the orbitopathy as well as the primary autoantigens involved in the disease are poorly characterized, it can be hypothesized that dormant autoreactive T cells once transplanted could have been activated by nonprofessional antigen-presenting cells, such as orbital fibroblasts. Afterwards, T-cell-driven stimulation of orbital fibroblasts to upregulate expression of MHC class II and the presentation of autoantigens could have occurred. This in turn could have further activated T cells to produce surface and/or diffusible factors that drive activation and proliferation of orbital fibroblasts, leading to expression of fibroblast-based diseases, i.e. proliferation of fibroblasts and excess connective tissue, deposition of matrix glycosaminoglycans, intramuscular fibrosis, and differentiation and proliferation of adipocytes.

Another interesting issue regards the time between BMT and the onset of GH and GO. A delay due to immune reconstitution of the recipient should be expected, but it can also be hypothesized that an additional stimulus like an infection, even subclinical, or an inflammation could have played a role in triggering the process. Indeed, orbital fibroblasts, upon stimulation with IFN-γ produced during infections / inflammations, are able to overexpress MHC class II molecules on their surfaces and to produce proinflammatory cytokines, such as IL-8 and IL-6. This suggests that orbital fibroblasts may be crucial in the
trafficking of bone marrow-derived immune cells to the orbit in states of infection/inflammation. 

Here, we propose that the recipient passively acquired dormant autoreactive T cells from his sister, although she was apparently healthy. This case report suggests to consider, if available, the use of a matched unrelated donor when a potential HLA-identical sibling donor presents relevant immune-mediated diseases. In the case where a matched unrelated donor is not available, a T-cell depleted rather than whole BMT might be an alternative when the donor is affected by ATDs or other T-cell-driven autoimmune disorders, although the role of bone marrow graft engineering is still under study. T-cell depletion of the graft might in theory change / prevent the occurrence of autoimmunity; however, we acknowledge that the evidence is very limited to make this statement, and we are aware that T-cell-depleted bone marrow has major drawbacks, such as an enhanced risk of graft rejection as well as delayed immune reconstitution, with a consequent increased risk of viral and fungal infections.
CHAPTER 8

References


Chapter 9

Supernumerary Extraocular Muscle in Graves' Orbitopathy

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Thyroid 2007;17:479-80
Chapter 9

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Thyroid 2007;17:479-80
Graves’ orbitopathy (GO), the commonest orbital disease, is due to autoimmune inflammation and swelling of the soft orbital tissues, including the extraocular muscles. The involvement of the extraocular muscles often leads to invalidating strabismus and diplopia. A 59-year-old man affected by GO with severe left hypotropia (Figure 1) presented a structure with computer tomography scan signal intensity similar to extraocular musculature, between the inferior and lateral rectus muscles left orbit. It appeared to course along the lateral edge of the inferior rectus up to the orbital apex (Figure 2 A-D, arrows).

Figure 1.

Figure 2.
Chapter 9

Graves’ orbitopathy (GO), the commonest orbital disease, is due to autoimmune inflammation and swelling of the soft orbital tissues, including the extraocular muscles. The involvement of the extraocular muscles often leads to invalidating strabismus and diplopia. A 59-year-old man affected by GO with severe left hypotropia (Figure 1) presented a structure with computer tomography scan signal intensity similar to extraocular musculature, between the inferior and lateral rectus muscles left orbit. It appeared to course along the lateral edge of the inferior rectus up to the orbital apex (Figure 2 A-D, arrows).

A better evaluation by means of magnetic tomography scan was not possible due to an irremovable dental prosthesis. Surgical exploration of the area confirmed the presence of a supernumerary extraocular muscle (SEM) (Figure 3, arrow).

Figure 3.

It was inserted onto the sclera by a 3-mm-long, 5-mm-wide tendon, 5 mm laterally to the insertion of the inferior rectus muscle at 7 mm from the cornel limbus, and its belly was swollen. Eight months after retrobulbar irradiation, the decreased swelling of the inferior rectus and SEM allowed a better visualization of the two muscles on computer tomography scans. Such an examination confirmed that the SEM was an autonomous structure that originated from the orbital apex and not from the lateral edge of the inferior rectus muscle (Figure 4 A, B, arrows).
This report illustrates an apparent causal relationship between a swollen SEM and the pattern of strabismus presented by a patient with GO, suggesting that SEMs can also be affected by the disease and can contribute to worsen the clinical picture. SEMs are rare in humans and, as in primates, not deemed to be vestiges of the retractor bulbi, a typical occurrence in other vertebrates that more likely have SEMs.\(^1\) Although the combination GO-SEM is exceptional, physicians involved in the treatment of GO should be aware of such a possibility in order to avoid diagnostic and/or surgical mistakes.
Chapter 9

Reference

Chapter 10

Traumatic Neuroma of the Infraorbital Nerve Subsequent to Inferomedial Orbital Decompression for Graves' Orbitopathy

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European Journal of Ophthalmology 2010;20:481-4
Abstract

Purpose: To present and discuss the occurrence of a traumatic neuroma subsequent to inferomedial orbital decompression surgery in Graves’ orbitopathy.

Method: Case report.

Results: Approximately 1 month after surgery, a patient who underwent bilateral rehabilitative inferomedial orbital decompression developed a mass with clinical and radiologic characteristics compatible with a traumatic neuroma of the left infraorbital nerve. The lesion, which was thought to be the result of unnoticed nerve trauma at the time of surgical dissection of the infraorbital canal, remained stable in shape and other imaging characteristics during the 39-month follow-up period. Symptoms of trigeminal neuralgia could be only partially controlled with medical therapy (oral pregabalin 75 mg 3 times daily).

Conclusions: The second branch of the trigeminal nerve may be damaged in the course of orbital floor removal decompression for Graves’ orbitopathy. This may potentially induce the formation of traumatic or amputation neuromas. Such lesions should be included in the potential complications of decompressions when counseling patients about to undergo this type of surgery, as they are difficult to treat and may cause persistent and disabling pain.
Introduction
Traumatic neuromas may be due to chronic nerve irritation or trauma that partially avulses or totally disrupts the nerve. In the case of chronic irritation, an undisrupted nerve gives rise to a focal fusiform swelling often referred to as “spindle neuroma.” Different degrees of nerve disruption and subsequent external axon growth, which represents an attempt at natural repair, leads to the formation of masses referred to as “lateral or terminal, traumatic neuromas,” the latter also referred to as “amputation neuromas.”

Traumatic neuromas may cause persistent pain and have been described in several anatomic locations including the orbit after enucleation. Orbital decompression surgery is a currently accepted, effective, and generally safe treatment for Graves’ orbitopathy. When decompression surgery entails removal of the orbital floor, the infraorbital nerve may be damaged by surgical maneuvers, by bone edges or fragments, or may be stretched by the soft orbital tissues which prolapse into the maxillary antrum. This generally causes hypoesthesia, rarely anesthesia or pain in the sensory distribution area of this nerve branch.

Herein we present and discuss a patient with Graves’ orbitopathy presenting with clinical and radiologic evidence of traumatic neuroma of the infraorbital nerve starting a few weeks after rehabilitative inferomedial orbital decompression, and who has been followed up at our department for 39 months afterwards.

We are unaware of previous reports that link traumatic neuromas of the infraorbital nerve to orbital decompression.

Case report
A 45-year-old Caucasian woman with stable inactive Graves’ orbitopathy for more than 5 years, on levothyroxine replacement therapy for 4 years following \(^{131}\)I, was admitted for bilateral inferomedial rehabilitative orbital decompression in June 2005. On admission, she had best corrected visual acuity (pinhole) of 20/20 bilaterally, bilateral slight increase of the eyelid aperture with 3 mm upper lid retraction, moderate periorbital edema, consistent retroocular tension, and Hertel readings of 23 mm bilaterally, and did not have diplopia.

Decompression was carried out uneventfully by an anterior trans-inferior-fornix approach and included the complete removal of the orbital floor. The immediate postoperative period was unremarkable. The patient left the hospital 2 days after surgery without any medication.
except for artificial tears. As expected, moderate bilateral hypoesthesia of the areas innervated by the infraorbital nerve was present.

At the first postoperative control, carried out 1 month after surgery, exophthalmos had decreased to 17 mm bilaterally, periorbital aedema and retroocular tension had disappeared, and eyelid aperture had normalized. The patient did not have diplopia and best-corrected visual acuity was unchanged. For a few days prior to the examination, the patient had been experiencing symptoms compatible with trigeminal neuralgia in the distribution of the second left branch. An orbital computed tomography (CT) scan showed a round mass approximately 12 mm in diameter involving the left infraorbital nerve at the level of the inferior orbital fissure. The lesion was not present on the predecompression CT scan. Signal intensity, shape, and relation of the lesion with the parent nerve on postdecompression CT scan and on the follow-up magnetic resonance images performed afterwards were compatible with that described for traumatic neuromas. The shape and other
radiologic characteristics of the lesion remained constant until September 2008, when the patient attended her last follow-up examination.

When the lesion was detected, the patient refused systemic glucocorticoids and truncular anesthesia of the infraorbital nerve. Persistent trigeminal neuralgia did not respond to medical treatment with oral gabapentin 600 mg 2 to 3 times daily, but could be partially controlled by oral pregabalin 75 mg 3 times daily until the present.

**Discussion**

Orbital decompression is mostly achieved by means of osteotomies which involve the lateral and the medial orbital walls, the orbital floor, and when necessary fat is removed possibly from the inferolateral orbital quadrant. The most effective and safest sequence of osteotomies and lipectomies to be used to gradually implement the effects of decompression surgery continues to be debated. Although orbital floor removal in course of orbital decompression is currently not favored in North America, a recent prospective survey of the European Group on Graves’ Orbitopathy (EUGOGO) showed that inferomedial bone decompression is still a widely used procedure in Europe. When clinical history and symptoms suggest the presence of a traumatic neuroma, the diagnosis can be further supported by radiologic imaging evidence of an abnormal bulbous appearance at the proximal end of or along a nerve which was respectively transected or damaged. CT and magnetic resonance imaging are optimal in detecting the location and shape of the lesion and its relation with the parent nerve, while their nonspecific signal intensity and variable enhancement after administration of contrast are less important for the diagnosis. Although we did not perform any confirmatory histopathology, in all likelihood the lesion we reported represents a traumatic neuroma, and we regard an unnoticed iatrogenic injury at the time of surgery as its most probable cause. As in the case we described, traumatic neuromas have been reported to become evident at approximately 1 month after acute trauma. The patient we described started presenting symptoms of trigeminal neuralgia and evidence of the lesion on imaging a few weeks after surgery, and this does not permit us to include in the possible pathogenesis “chronic” causative mechanisms such as nerve irritation due to aggressive bone edges left at the level of the anterior margin of the inferior orbital fissure. Other trauma to the nerve such as stretching due to the mechanical action of the soft orbital tissues prolapsing into the maxillary sinus,
which normally occurs after floor removal orbital decompression, are also unlikely to have been the cause of the lesion.

Traumatic neuromas of the infraorbital nerve, in fact, have never been described before, despite the elevated number of this type of surgery performed and reported in published series up until now. Although the rapid onset nature of the orbital mass might have been suggestive of an etiology ranging from inflammation to malignancy, with the patient’s consent, we elected not to perform incisional or excisional biopsies and histopathology on the lesion, but only to treat it medically and to closely follow it up with imaging. This choice, of course, implied accepting a diagnosis suggestive of traumatic neuroma and some risks, but surgery would have not been without risk either. Although medical therapy could offer only a partial control of the symptoms, we did not attempt to treat the lesion more aggressively, as more invasive treatment alternatives including intralesional injections of steroid or alcohol, phenolization, cryoapplications, and surgical resection do not offer any superior chance of pain relief.6

Common complications of orbital decompression are consecutive strabismus, infraorbital hypoesthesia and sinusitis, lower lid entropion, and eyeball dystopia, while leakage of cerebrospinal fluid, infections involving the central nervous system, damage to the eye and optic nerve or their vasculature, cerebral vasospasm, ischemia and infarction, and delayed decompression-related reactivation are rare events.7 Among these latter complications, traumatic neuromas deserve a special mention, because they can cause disabling trigeminal neuralgia with limited possibility of treatment. This retrospective case report was carried out following the tenets of the Declaration of Helsinki and of the Code of Conduct of the Dutch Federation of Biomedical Scientific Societies (http://www.federa.org/) as recommended by the Review Board of our institution. The Review Board of our institution declared that for retrospective studies its permission is not needed, nor is patient informed consent necessary if data are collected anonymously from the medical records used by the authors in their everyday practice.
Chapter 10

References


Chapter 11

General Discussion

Orbital Surgery in Graves’ Orbitopathy:
Where We Are, What Are the Novel Perspectives,
What Are Its Concealed Messages?
Where we are

In ancient times lacking any background experience, accurate tools, technology to guide the comprehension of diseases and adequate prescription drugs our ancestors struggled to learn how to repair the human body. Surgery came into being and with it, human life became more sophisticated. Man lived longer, and having gained a knowledge of themselves sufficient to break the boundaries built by ignorance, ultimately increased their quality of life. Later in eras wherein religious views took precedence over medicine and logic, surgical advancement was difficult. Some of the surgical technology developed in ancient times surpassed anything available in the modern world until the 18th or 19th century. Most of the knowledge we now have was obtained from prehistoric exploits. 1

Skull trephination and craniotomy performed by abrasion, scraping, crosscut sawing, and drilling are the oldest known surgical techniques used by primitive people for decompression of the brain after fracture or epidural haemorrhages, to cure epilepsy or osteomyelitis.2, 3

The indications for modern decompression surgery for GO are not too dissimilar from those which motivated the invention of surgery in ancient times, and the greatest bulk of it, bone decompression, conceptually continues to be based on principles and techniques similar to those for cranial trephination from as early as 7000 3, or even 20000 years ago. 4 Stone lancets and obsidian curettes, already used successfully in up to 80% of such prehistoric surgery2, 3, 5, have been substituted by more sophisticated equipment. Nevertheless, abrasion, scraping, crosscut sawing, and drilling are still in current use in the great majority of surgery for treating raised intraorbital pressure responsible of signs and symptoms of GO.

Modern bone orbital decompression surgery in GO started in 1911 when Dollinger 6 proposed the removal of the lateral orbital wall, which had been already used by Kroenlein 7 for the excision of an orbital dermoid cyst, as a possibility to increase the volume of the bony orbit in GO. Till since many other osteotomies and approaches have been proposed, abandoned, modified 7-26 and performed with minimally invasive techniques or more extensive incisions each carrying its distinctive advantages and disadvantages as discussed in the paper included in chapter 6.27

Starting from the end of the 1990s, the osteotomy entailing the removal of the lateral orbital wall, and in particular its deep portion, has
Where we are

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regained popularity\textsuperscript{23, 24, 26}, roughly reiterating what had been proposed one century before by Dollinger, when he described his pristine form of bone decompression surgery.\textsuperscript{6}

In essence over time human reasoning has not produced any substantial conceptual innovation in the field of decompression surgery, or of its execution. An exception was the introduction of fat decompression in 1920\textsuperscript{28}, which, however, never reached the popularity of its bone counterpart.

Real new short term conceptual breakthroughs in orbital surgery for GO appear to be very unlikely. Collective awareness which also extended to the possible discovery of specific immunological therapy, has been recently stated in “the Amsterdam declaration on GO”\textsuperscript{29, 30}, and it was also maintained that the overall quality of patient care can be implemented by reducing the inequality in expertise and delivery of existing treatments\textsuperscript{30-32}.

Recently introduced technical advances\textsuperscript{33}, and most importantly implementation of the scarce evidence and quality of literature concerning available surgical treatment for GO\textsuperscript{34-36} can also play a positive key role in the amelioration of surgical care, including orbital decompression.

\textit{Technical advances}

Technical advance in the field of decompression surgery has undeniably been substantial, and there is further potential.\textsuperscript{33} The current use of high-speed rotary instrumentation has facilitated the possibility of deeper lateral wall osteotomies than that achievable by means of conventional bone nibbling rongeurs.\textsuperscript{26} This has resulted in the possibility of more effective exophthalmos reduction\textsuperscript{24, 26}, but grinding with cutting-burrs or diamond-burr tips in tight spaces, such as those available in orbital surgery, has a potential, not negligible, risk of damage to soft orbital tissues or the dura. Ultrasonic bone removal recently proposed for orbital surgery represents a promising field of technical development.\textsuperscript{37, 38} Hand pieces which transmit 25-29 kHz vibrations can easily selectively carve/cut only mineralized tissues. The reliability of ultrasonic bone curettes in orbital surgery, however, still needs to be tested against large numbers, and issues of concern about possible damage to soft tissues when using such devices have been arisen in neurosurgery.\textsuperscript{39} Technical innovations for decompression surgery, however are limited when compared with those that are already available and constantly implemented for other rehabilitative surgical
procedures for GO such as blepharoplasty, forehead plasty, and eyebrow lift. This is the result of the benefits of technical solutions from the commercial dynamic world of cosmetic surgery.33

Decompression surgery: evidence and quality of the literature

A clear methodology is a basic requirement for any scientific paper. In clinical science a plain definition of the treatment, the circumstances under which it is administered, and an unambiguous description of the treated patient population are essential ingredients. These criteria guarantee that results are repeatable and that meaningful comparisons can be made among studies. Most articles on the outcome of decompression surgery do not fulfil these criteria. They are chiefly based on retrospective case series with inhomogeneous methodologies and definitions, heterogeneous anatomical and pathological substrates, none standardized modalities and timing of pre- and postoperative clinical assessments, differences in surgical techniques, modality, location, and amount of removed bone or fat.27 Consequently surgical choices continue to be left to local tradition and surgeons’ experience40 rather than being based on evidence that links the patient’s specific needs, and their background characteristics to one or another surgical approach.

At present patients’ access to high standard surgical treatments is still not prompt or available in many countries29, 30, and not many are the centres of excellence or the international organizations with a referral adequate enough to produce randomized clinical trials in the field of decompression surgery.40 Although a document such as the Amsterdam declaration29 might instigate a medium term desirable implementation in surgical care for patients with GO, it is not unforeseen that retrospective case series will continue to remain the commonest study design for decompression surgery.

While the evidence of the literature might not be easily implemented, its quality can. Limitations can be overcome, and overstatements and conceptual axioms are liable to critical review, thus potentially generating novel data and perspectives useful for clinical practice or future research.

The main ambition of this thesis was to stimulate a move towards a more systematic reporting and analytical style which can, more reliably and comprehensively, allow present
and future generations to use the data in clinical practice, the planning of new clinical trials and meta-analysis.

**Novel perspectives**

If present and future studies are to be used and interpreted adequately, it is essential that sufficient information be provided regarding the methods of data collection, and baseline characteristics: male gender, older age and heavy smoking are patient characteristics that are known to be associated with more severe orbital disease.\(^41, 43\) Preoperative Hertel values, extent and location of the osteotomy performed during decompression surgery, and differences in manipulation of the periorbita, are factors known to affect the extent of exophthalmos reduction.\(^26, 44-51\) Precise data collection, listing of inclusion and exclusion criteria followed by a careful evaluation of predecompression characteristics of the cohort and groups under evaluation are therefore essential methodological requirements. Only in this way can it be clear to whom the results of a survey apply, and whether or not the groups under evaluation present differences or are homogeneous.

All these methodological limitations, and misleading statements regarding the negative effects of long standing GO and previous orbital radiotherapy on the outcome of decompression surgery were addressed in the study published in chapters 2, and 3. A clear methodology and careful analysis of the results allowed us to compare homogeneous patient populations and to conclude that a long duration of GO and orbital radiotherapy do not have an adverse effect on decompression surgery\(^52, 53\), and that there was a decreased risk for developing post decompression diplopia in long duration GO as compared with shorter duration.\(^52\) Such strict methodology as in the papers included in chapters 2 and 3\(^52, 53\), was used in the case control study included in chapter 5 aimed at quantifying, in clinical practice, the previously unpublished contribution of popular lateral wall osteotomy to exophthalmos reduction and the influence of such an osteotomy on consecutive diplopia.\(^27\) We concluded that a deep lateral wall is an effective although not always available zone of possible orbital volume expansion, and that it is connected with a minimal incidence of decompression induced diplopia when performed as part of a 3-wall decompression through a coronal approach.
Despite the retrospective nature of these studies\textsuperscript{27, 52, 53}, they had the merit of showing that validity can be increased, by respecting as much as possible symmetry with strict methodology, and that bias and confounding factors can be controlled by adopting clear inclusion/exclusion criteria and by careful comparison of the groups under consideration for demographics and preoperative characteristics.

The prospective trial included in chapter 4 was aimed at a better assessment of outcome following decompression surgery. Demographics and pre decompression characteristics were addressed similarly to the studies included in chapter 2, 3, and 5. The context of the study allowed us to review the “time honoured axiom” which links the best results with the highest exophthalmos reduction and the lowest incidence of induced diplopia, and to assess the results of decompression surgery based on a novel methodology. The novel appraisal method with descriptive figures (achievement or not of the preoperative target) and easily interpretable quantitative indexes, precisely defined the extension of applied surgery and its outcomes, to whom they pertain and, empowered the survey to disclose new findings regarding pre-decompression characteristics and surgical results. The study showed that different pre-decompression medical regimens and the duration of orbitopathy at decompression may influence the targets to be pursued by decompression surgery and that the development of GO at an older age, with associated low Hertel readings necessitates targets in decompression surgery other than exophthalmos reduction, and that the “best results” are linked to the achievement of the desired targets which may or may not include reduction of exophthalmos. Additionally the paradigm that amount of exophthalmos reduction is proportional to the extent of the osteotomies was shown not to be always valid.

Although the novel appraisal method of this study took into account a large proportion of the variables which can play a role in determining the outcomes of decompression surgery, it still remains sub optimal. Morphology of the orbital cavity and its osteology, compliance of the soft orbital tissue, lipogenic versus the myogenic variants of the disease, all of which are potential determinants of surgical outcome, were not considered. The novel appraisal and the generated indexes, however, can already be of some benefit for straight forward study comparisons, patient counselling, and can be a valuable tool for balancing risks benefits when changing invasivety of the procedure during the course of surgery. This then might represent a step towards the final goal of a desirable, and as much as possible,
evidence based customized approach to orbital decompression. Customization may be required in unconventional situations as well, such as the case of a patient with an enlarged supernumerary extraocular muscle presented in chapter 9.54

While future studies on decompression surgery will likely fine tune and expand the evaluation criteria, the existing list should stimulate reflection among practising orbital surgeons.

Diplopia has a considerable impact on the patient’s quality of life, is a feared, debilitating eventual consequence of decompression surgery, and it often deters patients and physicians from undertaking decompression rehabilitative surgery. In the vast majority of cases, however it is correctable with straightforward surgery performed under topical anesthesia. Induced diplopia should therefore be considered a treatable side effect rather than a real complication of decompression surgery. Decompression surgery can also result in improving diplopia and instruments such as the diplopia index (ID) as proposed in the paper included in chapter 4 could prove to be valuable for study comparisons, or when counselling both, patients without or with diplopia about to undergo decompressions.

Only the irreversible, disabling or unwanted consequences resulting from decompression surgery should be considered real complications. Trigeminal neuralgia is one of them. In chapter 10 the case of a patient with GO who developed a traumatic neuroma and trigeminal neuralgia of the infraorbital nerve subsequent to inferomedial orbital decompression is presented.55 This previously unreported complication is unlikely to respond to any treatment and deserves to be mentioned when counselling patients about to undergo inferomedial decompression.

Concealed messages of orbital surgery

Careful clinical observations, particularly in a multidisciplinary setting can lead to new insights on pathogenesis as discussed in chapters 7 and 8.57-58 Orbital fibroblasts are key to the pathogenesis of GO. Fibroblasts from GO patients produce excess matrix glycosaminoglycans, and can differentiate into fatlike adipocytes. Proliferation of orbital fibroblasts is dependent on appropriate activation of T helper (TH) cells. However, effective T cell help requires the local expression of co-stimulatory molecules.59, 60 The discovery that orbital fibroblasts can express co-stimulatory molecules, such as CD40, and
MHC class II molecules, suggests that T-cell activation in orbital tissue can occur without
the traditional antigen presenting cells. Activation or perpetuation of the inflammatory
cycle can be sustained through the presentation of autoantigens by orbital fibroblasts. Inflammatory stimuli, for example, lipopolysaccharide and proinflammatory cytokines like interferon-\(\gamma\) (IFN-\(\gamma\)) can also drive the autoimmune process. These and other inflammatory signal mediators may be induced or released at the time of surgery leading to reactivation of disease as seen in the patients discussed in chapter 7.

Inflammation and infection have been suspected to trigger GO. The case described in chapter 8, extends and confirms that genetics play a role. A patient received a bone marrow transplant from a donor who years later developed Gaves’ hyperthyroidism. The recipient patient developed Graves’ hyperthyroidism and orbitopathy before the donor. While donor and recipient were siblings, the earlier onset in the recipient suggests that a preferential recruitment and expansion of orbital tissue responsive T cells occurred. Immunity constituted after BMT is not the same as during embryogenesis. The checks and counter check between self and non self are not as tightly established following BMT. Certain Treg populations may be missing, predisposing the recipient to certain viral infections or autoimmune disease. GO obviously is no exception to this state of affairs. The fact that orbital fibroblasts may bypass normal control mechanisms may be a further aggravating factor in the early onset of disease in this BMT patient.

While the exact mechanisms underlying the pathogenesis of GO will come from basic research, critical clinical observations as those presented in chapters 7 and 8 may help to drive such research and provide valuable information for basic scientists.
REFERENCE

Summary
Chapter 1 provides an overview of Graves’ orbitopathy (GO) and its current treatment modalities. GO is one of the phenotypic appearances of Graves’ disease, a multisystem disorder which usually leads to hyperthyroidism and goiter, less frequently to GO, and rarely to pretibial myxedema and acropachy. Its etiopathogenesis is poorly characterized and consequently a specific therapy is lacking. The European Group On Graves’ Orbitopathy (EUGOGO) has published a consensus statement on indications and timing of the various medical and surgical treatment options in GO (Figure 2, page 14). The current role of orbital decompression in the context of rehabilitative surgery for GO (the subject of this thesis) is reviewed.

The studies reported in chapters 2, 3 and 4 were designed to evaluate some unproven concepts in the existing literature on orbital decompression surgery.

Chapter 2 evaluated the concept that outcome of orbital decompression is worse when performed rather late in the course of the disease, because there is more fibrosis and less compliance of orbital soft tissues in the late inactive stage of GO. In a retrospective study among GO patients without preoperative diplopia, outcome of surgical decompression was compared between 70 patients with GO duration <4 yr and 55 patients with GO duration of 4 yr or longer. Baseline characteristics of both groups were similar, except for greater extraocular muscle enlargement in the patients with early decompression. The surgical outcome (applying the same technique in all patients) was not different between both groups, except for more postdecompression diplopia in the group undergoing early decompression. It is concluded that a long duration of GO does not adversely interfere with the results of surgical decompression, and is associated with a decreased risk for developing postdecompression diplopia.

Chapter 3 evaluated the concept that outcome of orbital decompression is worse when patients have been treated with orbital irradiation prior to surgery, because radiotherapy might induce fibrosis and less compliant soft tissues. In a retrospective study among GO patients without preoperative diplopia, outcomes of 3-wall orbital decompression through a coronal approach was compared between 29 patients previously treated with radiotherapy (20 Gy), 15 patients previously treated with glucocorticoids, and 17 patients previously treated with radiotherapy and glucocorticoids. All preoperative characteristics except smoking behaviour were similar in the three groups. Surgical outcome did not differ.
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between groups. It is concluded that previous orbital radiotherapy does not adversely interfere with the results of surgical decompression.

**Chapter 4** evaluated the concept that -according to a time-honoured axiom- the outcomes of orbital decompression in GO for rehabilitative reasons can be described in a satisfactory manner in terms of exophthalmos reduction and postoperative diplopia. These conventional outcome measures were compared to a newly designed set of outcome criteria in a prospective study among 84 GO patients who underwent a graded inferomedial bone decompression of 151 orbits through a minimally invasive sutureless transinferior fornix approach. The novel criteria allowed to assess surgical outcome in relation to the extent of surgery. Surgical targets were recorded prior to surgery, and included: 1) desired degree of exophthalmos reduction, 2) resolution of retroocular tension, 3) reduction of periorbital swelling, 4) cure of lagophthalmos; it allowed to calculate a mean index of targets achieved per orbit (MITAO) and per patient (MITAP), with values ranging between 0 and 1. Also an index of diplopia (ratio of decompression-induced de novo diplopia to decompression-induced cure of diplopia) was calculated. Invasiveness of surgery was quantified from minimally invasive (25%) to maximally invasive (100%), allowing to calculate a mean index of invasiveness per orbit (MIIO) and per patient (MIIP) ranging from 25% to 100%. The novel methodology described surgical outcomes in relation to the extent of surgery more precisely and meaningfully as compared to traditional evaluation of surgical outcomes.

The studies reported in chapters 5 and 6 were performed in order to evaluate and review current trends in decompression surgery with regard to ostetomies and approaches. **Chapter 5** evaluated the -previously undetermined- contribution of maximal removal of the deep lateral wall of the orbit to exophthalmos reduction, and its influence on the onset of diplopia. In a case-control study among GO patients undergoing 3-wall decompression through a coronal approach, 15 patients in whom the deep portion of the lateral wall had been removed (cases, extended decompression) were compared to 15 patients in whom the deep lateral wall had been preserved (controls, conservative decompression). There were no differences in baseline characteristics between cases and controls, but mean exophthalmos reduction was 2.3 mm greater in cases than controls; onset of diplopia was similar. It is concluded that removal of the deep lateral orbital wall as part of a coronal approach 3-wall
decompression enhances the degree of exophthalmos reduction without increasing the risk of diplopia.

**Chapter 6** reviews the advantages and disadvantages of small versus coronal incisions to orbital decompression surgery. An inferior fornix incision can be used for inferomedial bony decompression and/or for removing fat from the medial and lateral inferior orbital quadrants. Through the same route a lateral ostetomy can be performed, although an upper skin crease incision offers a wider access to the lateral orbital wall. The swinging eyelid technique provides adequate access to the bony orbit and to the orbital fat compartments; it is a versatile technique that can virtually be used as a standard approach for the majority of patients needing decompression surgery. Orbital decompression by coronal incision is an invasive technique, not to be used as a standard approach. Nevertheless, it should not be abandoned as it could be advantageous in particular patients who may benefit more from a tailored rather than a standardised approach. Practical implications of the choice between a standardized approach to orbital decompression surgery and a more desirable customized approach are discussed.

The studies reported in chapters 7, 8, 9 and 10 deal with rare conditions which may be encountered in GO patients who are about to undergo or who already had undergone orbital decompression surgery.

**Chapter 7** describes two patients who developed clinical and radiological evidence of reactivated GO a few weeks after rehabilitative bony orbital decompression during the static phase of the disease. We reviewed the charts of 249 consecutive GO patients who had undergone the same treatment for the same reason (excluded were patients with perioperative glucocorticoids, concurrent periorbital diseases, or who were immunocompromised). The incidence of delayed decompression-related reactivation of GO (called DDRR) was 1.3%. The reactivation took place a few weeks after surgery, after a normal convalescence period. No further episodes of reactivation were observed during a mean follow-up of 7.5 yr.

**Chapter 8** describes a patient with X-linked childhood cerebral adrenoleukodystrophy; he was treated for this condition with whole bone marrow transplantation from his sister, and developed Graves’ hyperthyroidism and GO six years later. His sister was euthyroid when she donated the bone marrow transplant, but developed Graves’ hyperthyroidism
afterwards. The case demonstrates passive transfer of thyroid autoimmunity from an asymptomatic donor during allogeneic stem cell transplantation.

**Chapter 9** describes a GO patient presenting with restrictive strabismus. Orbital CT scanning showed an enlarged supernumerary extraocular muscle, confirmed by biopsy. Supernumerary extraocular muscles are quite prevalent in cats but extremely rare in humans. The case underscores the importance of an accurate preoperative assessment of GO in order to avoid surgical mistakes.

**Chapter 10** describes a GO patient who after bilateral rehabilitative inferomedial decompression developed a traumatic neuroma of the left infraorbital nerve. This previously unreported but disabling complication is likely the result of unnoticed nerve trauma at the time of surgical dissection of the infraorbital canal. The lesion remained stable during 39 months follow-up. Symptoms of neuralgia could be controlled only partially with medical therapy.

The general discussion in **Chapter 11** puts the presented findings in GO patients who underwent rehabilitative orbital surgery into perspective. Sometimes astute clinical observations may contribute to better understanding basic mechanisms in the pathogenesis of GO. Systematic review of the results obtained with orbital surgical decompression proves to be invaluable in refining surgical techniques and improving surgical outcomes.
Samenvatting
Het inleidend Hoofdstuk 1 geeft een overzicht van Graves’ Orbitopathie (GO) en de huidige behandeling ervan. GO is een van de verschijningsvormen van de ziekte van Graves, een aandoening die zich op verschillende wijzen kan manifesteren: hyperthyreoidie en struma komen het meest voor, GO minder vaak, en pretibiaal myxoedeem en acropachie het minst. De pathogenese van de ziekte van Graves is niet goed opgehelderd, en een specifieke behandeling ontbreekt. De “European Group On Graves’ Orbitopathy” (EUGOGO) heeft een consensusverklaring gepubliceerd over de indicaties en de keuze van het juiste tijdstip van de verschillende medische en chirurgische behandelingsopties in GO (Figuur 2, pagina 14). De huidige rol van oogkasdecompressie in de context van rehabiliterende chirurgie voor GO (het onderwerp van dit proefschrift) wordt besproken.

De studies in hoofdstukken 2, 3 en 4 werden opgezet om bepaalde onbewezen opvattingen over oogkasdecompressie in de bestaande literatuur nader te onderzoeken.

Hoofdstuk 2 onderzoekt het idee dat de uitkomst van oogkasdecompressie slechter is als de operatie op een laat tijdstip in het beloop van de ziekte plaatsvindt, omdat er meer fibrose en minder compliantie van de weke weefsels in de oogkas zou bestaan in het late inactieve stadium van GO. De uitkomst van oogkasdecompressie werd nagegaan in een retrospectieve studie onder GO patienten zonder dubbelzien voor de operatie: de duur van de oogziekte was korter dan 4 jaar in 70 patienten, en 4 jaar of langer in 55 patienten. Preoperatieve kenmerken waren vergelijkbaar in beide groepen; alleen de oogspieren waren meer vergroot in de groep met een vroege decompressie. De uitkomst van de operatie (waarbij steeds dezelfde techniek werd toegepast) was tussen beide groepen niet verschilend, behalve dat dubbelzien na de operatie vaker voorkwam in de groep patienten die binnen 4 jaar werd geopereerd. Conclusie: langbestaande GO heeft geen nadelig effect op de uitkomst van oogkasdecompressie, en is geassocieerd met een afgenomen risico op het ontstaan van dubbelzien na de operatie.

Hoofdstuk 3 onderzoekt het idee dat de uitkomst van oogkasdecompressie slechter is als voorafgaand aan de operatie de oogkas is bestraald, omdat bestraling fibrose en minder compliantie van de weke weefsels in de oogkas zou induceren. In een retrospectieve studie onder GO patienten zonder preoperatief dubbelzien werd de uitkomst van een drie-wanden oogkasdecompressie via een coronale snede vergeleken tussen 29 patienten die tevoren...
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Samenvatting

retrobulbaire bestraling met 20 Gy hadden gekregen, 15 patienten die tevoren behandeld waren met glucocorticoiden, en 17 patienten die tevoren zowel bestraling als glucocorticoiden hadden gekregen. Preoperative kenmerken waren vergelijkbaar in de drie groepen op het rookgedrag na. De chirurgische uitkomst verschilde niet tussen de groepen. Conclusie: voorafgaande retrobulbaire bestraling heeft geen nadelig effect op de uitkomst van oogkasdecompressie.

Hoofdstuk 4 onderzoekt het idee dat de uitkomst van oogkasdecompressie in GO om reden van rehabilitatie bevredigend kan worden beschreven in termen van vermindering van exophthalmus en postoperatief dubbelzien. Deze conventionele uitkomstmaten werden vergeleken met een nieuw ontworpen reeks van uitkomstcriteria in een prospectieve studie onder 84 GO patienten bij wie een inferomediale decompressie van 151 oogkassen werd uitgevoerd via een minimaal invasieve transinferieure fornix benadering. De nieuwe criteria maken het mogelijk de chirurgische uitkomst te relateren aan de mate van uitgebreidheid van de operatie. Voorafgaand aan de operatie werden de chirurgische doelstellingen opgetekend. Deze konden zijn: 1/ de gewenste mate van vermindering van exophthalmus, 2/ het verdwijnen van een drukkend gevoel achter de ogen, 3/ vermindering van zwelling rond de ogen, 4/ het opheffen van lagophthalmus. Op grond hiervan kon een gemiddelde index van bereikte doelstellingen per oogkas en per patient worden berekend (varierend tussen 0 en 1). Ook een dubbelzien-index werd berekend als de verhouding van de frequentie van nieuw ontstane dubbelbeelden na de operatie tot de frequentie van verdwijnen van reeds voor de operatie aanwezige dubbelbeelden. De mate van uitgebreidheid van chirurgie werd gekwantificeerd van minimaal invasief (25%) tot maximaal invasief (100%), waardoor een gemiddelde index voor het invasieve karakter van de operatie per oogkas en per patient kon worden berekend (variërend tussen 25% en 100%). De nieuwe criteria beschrijven de chirurgische uitkomst in relatie tot de uitgebreidheid van de operatie nauwkeuriger en betekenisvoller dan de traditionele uitkomstmaten.

De studies in hoofdstukken 5 en 6 werden uitgevoerd om huidige trends in oogkasdecompressie nader te onderzoeken, met name wat betreft toegepaste osteotomicieën en incisies.
Samenvatting

Hoofdstuk 5 onderzoekt de -niet eerder vastgestelde- bijdrage van maximale verwijdering van de diepe laterale wand van de oogkas aan vermindering van de exophthalmus, en het effect hiervan op het ontstaan van dubbelzien. In een case-control studie onder GO patienten die een drie-wanden oogkasdecompressie ondergingen via een coronale snede, vergeleken we 15 patienten bij wie het diepe deel van de laterale wand was verwijderd (cases) met 15 patienten bij wie het diepe deel van de laterale wand was blijven staan (controles). Beide groepen verschilden niet van elkaar in preoperatieve kenmerken, maar de vermindering van exophthalmus was gemiddeld 2.3 mm groter in de cases dan in de controles; er was geen verschil in het ontstaan van dubbelzien tussen beide groepen. Conclusie: verwijdering van het diepe deel van de laterale wand als onderdeel van een drie-wanden oogkasdecompressie vergroot de afname in exophthalmus zonder toename van het risico op dubbelzien.

Hoofdstuk 6 geeft een overzicht van de voordelen en de nadelen van kleine incisies vs coronale incisies bij oogkasdecompressie. Incisie van de onderste fornix kan worden gebruikt voor inferomediale benige decompressie en/of voor verwijdering van vet uit de mediale en laterale onderste kwadranten van de oogkas. Een laterale osteotomie kan via dezelfde snede worden uitgevoerd, hoewel incisie van de bovenoorlidplooi een ruimere toegang tot de laterale oogkaswand biedt. De “swinging eyelid” (zwaaidend ooglid) techniek verschaf voldoende toegang tot de benige oogkas en het oogkasvet; het is een veelzijdige techniek die als standaardbenadering kan gelden voor de meerderheid van patienten die een oogkasdecompressie moeten ondergaan. Oogkasdecompressie via een coronale snede is een invasieve techniek, die niet geschikt is als standaardbenadering. De coronale incisie dient echter niet geheel verlaten te worden, daar deze van voordeel kan zijn bij sommige patienten bij wie een op het individu toegesneden benadering te verkiezen is boven de standaardbenadering. Besproken worden de praktische gevolgen van de keuze tussen een gestandaardiseerde benadering en een op de patient aangepaste benadering, die meer wenselijk lijkt.

De studies in hoofdstukken 7,8,9 en 10 handelen over zeldzame aandoeningen die zich soms voordoen bij GO patienten voor of na oogkasdecompressie.

Hoofdstuk 7 beschrijft twee patienten bij wie een klinisch en radiologisch bewezen reactivering van GO ontstond enkele weken na rehabiliterende oogkasdecompressie tijdens
Samenvatting

De inactieve fase van de ziekte. De ziektegeschiedenissen van 249 opeenvolgende GO patienten werden bestudeerd die dezelfde behandeling bij dezelfde indicatie hadden ondergaan; uitgesloten werden patienten die rond de operatie glucocorticoiden hadden gekregen, of bij wie sprake was van andere periorbitale ziekten of bij wie het immuunsysteem anderszins deficient was. De incidentie van uitgestelde decompressie-gerelateerde reactivering was 1.3%. Reactivering trad op enkele weken na de operatie, na een aanvankelijk voorspoedig verlopende herstelperiode. Bij het verder vervolgen van de patienten gedurende gemiddeld 7.5 jaar werden geen nieuwe episoden van reactivering van de oogziekte waargenomen.

Hoofdstuk 8 beschrijft een patient met X-gebonden adrenoleukodystrofie op kinderleeftijd; hij werd voor deze ziekte behandeld met beenmergtransplantatie van zijn zuster, en ontwikkelde Graves’ hyperthyreoidie en GO 6 jaar nadien. Zijn zuster had een normale schildklierfunctie toen zij haar beenmerg doneerde, maar kreeg later zelf Graves’ hyperthyreoidie. De ziektegeschiedenis illustreert passieve overdracht van schildklierimmuniteit van een asymptomatische donor tijdens allogene stamcel transplantatie.

Hoofdstuk 9 beschrijft een GO patient met restrictief scheelzien. Op een CT scan van de oogkas werd een vergrote boventallige extraoculaire oogspier gezien (bevestigd door biopsie). Boventallige, extraoculaire oogspieren komen frequent voor bij katten, maar zijn extreem zeldzaam bij de mens. De casus onderstreept het belang van een zorgvuldige preoperatieve beoordeling van GO teneinde chirurgische fouten te voorkomen.

Hoofdstuk 10 beschrijft een GO patient bij wie een traumatisch neurooom van de linker infraorbitale zenuw ontstond na een dubbelzijdige, rehabiliterende, inferomediale oogkasdecompressie. Deze niet eerder beschreven maar invaliderende complicatie is waarschijnlijk het gevolg van een onopgemerkt zenuwletsel tijdens de chirurgische ontleding van het infraorbitale kanaal. De laesie bleef stabiel bij het vervolgen van de patient gedurende 39 maanden. De klachten van neuralgie konden slechts gedeeltelijk met medicijnen worden bestreden.

De algemene discussie in Hoofdstuk 11 plaatst de bevindingen bij GO patienten die een rehabiliterende oogkasdecompressie ondergingen in perspectief. Een enkele maal dragen scherpzinnige klinische waarnemingen bij aan een beter begrip van basale mechanismen in
de pathogenese van GO. Systematische beoordeling van de verkregen resultaten van chirurgische oogkasdecompressie blijkt van grote waarde voor het verfijnen van chirurgische technieken en het verbeteren van operatieve resultaten.
Curriculum Vitae & Publications
Lelio Baldeschi was born in Pisa, Italy, on 24th March 1964, is married with Antonella and happy father of their little tiger, Giovanni.

He qualified in Medicine *cum laude* at the University of Pisa and graduated in Ophthalmology *cum laude* at the University of Florence, before he sub-specialized in oculoplastic and orbital surgery first under the guide of Richard Collin and Geoffrey Rose at Moorfields Eye Hospital in London and then with Leo Koornneef at the Orbital Centre, University of Amsterdam.

Afterwards he has been a Consultant surgeon to Orbital Centre, University of Amsterdam, where he trained in oculoplastic, lacrimal and orbital surgery residents in ophthalmology and nineteen international fellows, and had the opportunity to publish in the field of adnexal diseases. He has been member of the scientific advisory board, invited speaker and faculty member at a wide variety of international congresses, and courses, visiting professor to several European and North American universities, and had organised national and international congresses. Currently he is member of the Italian Society of Ophthalmology, European Society of Ophthalmic Plastic and Reconstructive Surgery, serve in the steering committee of the European Group on Graves’ Orbitopathy, and is the President of the Italian Society of Ophthalmic Plastic Surgery.

**Referee to:**

- Ophthalmology
- American Journal of Ophthalmology
- European Journal of Ophthalmology
- British Journal of Ophthalmology
- Clinical Ophthalmology
- Orbit
- Ophthalmic Plastic and Reconstructive Surgery
- Expert review of clinical immunology
- Clinical Anatomy
- Clinical Medicine
- Radiation oncology
- Journal of endocrinological Investigation
- Thyroid
- “Cochrane Eyes and Vision Group” of the Cochrane Library
Thirty of 145 invited lectures


8. Fine needle aspiration cytology versus open sky biopsy in orbital oncology. XVI Congress of the Sociedad Española de Cirugía Óptica y Orbitaria (Spanish Society of Ophthalmic Plastic and Orbital Surgery), Barcelona, Spain, 16-17 June 2006.


22. The treatment of eyelid retraction in Graves’ orbitopathy and other diseases. XXVII Congress of the European Society of Cataract and Refractive Surgeons (ESCR), Barcelona, Spain 12-13 September 2009.


30. Featured speaker lecture: The EUGOGO experience: take home messages for the oculofacial specialist. 41st Fall Annual Scientific Symposium of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS), 13-14 October 2010, Chicago (IL), USA.
Upcoming invited lectures at:

- EUGOGO Russian course, University of Moscow, 12-15 May 2011, Moscow Russia.
- Congress of the European Society of Ophthalmology (SOE), 4-7 June 2011, Genève, Switzerland.
- 10th World Congress of the International Society of Dacryology and Dry Eye (ISD&DE), 30 November - 02 December 2011, Manila, Philippines.
- World Congress of Ophthalmology, 16-20 February 2012, Abu Dhabi, United Arab Emirates.

Publications


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It’s what you do next that counts, ad maiora!