Dynamic Rectus Abdominis Muscle Sphincter for Stomal Continence

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Dynamic Rectus Abdominis Muscle Sphincter for Stomal Continence

Dynamische Musculus Rectus Abdominis Sfincter voor Stoma Continentie

(met een samenvatting in het Nederlands)

Proefschrift

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door

Janou W. J. M. Bardoel
geboren op 22 oktober 1971 te Venray

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To my mother, sister and friends from all over the world

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Chapter 1

General Introduction

Some life-saving surgeries result in the necessity to establish permanent stomas; this outcome has an undeniable physical and emotional effect on the patient's life. For these patients the presence of the stoma and external pouching system may be lifelong reminders of the societal stigmas regarding elimination. The need to provide long-term physical and emotional support for many of these patients also has resulted in significant costs for the health care system. Although patients with permanent stomas reasonably adjust, complications that include peristomal skin irritation, pouching system dysfunction, stoma problems, renal deterioration (in patients with a urinary diversion), social inhibition, depression, and sexual dysfunction also have been reported.[1-10]

The underlying issue is continence: the ability to control and evacuate feces, flatus, or urine at socially acceptable times and places. In fecal incontinence the definition extends to being able to distinguish between gas and stool. Surgeries resulting in traditional abdominal stomas render the patient incontinent. The use of a pouching system provides a measure of continence or control over elimination. Even infrequent leakage and odor, however, are frank reminders of underlying incontinence. There remains a need to be continent. Research in this area also has been motivated by the prolonged survival of these patients. With operative survival routine and cure of cancer common, patients are living longer and therefore are willing to have a type of surgery that promises a more "natural" result. That is, patients no longer are universally grateful to be alive; they also seek an improved quality of life.

The quest for fecal continence has resulted in numerous non-surgical and surgical continent diversion techniques.[11-32] The use of dynamic myoplasty is one of them. Dynamic myoplasty is a term given to the use of electrical stimulation devices to stimulate surgically elevated muscle flaps. Using new electrical stimulation devices and skeletal muscle flaps dynamic myoplasty has been used to treat fecal[33] and urinary[34] incontinence using a gracilis muscle flap neo-sphincter. Another clinical example is use of the lattissimus dorsi muscle to augment the pump function of the heart in patients with chronic heart failure.[35] None of the attempted techniques to maintain stomal continence have enjoyed widespread use because of associated complications or because these techniques were not able to provide complete continence. Failure of the surgical techniques has been mainly due to foreign body related complications like wound infections or ischemic complications related to the surgical procedure.[24,25,36,37] These eventually lead to necrosis of the stoma and peristomal area[27,38] resulting in narrowing of the stoma. In dynamic myoplasty these complications should not occur since the stoma sphincter is constructed of innervated and vascularized autogenous skeletal muscle. However, like the many other attempts, the use of dynamic myoplasty to achieve stomal continence has also met with limited success. The results do not support dynamic myoplasty as being a better alternative treatment for fecal stomal incontinence than those methods already available. *Denervation* atrophy caused by flap elevation to construct the sphincter and early *muscle fatigue* caused by continuous electrical stimulation were responsible for these disappointing results and constitute the major obstacles standing in the way of dynamic myoplasty becoming an effective solution to stomal incontinence in the clinical setting.

Aim and outline of this thesis

Aim

The aim of this thesis was to create an abdominal stomal sphincter with an electrically stimulated skeletal muscle flap (dynamic myoplasty) in order to maintain long-term stomal continence.

The following questions were investigated in this thesis:

- Is it possible to use an innervated pedicled skeletal muscle flap, using local available skeletal muscle, for stomal sphincter construction?
- Which muscle flap design is the best for stomal sphincter construction while keeping its innervation intact?
- Is the developed muscle sphincter able to function as such, e.g. able to generate sphincter pressures that are consistent with stomal continence?
- Is it feasible to make the stomal sphincter fatigue-resistant by means of training resulting in long-term stomal continence?
- What type of electrical stimulation (intramuscular or direct nerve) is the best in terms of generating long-term stomal continence?
- What is the effect of chronic stimulation on the stomal sphincter muscle fiber type transformation, muscle fiber histology and its bowel wall morphology?

Outline

Based on previous reports on dynamic myoplasty for stomal incontinence and our laboratory success using dynamic myoplasty techniques[39-43] it was believed that a continent stoma sphincter could be designed and could provide continence for at least several hours. A multiphase project was undertaken that was designed to solve the critical issues of denervation atrophy and early muscle fatigue.

Chapter 2 describes the types of intestinal stomas, epidemiology of stomas, problems associated with stomas and it focuses on the problem of stomal incontinence. Past and current treatment options for stomal incontinence are outlined in detail in this chapter.

The phenomenon muscle plasticity, dynamic myoplasty and its clinical applications are described in **Chapter 3**. This is followed by description of the former attempts in applying dynamic myoplasty to the problem of stomal incontinence.

In **Chapter 4** the basic knowledge of physiologic and electrical muscle stimulation is described to better understand and approach the problems encountered with functional electrical stimulation (FES). The problem of muscle fatigue and methods of approaching it will be described in detail.

The first phase of our multiphase study is described in **Chapter 5**. This first study addressed the problem of denervation atrophy. It involved identifying an ideal muscle to use as a stomal sphincter and determining the anatomical feasibility of using that muscle to wrap around a fecal stoma in fresh human cadavers. Two different flap designs were investigated.
The second phase is described in **Chapter 6**. The proposed rectus abdominis muscle island flap design, developed in the first study, was attempted in an acute canine model. The aim of this study was to determine if the elevated flap wrapped around a stoma would function as such e.g. would be able to generate stomal pressures sufficient for stomal continence.
In order to solve the problem of muscle fatigue we performed two chronic canine studies (third and fourth phase). In the first chronic study we defined a methodology for training the muscle sphincter. This study was designed to determine if the rectus muscle could be "trained" to become fatigue resistant in a chronic canine model. In the first part of the chronic study (Part I. Intramuscular stimulation) we investigated two training protocols (A and B). The best was defined to be the one that led to stomal continence for a couple of hours. The second chronic study (Part II. Direct nerve stimulation) involved the application of the best training protocol found in Part I with the use of nerve cuff electrodes instead of intramuscular electrodes. These chronic studies are described in **Chapter 7**.
In **Chapter 8** the effect of chronic stimulation on sphincter muscle fiber type transformation and muscle fiber histology was analyzed. In addition the examination of the morphologic changes in the small bowel was investigated in this chapter.
Chapter 9 includes the summary and epilogue of this thesis.

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Chapter 2

Stomal Incontinence: Treatment Options

Introduction

An intestinal stoma or ostomy is a surgically created opening in the anterior abdominal wall that allows the passage of fecal material or urine from the intestines. There are two types of intestinal stomas. A colostomy is a connection of the colon to the skin of the abdominal wall. An ileostomy involves exteriorization of the ileum on the abdominal skin. A variety of clinical situations (neoplastic, congenital, traumatic, inflammatory and ischemic disorders of the intestinal tract) necessitate the surgical formation of an intestinal stoma. The most common indication for a colostomy is colorectal cancer. The indication for ileostomy construction is for patients who require removal of the entire colon, and usually the rectum, for inflammatory bowel disease either Crohn's disease or ulcerative colitis. There are an estimated 750 thousand persons with ostomies in the United States and 100 thousand ostomy operations are performed annually in the United States.[1] Worldwide the numbers are not insignificant either. For example in The Netherlands the prevalence of patients with a stoma is approximately 20 thousand and in the United Kingdom the prevalence of colostomy patients is 100 thousand.

The type and anatomical location of the stoma determines the frequency of effluent, nature of the effluent (the consistency, the odor, the presence of corrosive enzymes), and the care required in terms of pouching, or application of an external collection device. The physiology of the colon should be taken into account when considering the construction of a colostomy. The right side of the colon absorbs water and has irregular peristaltic contractions. Stomas made from the proximal half of the colon usually expel a liquid content. The left colon serves as a conduit and reservoir and has a few mass peristaltic motions per day. The content is more solid. A colostomy is usually located in the left lower quadrant. An alternative location is through the midline fascia. The surgical construction of an ileostomy must be more precise than for a colostomy because the content is liquid, high volume, and corrosive to the peristomal skin. An ileostomy is most of the time located in the right lower quadrant.

Individuals with stomas often have poor psychosocial outcomes that range from failure to return to occupation, withdrawal from social and intimate contact, to depression and anxiety.[2] Emotional and social withdrawal include feelings of degradation, damage, isolation, restriction, and mutilation. Embarrassment of the presence of an appliance or fear of leakage and odor may cause them to limit their social, sexual, recreational, and work activities. The lifelong stoma maintenance required by patients with permanent colostomies and ileostomies decreases the quality of life for many people.[3-7]

Because the stoma lacks a sphincter, elimination is not under the voluntary control of the individual. The presence of stool or urine on a plane of the body that may be visible (or at least detectable) to others during social contact poses a major concern to the person with a stoma. Involuntary passage of flatus, and the sound created by the passage, is also a major concern to the person with an intestinal stoma.
Many efforts have been done in the past to address the problem of stomal incontinence. Most current methods for stomal continence use an external pouching system (plastic bag reservoir) into which the fecal material or urine empties constantly and over which the patient has little or no control. These methods have many disadvantages such as a bulky, inconvenient external appliance filled with malodorous fluid that threatens to leak or cause odor and which may be associated with audible, embarrassing intestinal sounds. Through the years, multiple techniques have been proposed to improve the quality of life of these individuals by providing them with stomal continence.[8-10] These include nonsurgical and surgical techniques.

Nonsurgical Techniques

Nonsurgical techniques consist mainly of an irrigation technique or the use of devices that occlude the stoma when desired. The most frequently used non-surgical treatment option for patients with a distal colostomy is intermittent irrigation of the stoma to wash out formed stool.[11-14] The technique of irrigation uses a cone tip that fits into the stoma only enough to provide a seal and to allow the instillation of 500 to 1000 ml of water. Once the water has been instilled, a drainage bag is applied, and the colostomy empties in response to this stimulation. Between irrigations the patient usually wears a security pouch, which permits passage of gas through a filter. This is only recommended for colostomies of the distal colon where stool is more solid and well formed, and for patients who are physically and mentally capable of performing self-care. Another non-surgical strategy for continence is a disposable colostomy plug.[15,16] Success rates associated with the use of this plug have varied.[17,18] Recently a colostomy tube was developed, consisting of a silicone funnel and tube. Using a canine model, the funnel and tube were inserted in the bowel lumen after colostomy creation.[19] Although promising results were reported in these dog studies, clinical trials have not yet been published. Another option is behavior modification. This technique involves training patients to sense bowel evacuation and respond by contracting their abdominal muscles to close the stoma. Reboa *et al.* investigated biofeedback training to obtain continence in patients with a permanent colostomy.[20] Results were considered good when patients attained at least 70% continence. Of 18 patients investigated, 15 achieved said levels.

Surgical Techniques

Numerous surgical techniques have been designed to obtain stomal continence. Ceulemans and Van Baden developed a technique that involved positioning a very small colostomy as high as possible along the left costal margin of the rectus abdominis muscle.[21] This design was based on the idea that a stoma on the superior aspect of the abdominal wall would not drain stool in a dependent gravity-assisted fashion. Despite some reported success, this procedure has not gained widespread acceptance and is no longer performed.

Kock *et al*. developed an intestinal nipple valve by intussuscepting a segment of bowel that was interposed between a bowel reservoir and the stoma.[22] This procedure is used most often with ileostomies and in a few clinical cases in colostomies.[23] With this technique the patient no longer needs to wear an external appliance. However, intermittent intubation of the reservoir with a silicone catheter is still required to evacuate stool. Evacuation becomes difficult if the stool is allowed to become too thick. Complications of this latter technique are frequent and are due to dysfunction of the nipple valve. Nipple valve dysfunction is due to sliding or prolapse of the nipple valve, internal fistulae bypassing the valve or stomal strictures.[24-26] Concurrently, complete replacement of the valve by various prosthetic mechanisms was under investigation. Beahrs *et al.* found that a cuffed Silastic catheter, similar to an endotracheal tube, restored continence in “failed” Kock ileostomies.[27] Fendel and Fazio replaced the nipple valve by a porcine aortic valve in an experimental model.[28] A mucosal “flap” valve was created in another experimental setting.[29] Magnetic closing caps were implanted successfully in two patients[30] Although the devices subjected to clinical trials were able to maintain continence, various complications and limited patient acceptance prevented widespread adoption of their use. A different approach was taken by Fazio, Cohen, Barnett, and others. They found that the intussuscepted nipple valve was more stable when it was mechanically supported at its junction with the pouch and the outflow tract. A strip of fascia,[31] Marlex or Prolene,[32] and later, an ileal limb[33] were used to buttress the valve. Short-term results were promising. A dramatic decrease in the rate of valve desusception was reported. However, an equally dramatic rise in the rate of late fistula formation was associated with the use of the various plastic materials.[34,35]

Another surgical technique designed to create a continent stoma involved construction of a sphincter using a smooth muscle graft of the large intestine.[36] The transplanted smooth muscle was wrapped around the distal portion of the intestine and the intestine with its new smooth muscle coat was brought through the abdominal wall as a stoma. In a series of nearly 500 patients, almost 80% were able to go for a 24-hour period without the need for an appliance. Continence of liquid stools and gas, however, was not sustained and postoperative complications ultimately led to the abandonment of this procedure. Autotransplantation of the stomach pyloric sphincter muscle around the colon has been attempted in a canine model. However, narrowing of the neo-sphincter produced obstruction and fecal continence was not achieved.[37] Artificial sphincters in the form of implanted devices are another surgical treatment option. A magnetic stoma mechanism was introduced by Feustel and Hennig[38] and described by Kubchandani and coworkers.[39] The system consisted of a magnetic ring implanted subcutaneously in the abdominal wall. The bowel was brought through the ring and a stoma was created. After a recovery period, the magnetic external cap was inserted into the stoma. Complete continence varied from 23% to 76% of the patients in different clinical trials. Complications with this procedure varied in terms of severity[40] and included wound infections, necrosis of the stoma and peristomal area, development of fistulae, and incontinence due to suboptimal seating of the internal magnetic ring. A two-part silicone device was developed by Prager *et al.*,[41] but complications were similar to those encountered with the magnetic device.

Last but not least dynamic myoplasty has been attempted as one of the surgical techniques to generate stomal continence.[42-44] Dynamic myoplasty uses own skeletal muscle and therefore prevents foreign body related complications at the level of the stoma.

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Chapter 3

Dynamic Myoplasty

Introduction

Myoplasty encompasses a variety of clinical processes involving transfer of skeletal muscle for replacement or enhancement of body parts. Depending on whether the purpose of using the skeletal muscle flap is for filling a defect or restoration of contractile function, innervation is not, respectively is of major importance.

Muscle flaps are mainly used for bulk to cover defects of the upper and lower extremity caused by trauma[1] and osteomyelitis,[2,3] deformities of the face[4] and to cover defects caused by oncological resections.[5] For breast reconstruction the rectus abdominis muscle has been used extensively. For this application the muscle serves as a carrier for the vascular supply but nowadays can be omitted when the vessels are dissected out (perforator flaps).[6] The result is an inferior epigastric artery skin flap without rectus abdominis muscle.

Restoration of upper and lower extremity function is made possible by transposition of tendons (local muscle flaps), transposition of distant pedicle muscle flaps and by microneurovascular reanastomoses in free muscle flaps. Restoration of function of the upper extremity by a gracilis muscle free flap for replacement of the flexor muscles of the forearm is an example.[7,8] Restoration of function using a distant pedicle flap has been described by Mackinnon *et al*. They transposed the latissimus dorsi muscle to the upper arm to replace a non-functioning biceps femoris.[9] As free revascularized muscle flaps the gracilis[10,11] and pectoralis minor muscle[12,13] have been used for dynamic reanimation in patients with facial paralysis. Restoration of function could be established after a microneurovascular anastomosis. In the given functional myoplasty examples the contraction characteristics of the transposed muscle flap are in close proximity to the original muscle (extremity musculature) or far from the normal function (face musculature) but no electrical stimulation is required because of reinnervation.

In the eighties there was felt to be a need for muscle flaps that could be more versatile in terms of performing a different function from its original one. This led to the development of *dynamic myoplasty*, in which the addition of electrical stimulation allows the transferred skeletal muscle to provide a function different from its original one. The two major applications presently under clinical investigation are dynamic cardiomyoplasty for the treatment of heart failure and dynamic myoplasty for the treatment of fecal or urinary incontinence (dynamic anal respectively urinary graciloplasty).

Muscle Plasticity

The term muscle 'plasticity' refers to the ability of muscle tissue to undergo profound changes in its contractile speed and other properties long after the primary processes of differentiation and growth have been completed. The contractile properties of muscle can be changed by exercise and electrically induced exercise. The latter involves the placement of an electrode in a muscle or on a nerve followed by a conditioning period of electrically induced exercise. During this period the muscle is subjected to continuous or interrupted electrical stimulation in a graded incremental fashion until the desired properties are achieved. The effect of exercise is to convert the muscle from one that fatigues rapidly (fast-twitch glycolytic (type II) fibers) to one that can sustain a reasonable force for a protracted period of time (slow-twitch oxidative (type I) fibers).
From animal experimentation it is known that continuous stimulation, at a low frequency (5-10 Hz), can convert a muscle with a mixed fiber type population to a muscle with a uniform population of slow-twitch fibers, which have a high capacity for oxidative metabolism.[14-17] It is also known that a muscle subjected to electrically induced exercise with a low frequency (10 Hz) paradigm will undergo a decrease in mass and a decrease in the magnitude of the maximum force the muscle can generate.[18,19] Muscle property changes can be predicted and fashioned for a particular purpose, depending on the stimulation paradigm involved. Hudlicka *et al*. found that a paradigm that allowed the muscle to generate greater sustained muscle tension was the 30 Hz pattern. Muscles adapted to a particular paradigm functioned more effectively in concert with that paradigm. However, histochemical, histological, and biochemical results did not explain the different effects of the stimulation paradigms. No difference was found in the extent of fiber conversion present for muscles stimulated at 10 and 30 Hz in the same animal despite the improvement in sustained and tetanic tension seen for muscles stimulated at 30 Hz.[20] Changes in muscle properties have been mainly attributed to the total hours of stimulation per day and not the pattern of stimulation.[20,21]

Dynamic Cardiomyoplasty

Dynamic Cardiomyoplasty is a technique that uses skeletal muscle to augment ventricular function.[22-24] It is aimed at treating patients with chronic heart failure, refractory to medical therapy, that severely limits their daily life, a Class III or intermittent Class IV condition, according to the New York Heart Association (NYHA) classification.[25] In dynamic cardiomyoplasty, the latissimus dorsi muscle is elevated as a flap based on its thoracodorsal neurovascular pedicle, transferred into the thorax, and wrapped around the ventricles of a failing heart. The most common form of the procedure involves wrapping the left latissimus dorsi muscle around the heart as a posterior wrap.[26] Subsequently, the muscle is trained over an 8-12 week period to contract in synchrony with cardiac systole by means of a programmable, implantable nerve-muscle stimulator.[27,28] In this way, cardiac function is augmented. The first procedure was performed in 1985 in Paris by Carpentier *et al*.[29] and to date has been performed clinically in more than 600 patients worldwide.

Whilst many patients do well after cardiomyoplasty procedures in the literature there exists a large variability in the actual improvements in cardiac haemodynamic indices described.[30,31] The reason for this variability is unclear. One of the possibilities could be related to the viability of the latissimus dorsi muscle used to wrap the heart. It is known that when the latissimus dorsi muscle is lifted in its entirety on its thoracodorsal pedicle the distal region of the flap will experience ischemia and often go on to necrosis.[32] In experimental studies vascular delay has been found to improve latissimus dorsi muscle perfusion and contractile function.[33,34]

Another determining factor of the functional outcome could be the training protocol used. Different methods of electrical stimulation have been compared in their effectiveness of creating fatigue resistance[35] and their effect on damaging the muscle.[36] Chronic electrical training of the latissimus dorsi muscle prior to cardiomyoplasty has been studied in various experimental models. Mannion *et al*. examined chronic electrical stimulation and vascular delay as done before cardiomyoplasty. They demonstrated that, after mobilizing the latissimus dorsi, chronic electrical preconditioning of the latissimus dorsi muscle prior to cardiomyoplasty significantly increased, but did not totally restore, exercise-induced blood flow to the distal part of the muscle when compared to contralateral in situ latissimus dorsi muscle.[37] Ali *et al*. found that preconditioning the latissimus dorsi muscle with vascular delay resulted in improving performance of the latissimus dorsi muscle with consistent increases in left ventricular hemodynamics. However, this was not observed after preconditioning with chronic electrical stimulation.[38]

Dynamic Anal Graciloplasty

Fecal incontinence is an underreported condition that affects 2.5 percent of the population. It is a huge problem in human terms with high direct economic costs and indirect costs that result from the unwillingness of people to leave their homes. If anal sphincter repair or biofeedback training is not successful, dynamic graciloplasty is an effective option.

In the 1950s, surgeons developed a passive wrap of gracilis muscle around the anal canal.[39,40] It failed because the patients were unable to maintain the necessary contraction of the muscle voluntarily because the muscle fatigued. The electrically stimulated, skeletal muscle neo-sphincter was developed later on. It adds to the passive muscle wrap a neural or intramuscular electrode that stimulates the muscle.[41,42] An electrical stimulation protocol lasting eight weeks is used to transform the muscle into a fatigue-resistant fiber type. During this period the muscle is stimulated using a graded incremental training regimen until continuous stimulation is achieved. The patient controls fecal continence at will by turning an electrical stimulating device on and off to open and close the skeletal muscle neo-sphincter. Widespread applicability of the procedure was limited initially by the need for an external stimulator. Technological advances in the field of electronics have made available electrical stimulation devices that are small, implantable and have long battery lives.

In 1988, Baeten *et al*. reported the implantation of a neuromuscular stimulator in a patient who had been treated previously with a gracilis muscle transposition because of anal atresia. This resulted in a perfectly controllable sphincter function.[43] In 1989, Williams *et al*. reported a case of construction of a neoanal sphincter following proctectomy.[44] In 1991, Williams *et al*. then described the use of a neoanal sphincter in 20 patients with fecal incontinence.[42] Although there were six failures, the results were encouraging because in all patients with functioning neo-sphincters, continence was improved. Complications included severe perineal sepsis in nine patients, including muscle necrosis in four, electrode displacement in four, difficult evacuation in four, fibrosis and stricture in two, and transient neuralgia in two. This high complication rate must be taken in context with the fact that the only other option for these patients was a permanent stoma.

Vascular delay of the gracilis muscle is described as a possible solution to improve blood supply in the distal part of the gracilis muscle.[45] This concept was applied by Williams *et al*.[42] and Wexner *et al*.[46] To prevent ischemia of the distal part of the gracilis muscle vascular delay 4-6 weeks before transposition of the gracilis muscle was used. It was suggested that improvement of the results was attributable to vascular delay prior to muscle transposition. However, Williams *et al*. reported later on elimination of the delay without adverse effects.[47]

So far no randomized study has been performed to explore whether the final result depends on the type of loop used to wrap the gracilis muscle around the anal canal. Good results have been reported with the gamma loop,[41] the epsilon loop,[42] the alpha loop[48] and the modified epsilon loop.[49]

Dynamic Urinary Graciloplasty

Deming was the first to describe the graciloplasty for urinary incontinence in 1926.[50] In a population of children with total incontinence because of epispadia, he detached the gracilis muscle at its insertion under the knee and wrapped it around the urethra. While pressing the knees tightly against each other by activating the adductors, including the gracilis muscle, the patients could actively evoke urinary continence. In 1956 Pickrell *et al*. reported the same procedure in a series of patients as a success.[51] However, the drawback of this technique was that it is not possible to maintain continence for a long time, because of muscle fatigue. The success of the anal dynamic graciloplasty for treating fecal incontinence led some investigators to explore a similar approach to restoring urinary incontinence. Janknegt *et al*.[52] and Williams *et al*.[53] reported use of the same procedure with the addition of an implantable stimulator to electrically stimulate the gracilis muscle flap. Despite the promising potential of this new application of dynamic myoplasty, preliminary outcomes have been disappointing. The main problems seemed to be associated with stricture of the urethra created by the neosphincter as a result of distal muscle ischemia.[53,54] In an experimental study van Aalst *et al*. addressed this problem by introducing a new procedure whereby the gracilis muscle is used as a free flap by dividing the main vascular pedicle and the muscle's origin at the pubic bone and reanastomose its vascular supply.[55] The well-vascularized proximal part of the gracilis flap could now be used to form the neo-sphincter and showed no evidence of stricture of the urethra for a follow-up of 16 weeks.[56]

Dynamic Myoplasty for Stomal Incontinence

A new, and yet to be clinically tested, option for stomal incontinence is the use of dynamic myoplasty. To date, few studies have been done to investigate the feasibility of using dynamic myoplasty to provide stomal continence. The few reported cases done have been discouraging. Cavina *et al*.[57] electrically stimulated the internal oblique muscle in an attempt to create a continent stoma. However, only one patient was treated using this technique and no follow up has been reported. Merrel *et al*.[58] reported two different methods of using a free microneurovascular gracilis muscle flap in a dog model for stoma neo-sphincter construction. However, in both cases denervation atrophy of the gracilis flap (fatigue in one and closure of the stomal orifice in the other) was reported to have lead to failure. Konsten *et al*.[59] used electrically stimulated rectus abdominis muscle flaps in the pig. They described three different designs of using the rectus abdominis muscle for stoma sphincter construction. The first design was the proximal rectus abdominis muscle wrapped around the stoma. The second design was bowel pulled through the middle of the rectus abdominis muscle. Finally a sling was constructed using the distal part of the rectus abdominis muscle. They found that muscle denervation and fatigue lead to failure.

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Chapter 4

Functional Electrical Stimulation

Introduction

The reanimation of contractile function of muscle is an important advance in the field of reconstructive surgery. Contraction can be either done voluntarily after a few months when the muscle's nerve is coapted (e.g. dynamic reanimation in patients with facial paralysis[1]) or with the help of an external stimulator. The latter is needed when there is an upper motor neuron injury.[2] In this situation the paralyzed muscles have an intact lower motor neuron pathway from the spinal cord to the muscle endplate. To activate the paralyzed muscles an external electrical stimulus is needed. External stimulation is also required when a muscle is transposed and has to perform a function different from its native one even with intact nerve supply.[3]
The most optimal would be an electrical stimulation system that imitates the natural activation of skeletal muscle. The physiological route for activating skeletal muscle is via a complex mechanism in which the brain, spinal cord and peripheral nervous system are involved and interact.[4] The activity imposed by chronic electrical stimulation is simple but on the other hand can have adverse effects because of improper use. Therefore, by understanding the basic knowledge of physiologic and electrical muscle stimulation one can better understand and approach the problems encountered with electrical muscle stimulation.

Functional Electrical Stimulation (FES)

Functional electrical stimulation (FES) covers the general field of using electrical stimulation to recover a lost function. This applies to the central nervous system directly (e.g., cerebellar stimulation[5]), to cranial nerves (e.g., auditory prostheses[6]) and to the peripheral nervous system.[7] When applied in the last group to achieve functional movement, it is often referred to as functional neuromuscular stimulation (FNS). FNS is generally applied to stable neurological lesions where no further recovery is expected and it is accepted that the procedure should be effective for the lifetime of the user. Peripheral nerve stimulation also covers therapeutic stimulation, which is usually applied to enhance residual or temporarily diminished voluntary function and is of shorter duration. Finally peripheral nerve stimulation covers the field of dynamic myoplasty.

Peripheral Nerve Stimulation Physiology

Stimulation of excitable tissue is initiated by depolarizing the cell membrane. The resting transmembrane potential arises as a result of an ionic concentration difference in the intracellular and extracellular fluids of the cell

body and axon. Normally, action potentials are generated by membrane potential changes following synaptic currents. Lowering this potential artificially results in the generation of a propagated action potential. Unmyelinated axons carry the action potential smoothly, while myelinated axons carry it in discrete steps but at faster speeds.
The threshold of stimulation is the minimum stimulus amplitude or duration needed to initiate an axon potential, and this translates to a minimum amount of cathodic charge transfer necessary. Peripheral nerve stimulation to gain muscle contraction depends on delivering a controllable amount of charge to the nerve through an extracellular electrode.[8] Action potentials can also be generated by anodic break currents. Since the thresholds for these are much higher, for practical FNS cathodic stimulation is universally used.
The amplitude of the pulse needed to start an action potential is greater for pulses of shorter duration. Though one would use long duration pulses to minimize the current amplitude needed, total charge transfer should be minimized to decrease the chance of tissue injury. The threshold charge also increases with pulse width increase. This increase is due to the fact that with long duration pulses, the charge is distributed rather than being concentrated at the excitation site.
In myelinated axons there is a constant relationship between the internodal distance and the diameter of the axon (internodal distance = 100 x diameter). Thus large-diameter axons have nodes further apart than small-diameter axons. As a result, under a uniform electrical field the large fibers have a larger potential difference between adjacent nodes. The result of this is that larger fibers have lower thresholds and fire before smaller fibers, which is the reversal of the physiologic recruitment order. Although this does not affect applications where the stimulation is delivered to the muscle through epimyseal or intramuscular routes, it does have importance in nerve cuff applications. Techniques have been developed using a special stimulation waveform to recruit small fibers before large.[9] In applications in which direct nerve cuff stimulation is used, the diameter of the axons in the nerve and their distances from the stimulating electrodes have an effect on the recruitment domain and order. There are strategies by which axons can be selectively activated. Thus, only large fibers or small fibers or a group of localized fibers can be stimulated.[10,11] During epimyseal and intramuscular stimulation the muscle is activated by direct nerve stimulation of the intramuscular muscle branches and not through muscle fiber stimulation. The thresholds for muscle fiber activation are much higher for direct muscle stimulation as compared to direct nerve stimulation.[12]

Electrophysiology

The use of metal electrodes for electrical stimulation necessitates the flow of ionic charge into tissues. This can occur by capacitative or faradic mechanisms. In the former there is alternate attraction and repulsion of ions but no net transfer of electrons. Thus there is no chance of chemical changes occurring. This is an ideal mechanism of charge injection, but is limited by the maximal amount of charge that can be transferred before the dielectric breaks down. Because the charge required for physiological stimulation far exceeds that available from capacitative mechanisms, FNS depends on faradic charge injection. Faradic mechanisms involve transfer of electrons, which means that some chemicals are oxidized or reduced. This can be reversible, as when an opposing current reverses the chemical changes of the preceding stimulation pulse and no new chemicals are formed or destroyed. Thus there is no corrosion of the electrode. In irreversible processes, material is lost into the extracellular fluid.

The guiding principle for selection of electrode materials and stimulation protocols is chemical reversibility. For a particular electrode material, there is a limit to the amount of charge that can be injected before reaching the limits of the reversible processes. This charge limit depends on the electrode material, its shape and size, and the stimulation waveform. The temporal pattern of the stimulus waveform is probably the most important criteria.[13] The least damaging waveforms are biphasic with no net direct current and charge densities within the reversible spectrum. The charges in each half of the waveform may be balanced with a symmetrical or asymmetric wave and there may be delays between the two parts of the biphasic pulse.

Biomaterials

Platinum and its alloys with iridium have been most widely used for electrical stimulation. Platinum is ideal for peripheral applications, while the addition of iridium oxide coatings allows smaller sized electrodes to be used.[13] Of the non-noble metals, 316L stainless steel has been widely used for intramuscular electrodes.

Leads are one of the critical parts of any stimulation system, either percutaneous or implanted, since they have to be able to withstand fatigue failure from shear and joint movement. The implanted stimulators are packaged in titanium with hermetic feedthroughs for the leads. With this type of packaging, the receiving coil has to be outside the main package to avoid significant loss of radiofrequency signal.[14] They also have been packaged in ceramic material, which allows all the components to be in one package, thus reducing the size of the stimulation device.

Adverse Effects

Potential adverse effects of peripheral neuromuscular stimulation are the possibility of tissue damage, unwanted spillover patterns and pain. The mechanism of tissue damage falls into two categories: first, from toxicity from products of electrode dissolution, and second, from non-electrochemical mechanisms like vascular damage or neural membrane damage from passage of the electrical current.[15] The electrochemical problem can be migated by following safe stimulation techniques as previously discussed. Long-term stimulation of muscles using intramuscular or epimyseal electrodes can be done with no deleterious effects. Nerve cuff electrodes have the potential for causing greater damage, but careful regulation of the stimulation parameters, charge densities, total charge delivered, and electrode configurations can minimize this.

Nerve cuff electrodes have been used for many applications ranging from phrenic nerve stimulation for respiratory assist to dynamic cardiomyoplasty. As various the applications are as diverse the long-term effects are, even within the application. Glenn *et al*. reported a study in which quadriplegic patients with respiratory paralysis have been treated by electrical stimulation of the phrenic nerves to pace the diaphragm.[16] The average time the 13 patients have had bilateral diaphragm pacemakers is 26 months. Injury to the phrenic nerves either by initial trauma to the cervical cord or during operation for implantation of the nerve cuff was the most significant complication. In spite of this, nerve damage from prolonged electrical stimulation has not been a problem in this study.

Application Basics

Stimulation parameters selected for electrical stimulation have the objective of depolarizing the specific fibers in the peripheral nerve generally to effect movement of a particular muscle group or groups without evoking an undesirable sensation. Because recruitment is affected by the number of active motor units and the rate of their firing, the stimulation parameters must allow these two variables (i.e., recruitment and temporal summation).

There are different anatomic routes and sites for the placement of electrodes, and this diversity affects the efficacy, selectivity, adverse effects, and the stimulation parameters needed. Three types of electrodes are used, classified by invasiveness as surface, percutaneous, and implanted. With each of these electrodes, stimulation can be monopolar or bipolar. The stimulus waveform used to affect excitation is generally a biphasic current controlled waveform with equal charge contained under the negative and positive going components of the stimulus and waveform. The current controlled phase (in

contrast to using a voltage controlled phase) insures delivery of the desired amount of current to the nerve regardless of tissue impedance changes that might occur at the electrode with encapsulation.
Control of activation of the number of motor units is obtained by increasing either the current or the pulsewidth of the stimulation. Recruitment obtained in this way activates more and more motor units as either the stimulus amplitude or pulse width is increased. However, recruitment is a nonlinear property and the force versus stimulus characteristics generally show no force generated up to a specific stimulation level (known as threshold), followed by a nonlinear in the magnitude of force with increasing magnitude of stimulation. The specific relationship between the stimulus input and the force developed is unpredictable and depends significantly on the geometric relationship of the electrode to the desired nerve fibers. Thus this must be determined experimentally.
In a case of muscle-based electrodes, muscular contraction is elicited through activation of the peripheral nerve, but the electrode generally is not immediately adjacent to the nerve itself, but is rather based on or in the muscle. These electrode types generally are thus less efficient in affecting neural activation and may require a stimulus as high as 20 mA and a stimulus pulse width of as high as 200 μsec to affect strong activation of the muscle.

Muscle Fatigue

General

A universal complication of all functional electrical stimulated muscle in situ or transferred muscle (dynamic myoplasty) is muscle fatigue. Muscles require maintenance of adenosine triphosphate (ATP) within the myofibers to generate force through the contractile interaction of actin and myosin proteins. In the absence of adequate oxygen delivery, muscle dependence upon aerobic mechanisms of metabolism for ATP generation will become limited and dependence upon anaerobic metabolic mechanisms will prevail. A consequence of this shift to anaerobic metabolism is a reduction in ATP production and an increase in lactic acid production. While the etiology of muscle fatigue is complex and can result from many contributing factors, the combination of decreased ATP availability and decreased intracellular pH from lactic acidosis certainly contribute to the failure of muscle to produce contractile force.[17]
In activation of muscle, electrical stimulation provides an unnatural means of eliciting firing of the motor units. All other factors considered equal, the recruitment order achieved for electrical stimulation is through large motor units (innervating fast-contracting, fast-fatiguing motor units) being excited at lower thresholds than those for slow contracting, slow twitch motor units.

This is the reverse order of recruitment of that achieved during normal voluntary contraction.[18,19] In actual implementation the activation pattern is considerably more complex because smaller motor units may be closer to the electrode than larger motor units. Thus, the inverse size principle may not be as critical in differentiating the recruitment order. These alterations of the metabolic properties of the muscle are important in its ultimate clinical use. In particular one encounters reductions in either the maximum force that can be generated or the ability to sustain muscle contraction.

With regard to fatigue, two properties are known to be most important. They are the metabolic profile of the muscle which is being excited and the frequency of stimulation which is delivered to the nerve. For the metabolic profile it is well known that most muscles are composed of motor units that possess different contractile properties, which allow them to act over a wide range of speed of contraction and endurance. In upper motor neuron injury paralyzed muscle is distinguished by having lost many characteristics and is composed of a greater uniformity of fibers, which contractile speeds are similar to fast contracting and relaxing and fast fatiguing.[20] Because of this, electrically stimulated muscle fatigues quite rapidly and generates little force.

A second factor with a significant influence on muscle fatigue is the frequency of activation. It is well known that the muscle generates greater force at higher stimulus frequencies and that a minimum stimulus frequency of 10 to 15 Hz is required to produce a fused contraction of a muscle with slow contraction characteristics. Stimulation at low frequencies is desired, because the force-time properties of the muscle are extended. Thus, in obtaining functional use of muscle, one desires low frequencies for greater endurance but higher frequencies for increased force.

Fatigue in FES

Various methods have been used to reduce fatigue in functional electrical stimulation. These include 1. Chronic electrical stimulation in an attempt to convert fast type II fatigue prone fibers to slow type I fatigue resistant fibers; 2. Modulation of electrical parameters; 3. Alternate stimulation, whereby the different muscles that do the same function are stimulated alternately (e.g. stimulating different muscles in the lower limb alternately to maintain tedious tasks as standing); 4. Sequential stimulation and 5. Varying regimens of nerve stimulation. Each of these methods has its advantages and disadvantages.

In dynamic myoplasty typically muscles are moved to new locations while maintaining only one neurovascular pedicle and then forced through extraneous pulse generators to functionally perform in this new location. The new functional demand is not normal for this muscle and thus fatigues fairly easily. In dynamic myoplasty muscle fatigues primarily for two reasons: they have inadequate perfusion and or they are stimulated to contract at a frequency that is incompatible with their basic muscle fiber type (the latter being in all functional electrical stimulation applications). The use of extraneous stimulation devices produces skeletal muscle contractions capable of generating significant force but the muscle cannot maintain force generation due to fatigue of the muscle. As an anatomical muscle contracts, the individual myofibers within the muscle place significant pressure on the blood vessels within the muscle. Due to these high transmural pressures, a tetanic contraction has the effect of occluding blood flow through the muscle during contraction. This reduction of perfusion due to internal muscle pressure contributes to the failure to deliver adequate oxygen and nutrients to the contracting muscle and precipitates fatigue of the muscle and failure to generate force despite continued stimulation.

Another factor in dynamic myoplasty that indirectly contributes to fatigue might be the unfavorable resting length from which the muscle has to start contracting. It is known that the length of the muscle in terms of bridge kinetics has a determining influence on the force it can generate.[21] In a sphincter model the muscle is wrapped in the shape of a cylinder. Since the muscle is not fixed any more via its tendons it shortens because of its elastic components. In the shortened position maximum contractile strength cannot be developed since there is not an optimum overlap of actin and myosin filaments.

Training Regimen

An approach used in dynamic myoplasty to avoid muscle failure due to fatigue is to train the muscle to enhance fatigue resistance.[22-24] Training protocols currently in use require an 8 week period of stimulation at increasing frequency until the muscle is converted to a fatigue resistant fiber type. Skeletal or striated muscles are normally a mixture of fatigue-prone, fast-twitch, glycolytic (type II) and fatigue-resistant, slow-twitch, oxidative (type I) muscle fibers. The innervation and the function of the muscle determine the predominance of one fiber type over another and all fiber types in a given motor unit are the same. But striated muscle is plastic in nature and the training regimen transforms the muscle to predominantly type I. The trade-off for producing fatigue resistance is a slower contracting muscle capable of generating less power than its innate character.[25]

Sequential Stimulation

While there are many factors that probably contribute to the found difficulties in using a training protocol to enhance fatigue resistance, one reason for the variable outcomes could relate to the way the muscle is being electrically stimulated. Under normal circumstances, a given anatomical muscle can respond and adapt to generation of fine control, prolonged sustained activity, or brief intense activity. The response generated by muscle depends upon the types of motor units (and therefore myofiber types) contained within the muscle and the pattern of activity in which they are engaged.[26] Current applications of dynamic myoplasty call for tetanic stimulation and contraction of all myofibers simultaneously. This tetanic type contraction occurs rarely in normal conditions and can lead to irreversible muscle damage.

On the basis of the earlier described drawbacks of training regimens an entirely different -more physiologic- approach to minimize skeletal muscle fatigue was developed by Zonnevijlle *et al*. Rather than stimulating an entire gracilis muscle in one electrical burst and thus recruiting the same fibers simultaneously, they studied the feasibility of stimulating different gracilis muscle segments sequentially. This approach allows parts of the muscle to rest while other parts work. This sequential segmental neuromuscular stimulation (SSNS) of the gracilis significantly enhanced resistance to fatigue in comparison with whole muscle stimulation.[27] These findings agreed with literature addressing endurance enhancement in neuromuscular prosthesis research for gait, in which alternation between agonistic muscles proved to be beneficial.[28,29] They are also in agreement with observations described in the literature concerning the indirect or neural multichannel stimulation, which was also developed to sequentially recruit separate parts of a muscle.[30-32]

Feedback Control

The control paradigms used in FNS have been described as open-loop and closed-loop systems. In the open-loop paradigm, a single command or group of commands is used to supply a stimulus to the muscle, which then for example generates a force acting across the joint. The resulting torque is balanced by the load, gravity, or an opposing muscle. In the open-loop system, a single command is used to simultaneously control the stimulus levels, which are provided to an entire group of muscles that generate a coordinated action. This system does not incorporate any changes in the performance of the muscle, such as fatigue or changes in the load, in the predicted performance. Rather, the subject has the entire responsibility of using the command to regulate the output performance. In contrast, closed-loop control uses sensors to alter the performance of the system.[33] An example of a closed-loop system would be one in which detection of muscle force is required because of fatigue. In this case, by measuring muscle force, the control system can automatically compensate for changes in the muscle force due to an alteration in muscle performance. There are many other examples of such closed-loop control systems, including walking systems, in which the contact of the foot on the floor is used to regulate subsequent stimulus actions, and control systems, in which a sensor is provided to the joint to ensure that the joint moves through its desired trajectory at a known rate.[34] Closed-loop systems clearly require sensors as a critical element in their implementation. Significant effort has gone into developing sensors for measuring parameters such as foot to floor contact, force grasp, individual muscle force through the bioelectric signal, intramuscular bioelectrical signal, intramuscular pressure and tendon force, joint angle and so forth.[35] Complex arm movements, involving grasp and release control of the forearm, wrist, elbow, and shoulder, have been achieved by using feedback control.[36]

SSNS was introduced by Zonnevijlle *et al.* to reduce muscle fatigue in applications like graciloplasty, so that a prolonged training period could be avoided and the neo-sphincter could be activated soon after surgery to improve patient quality of life more immediately than current approaches permit.[27] To produce this most desired effect, the muscle was proposed to animate in a fashion that allowed it to contract according to need. A normally functioning native sphincter utilizes control mechanisms to regulate when and to what degree contraction occurs, thus maintaining continence without resorting to maximal sphincter contraction for prolonged periods of time. Therefore, closed-loop control of the force generated by the neo-sphincter was applied and combined with SSNS to mimic true physiologic sphincter function.[37] This study showed that closed loop control and sequential segmental stimulation can be effectively combined to acutely control force generation.

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Chapter 5

Use of the Rectus Abdominis Muscle for Abdominal Stoma Sphincter Construction: An Anatomical Feasibility Study

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Introduction

In the few studies that have been done to investigate the feasibility of using dynamic myoplasty to provide stomal continence *denervation atrophy* was one of the two main problems that lead to failure.[1-3] To approach this problem of denervation atrophy we conducted an anatomic study to design a muscle flap sphincter that would preserve as much innervation as possible and be anatomically situated for stoma formation. The most likely would be a muscle flap that would not need a neuro-vascular micro-anastamosis.

Muscle Selection

Following initial anatomical pilot studies we selected the rectus abdominis muscle (RAM) as the ideal muscle for creation of a stomal sphincter. The rectus abdominis muscle has been extensively used in reconstruction of breast,[4] thorax,[5] vagina,[6,7] bladder[8,9] and extremity defects.[10,11] For these purposes the RAM was used to replace or cover a defect. In far less of an extent the RAM has been used for replacing lost contractile function. A part of the RAM, after neuro-vascular micro-anastamosis, has been used for dynamic reanimation in patients with facial paralysis.[12,13] The RAM has also been used as a skeletal muscle ventricle in the dog heart.[14]
The RAM appeared to be the most promising myoplasty muscle for stomal sphincter construction for the following reasons: 1. The RAM is ideally located in close proximity to the lower abdominal quadrants where fecal stomas are most often brought out through the abdominal wall. Therefore the RAM could be transferred without the need for neuro-vascular micro-anastamosis. 2. It is a long, broad muscle that can provide adequate muscle length for a circumferential wrap around a stoma. 3. It has an axial blood supply from the deep inferior epigastric artery and veins that is very reliable and consistent.[15-17] 4. Dissection can be performed through the same laparotomy incision used to expose the bowel. 5. It has minimal donor-site morbidity.

Donor-site Morbidity

The rectus abdominis muscle is one of the muscles concerned in regulating the so-called intra-abdominal pressure and in acting, together with others, as a muscle of expiration. It flexes the lumbar spine, increases intra-abdominal pressure, pushes the diaphragm upwards in forced expiration, and acts in sneezing, lifting heavy objects and during parturition and vomiting. Great exertion is demanded on the muscle when the body is raised from the horizontal to the sitting posture without the aid of the arms, and also by violent coughing and the strain of defecation.

Most of the published studies concerning the donor-site morbidity of using the rectus abdominis muscle have been after pedicled or free TRAM-flap surgery for breast reconstruction.[18,19] Kroll *et al*. reviewed the incidence of postoperative abdominal bulge, hernia, and the ability to do sit-ups in a series of 268 patients who had undergone free (unilateral and double-pedicle bilateral) TRAM or conventional (single-pedicle and double-pedicle or bilateral) TRAM flap breast reconstruction.[19] The incidence of abdominal bulges (3.8%) and hernia (2.6%) was similar in the four groups. However, the ability to perform sit-ups was greatest in the unilateral free TRAM group (63%) and lowest in the double-pedicle or bilateral conventional TRAM group (27%). At the same time there are reports about incidences of serious weakness and hernias of the abdominal wall in patients undergoing TRAM-flap breast reconstruction of up to 35%.[20] To reduce donor site morbidity, more attention has been given recently to limiting the amount of muscle resection. This has led to the development of the deep inferior epigastric perforator (DIEP) flap.[21] These perforator flaps reduce donor site morbidity to the lowest level yet possible.[22]
Free transfer of the segmental rectus abdominis muscle flap is one of the standard procedures for free flap coverage of medium-size defects.[11] Geishauser and co-workers evaluated the donor-site morbidity of the segmental rectus abdominis muscle flap for lower extremity defects in 20 patients with an average follow-up time of 47-months. In the cases included in this investigation only the caudal segment of one rectus muscle and les than one-third of the total length of the rectus abdominis muscle had been harvested.[23] In only 1 patient they found one small hernia in the region of the scar. Grading of the muscle strength of the anterior abdominal wall using the test described by Janda (three exercises, Grades 0-5) was 5 in fourteen patients (70%) and 4 in five patients (25%).
The amount of rectus abdominis muscle we need for stomal sphincter construction is in between one-third and half of the total length of the rectus. In contrary to Geishauer *et al*. we need to make an opening in the anterior and posterior rectus fascia to let the stoma pass through.

Flap Design Rectus Abdominis Muscle: Anatomical Feasibility

The RAM has been used for a variety of different reconstructive procedures and its anatomy has been well documented. In spite of this, a detailed anatomical description of the RAM's nerve and blood supplies relative to it's being used to create a fecal stomal sphincter has not been published.[24-28] The purpose of the following experiment was to describe the anatomy of the RAM in the context of creating an innervated and pedicled fecal stoma neo-sphincter. To determine the anatomical feasibility of creating a flap that, in future studies, could be electrically stimulated, we performed detailed dissections in fresh human cadavers. The objectives addressed include the following: (1) definition of the innervation pattern of the entire rectus abdominis muscle; and (2) determination of the ideal rectus abdominis muscle flap configuration for constructing a stoma sphincter and preserving as much of its native innervation and vascular supply as possible.

Materials & Methods

A total of 24 RAMs in 14 fresh human cadavers (9 male, 5 female) were investigated. Of the 14 cadavers, 10 underwent bilateral dissections. In the remaining four cadavers only one RAM could be dissected due to the presence of surgical scars on the contralateral side.

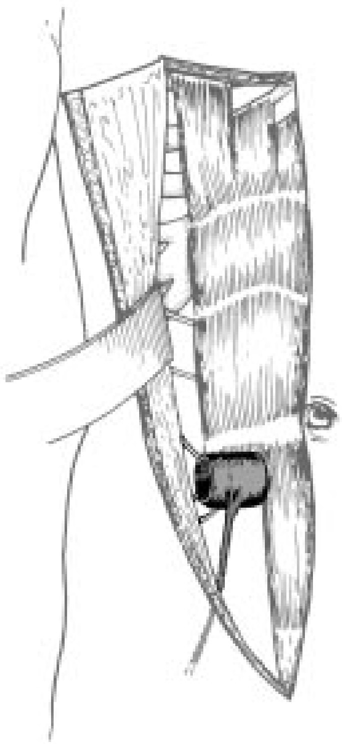
The first part of the investigation consisted of defining the neurovascular anatomy of the RAM. The following measurements were carried out in each mobilized RAM: 1. the vertical and horizontal distance of the point of entrance of all the intercostal nerves innervating the RAM along its posterior surface using the caudal insertion and the lateral muscle margin as reference points. 2. the number of intercostal nerves innervating the most caudal segment of the muscle (between the symphysis pubis and the most caudal tendinous intersection). 3. the vertical and horizontal distance of the point of entrance of the vascular pedicle using the caudal insertion and the lateral muscle margin as reference points.

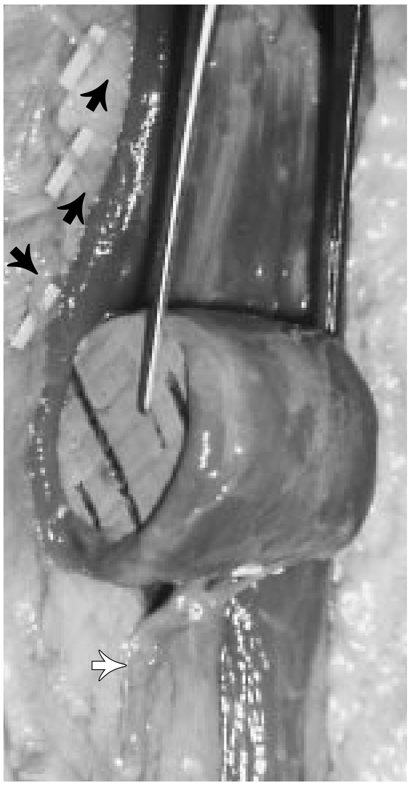
The second part of the investigation consisted of defining the best possible RAM flap sphincter design that would both preserve the muscles' nerve and blood supply.

A mid-line laparotomy from the xiphoid process to the pubic symphysis was used to expose one or both RAMs. The anterior rectus fascia was incised along the medial border of the muscle and was reflected laterally to the lateral margin of the RAM. Marking sutures were placed at the tendinous distal insertion and tendinous intersections to insure that the muscle was returned to its original length after detaching it from its distal insertion. The inferior insertion of the RAM was transected from its bony insertion on the pubic symphysis. The deep inferior epigastric vascular pedicle consisting of an artery (DIEA) and two veins was dissected back to its take off at the external iliac artery. Muscle mobilization was carried out by individually dissecting each intercostal neurovascular bundle laterally with the assistance of an operating microscope (Zeiss, Gera, Germany). The most caudal segment of the RAM was divided longitudinally in the para-sagittal plane. The lateral segment was wrapped around a 3-cm diameter stent that simulated a fecal stoma.

The following two sphincter configurations were compared: a peninsula flap (n = 24) and an island flap (n = 16). With the superiorly based peninsula flap design, the detached caudal portion of the rectus muscle was rolled circumferentially around the stoma stent with the ventral surface of the muscle coming to lie against the stent (Fig. 1). The cranial portion of the muscle was not divided from the caudal segment that was wrapped around the stoma. The long axis of the stoma sphincter was parallel to the abdominal wall. The following measurements were undertaken: 1. the length of the most caudal segment of the rectus muscle with and without the tendinous insertion; 2. the RAM thickness of the caudal segment at its midpoint; and 3. the degree of muscle overlap around the stent after the wrap.

Figure 1
Rectus abdominis muscle, peninsula flap stoma sphincter design in human cadavers. (*Left*) Line drawing representation. (*Right*) Cadaver dissection. The detached caudal portion of the rectus abdominis muscle is wrapped circumferentially around a stoma stent, with the ventral surface of the muscle coming to lie against the stent. The *solid arrows* indicate the segmental intercostal nerves. The *open arrow* indicates the vascular pedicle.

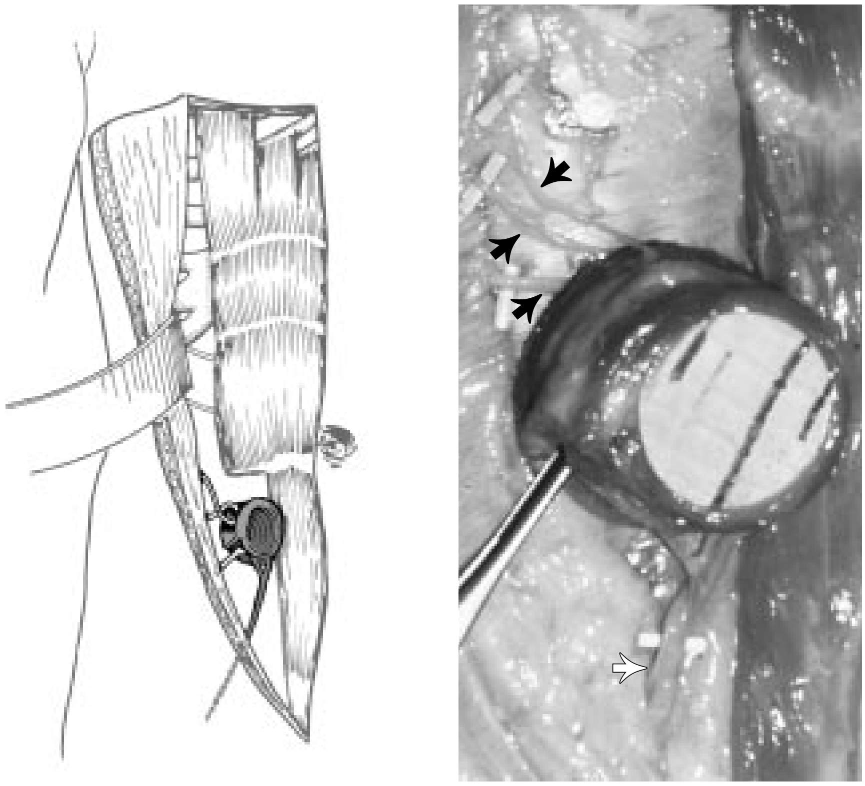




The second sphincter configuration was the island flap (n = 16). The island flaps were constructed by modifying the last consecutive 16 peninsula flaps. This configuration is the same as the peninsula flap with the major difference that the RAM is transected at the caudal most intersection. The distal muscle segment was then rotated 90^0 laterally to allow the stoma sphincter to stand perpendicular to the abdominal wall (Fig. 2). The following measurements were taken for this sphincter design: 1. the amount of muscle overlap after it

Figure 2

Rectus abdominis muscle, island flap stoma sphincter design in human cadavers. (*Left*) Line drawing representation. (*Right*) Cadaver dissection. The rectus abdominis muscle is transected at the most caudal intersection, followed by 90-degree, lateral rotation of the distal muscle segment that allows the created stoma sphincter to stand upright. The *solid arrows* indicate the segmental intercostal nerves. The *open arrow* indicates the vascular pedicle.



was wrapped around the stent; 2. the degree of nerve mobilization proximal to the rectus fascia needed to allow for tension-free stoma sphincter construction; and 3. the amount of sphincter projection above the abdominal wall.

Results

The location at which the intercostal nerves enter the RAM along its posterior surface is shown in Figure 3. The number of intercostal nerves innervating the caudal segment was two in 13%, three in 54% and four in 33% of the RAM dissections. The Deep Inferior Epigastric Pedicle was 10.0 ± 0.5 cm (*VD*) from the pubic symphysis and 2.7 ± 0.2 cm (*HD*) from the lateral margin of the RAM (Fig. 3).

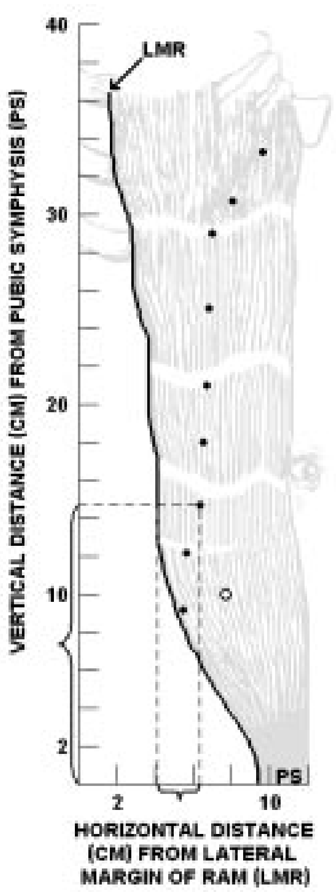
The average length of the caudal rectus segment was 13.3 cm (10.5 to 18.5 cm) without the tendinous insertion of the muscle and 15.5 cm (12.5 to 20.5 cm) with the tendinous portion included. On average, the distal tendinous portion of the muscle was 2.7 cm long (1.5 to 3.5cm). The RAM thickness of the caudal segment at its midpoint was 5.7 ± 0.5 mm (range 3.0 to 12.0 mm).

The amount of muscle overlap around the three-centimeter stent varied with the type of flap being used. Using the peninsula flap the overlap was 0.5 cm (-2.0 to 2.9 cm). In two of the 24 peninsula flap sphincters there was no muscle overlap. In all the island flap sphincters there was complete muscle overlap the extent of which depended on the length of the caudal segment. The average amount of overlap for the island flap was 4.8 cm (1.0 to 9.0 cm).

In all peninsula flap sphincters, the amount of mobilization achieved by dissecting the intercostal nerves up to the lateral border of the rectus muscle was sufficient to allow the wrap to occur without tension on the nerves. No further nerve mobilization was needed. In the island flap design, nine of the 16 flaps (56%) could not be wrapped around the stent unless one or more of the intercostal nerves were dissected from the fascial plane between the internal oblique and the transversus abdominis muscles. One nerve in seven flaps and two nerves in two flaps had to be dissected anywhere from one to three centimeters in order to permit the wrap to occur without placing undue tension on either the nerves or the vascular pedicle.

The sphincter projection as determined by the width of the island flaps, was 4.0 ± 0.2 cm (range 3.0 to 7.0 cm). In only one dissection was it necessary to use almost the entire width of the muscle due to a very medially located insertion of the vascular pedicle.

Figure 3
Location of the entrance of the intercostal nerves (*solid dots*) and the deep inferior epigastric pedicle (*open dot*) into the rectus abdominis muscle along its posterior surface. The vertical distance (*VD*) of the point of entrance uses the caudal insertion at the pubic symphysis (*PS*) as a reference point (*y-axis*). The horizontal distance (*HD*) of the point of entrance uses the lateral margin of the rectus abdominis muscle (*LMR*) as a reference point (*black solid line*). As an example, the brackets indicate the actual distance (in centimeters) at which the third intercostal nerve enters the muscle.



Discussion

Fecal stomal incontinence continues to pose a major problem for patients who suffer with them, for health care professionals responsible for caring for these patients and for the health care system responsible for their costs. Previous attempts to create a continent stoma using dynamic myoplasty procedures have met with less than ideal outcomes. Failures were reported to have been due primarily to denervation atrophy and muscle fatigue of the newly created sphincter. In an attempt to solve the problem of muscle denervation we performed the present anatomical studies. We designed a muscle flap that required minimal muscle denervation in its creation.

Ideally, a muscle chosen for stoma sphincter construction should be situated in close proximity to the proposed stoma location so that local muscle flaps could be used to create the sphincter. In addition, a muscle flap designed for stoma sphincter construction should preserve as much innervation as possible so that sphincter function is not compromised. After carefully considering various muscles for creating a stoma sphincter we chose the rectus abdominis muscle since it appeared to be the best suited choice for this application.

In a thorough literature search we could not find anatomical descriptions of the RAM's innervation that pertained to our specific application i.e. creation of a stoma sphincter. Previous anatomical studies that described the innervation pattern of the RAM did not include exact data pertaining to the number of nerves entering the RAM and at what distance from the pubic symphysis they entered. According to Duchateau *et al.*[29] six to eight intercostal nerves were found to pass into the RAM along a line extending from the costal margin and xiphoid process down to the pubic symphysis. Below the umbilicus, two to three nerves were reported to enter the segment of muscle below the arcuate line. These nerves were noted to become intramuscular shortly after passing beneath the lateral margin of the muscle. Information concerning the vertical distribution of the intercostal nerves entering the RAM, however, was not presented. Similar findings were presented by Bishop *et al.*[26], Rouvière *et al.*[27] and Testut *et al.*[28] According to Cullen *et al.*[25] at the lateral margin of the rectus sheath, there are 5 to 8 fascial perforations through which the intercostal nerves and vessels enter at fairly regular intervals. However, the location of the end distribution was noted to be highly variable. Other published anatomical studies did not provide us with the specific data needed for our application.[30,31]

Our anatomical dissections revealed that the RAM is in the appropriate anatomic location for a stoma; indeed many current methods of stoma creation include delivering the intestine directly through this muscle. The RAM is a long, broad muscle that can easily be circumferentially wrapped around a stoma when lifted as a flap. The muscle has a robust vascular supply from the dominant deep inferior epigastric artery and veins,[15,16] and as our dissections demonstrated, its nerve supply can be kept intact without limiting its arch of rotation. There were, however, some limitations encountered in positioning the sphincter on the abdominal wall. The length of the DIEA pedicle supplying the RAM sphincter limited the distance that the stoma could be positioned cephalad to the pubic symphysis. Conversely, the factor determining the cephalad position of the sphincter depends on the flap design used. With the island flap, the most cranial intercostal nerve(s) limited the mobility of the sphincter. In 9 of 16 island flaps a more extensive mobilization of the intercostal nerves was needed to provide enough mobility to complete the wrap. In case of the peninsula flap the muscle itself limited the mobility of the sphincter. The fact that the peninsula flap design consisted of not dividing the muscle above the most caudal tendinous intersection caused the muscle itself to functionally tether the sphincter superiorly. This tethering of the peninsula flap accounted for not being able to use contractile muscle for the entire wrap. Instead, part of the distal tendon had to be used to complete the wrap in two cases. This was not a problem in the island flap design.

In addition to the above a number of other key features of the island flap design made it better suited for stoma sphincter construction. For example, the island flap design was more versatile in terms of positioning. It could be positioned perpendicular to the abdominal wall allowing the stoma to be delivered to the abdominal skin over the shortest distance without acute angulations. This feature minimizes the risk of distal bowel ischemia. On the other hand, the fact that the island flap was only tethered by its nervous attachments and the vascular pedicle could conceivably place traction on one of the innervating nerves when the muscle is electrically stimulated and contracts. However, one would expect that as the sphincter heals and forms attachments to the surrounding tissues it would become fixed in position making this concern more theoretical than real.

An advantage of the peninsula flap design over the island flap was its dual blood supply. However the disadvantage of the peninsula flap design was that it causes the sphincter to lie parallel to the abdominal wall thus requiring that a greater length of bowel be used to pass through the sphincter. This could increase the risk of distal bowel ischemia. In addition, the parallel orientation of the peninsula flap relative to the abdominal wall would cause two acute angulations in the bowel resulting in further potential risk of local ischemia and resultant stenosis. Finally stimulation of the peninsula flap sphincter would likely cause the entire contiguous muscle to contract resulting in distortion and upward displacement of the stoma. This could cause discomfort for the patient.

As with other striated, voluntary fast-twitch muscles, the rectus abdominis muscle fatigues rapidly if repeatedly stimulated. To apply this method clinically as in other dynamic myoplasty applications the RAM would have to be made fatigue-resistant in order to function as a stoma sphincter. This can be achieved by "training" the muscle as is done in cardiomyoplasty or graciloplasty,[32] in which case the latissimus dorsi and gracilis muscles are transformed from fatigue-prone to fatigue-resistant. We are currently conducting experiments in a dog model designed to define optimal electrical stimulation parameters that can be used to train the RAM flap stoma sphincter.
In summary, we have shown through detailed anatomical dissections that the RAM is ideally suited for constructing a stoma sphincter. The muscle is located in the appropriate anatomical location for stoma creation, it has a long vascular pedicle, and the preserved segmental intercostal innervation pattern allows the muscle to be tailored and mobilized in such a way to completely wrap a fecal stoma without significant muscle denervation. We found that the RAM island flap design is superior to the peninsula flap design for stoma sphincter construction. If in our future "functional" studies the RAM can be successfully trained to become fatigue-resistant, this technique could put the problem of stomal incontinence one step closer to being solved.

Acknowledgments

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Chapter 6

Dynamic Rectus Abdominis Muscle Sphincter for Stomal Continence: An Acute Functional Study in a Dog Model

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Introduction

With the anatomical study as a base we felt there was a need to first perform an acute functional study using this same rectus abdominis island flap design in an animal model before going on to chronic studies.

It is of importance how "tight" a muscle is wrapped. Tightness not only is of significance for the resting pressure but also is it directly related to the squeezing pressure. In an animal model Buie *et al*. wrapped sartorius muscles around stents with different diameters and measured resting and squeeze pressure.[1] They found the tighter the wrap the higher the resting pressure and the higher the squeezing pressure. It must be taken into account that this cannot be done unlimited since the higher the resting pressure the more chance of getting venous congestion of the stoma and the more difficult it becomes to let stool pass through. Clinically the issue of the tightness with which to wrap the gracilis muscle around the anal canal in dynamic anal graciloplasty has not been resolved. At the present time, the most satisfactory course appears to be a "snug" wrap around the surgeon's contralateral index finger.[2]

In pilot studies we found that wrapping the rectus abdominis muscle island flap around a segment of distal ileum into which a 1.0 cm diameter stent was placed was able to occlude the stomal lumen completely during electrical stimulation and was patent while resting. The purpose of this acute functional study was to determine whether the rectus abdominis island flap when made into the shape of a sphincter could function as such e.g. would be able to generate stomal pressures sufficient with stomal continence (60 mm Hg). In this acute functional study we first outlined what the generated intraluminal stomal pressures were using different stimulation frequencies and if these were consistent with stoma continence. In a second part we determined the ability of this rectus abdominis stomal sphincter to generate continence at different intraluminal bowel pressures.

Materials & Methods

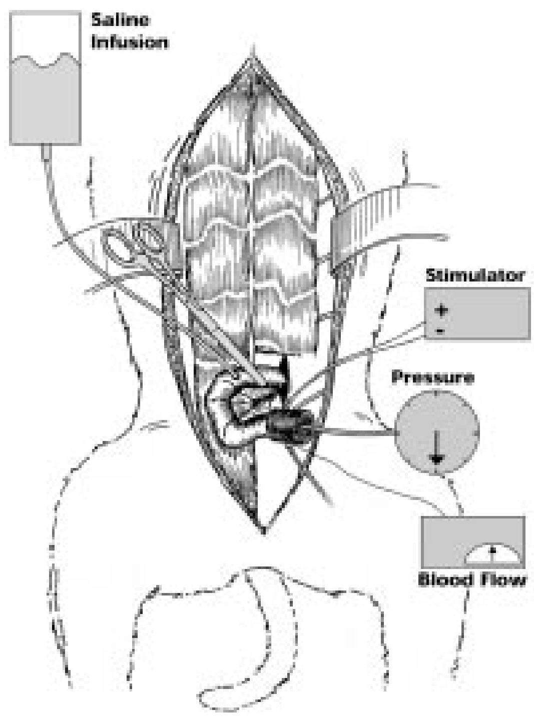
Eight rectus abdominis island flap stomal sphincters were created around a segment of distal ileum in six dogs (two dogs had two rectus abdominis island flap stoma sphincters created and four dogs had one). Sphincter function was assessed by measuring peak pressure, fatigue rate and continence time (Fig. 1). Furthermore, the arterial blood flow to the rectus abdominis muscle island flap sphincter was measured before and during electrical stimulation.

Animal Care

Male mongrel dogs (23 to 27 kg) were used in these experiments. Prior to surgery, animals were housed in separate cages in temperature (22^{0}C), light (12-hour light-dark cycle) and airflow controlled rooms. They were fed a commercial dog diet with ad libitum access to water. At the end of each experiment, dogs were euthanized using an intravenous overdose of Beuthanasia (390 mg of pentobarbital sodium and 50 mg/ml of phenytoin

Figure 1

Experimental set-up in dogs. A rectus abdominis sphincter is constructed around a segment of distal ileum. A pair of stimulation electrodes is inserted into the muscle near the nerve entry zone. Stomal pressure and fatigue rate measurements are obtained using a microtransducer catheter placed into the stoma lumen encircled by the sphincter. To perform continence measurements, a catheter connected to a saline bag is inserted into the ileum 20 cm proximal to the stoma.



sodium [Schering-Plough Animal Health Corp., Kenilworth, NJ]). The protocol for the use of dogs in this study was approved by the Institutional Animal Care and Use Committee at the University of Louisville and adhered to the National Institutes of Health and APS "Guide for the Care and Use of Laboratory Animals".

Surgical Technique

On the day of surgery, dogs were preoperatively medicated with atropine sulfate (0.1 ml/kg body weight; subcutaneously, Vedco, Inc., St. Joseph, MO.), and anesthetized using Pentothal (thiopental sodium, 6 to 12 mg/kg body weight; intravenously, Abbott Laboratories, Chicago, IL.). Animals were intubated and mechanically ventilated with a halothane/ oxygen/ nitrous oxide mixture (2:94:4, 0.2 liter/min/kg body weight, Halocarbon Laboratories, River Edge, NJ) to maintain a surgical level of anesthesia. An intravenous infusion of lactated Ringer's solution (5 ml/kg body weight/hr) was maintained for the duration of the procedure with continuous monitoring of arterial blood pressure and heart rate.

With dogs in the supine position, a longitudinal midline abdominal incision was made to expose the rectus abdominis muscle. The anterior rectus fascia was incised along its medial border and reflected laterally. The rectus abdominis muscle was elevated while preserving the integrity of the posterior fascial sheath. Marking sutures were placed at the tendinous insertion and at the most caudal intersection, so that after it was detached from its distal insertion the muscle could be extended back to its original resting length. The deep inferior epigastric artery and veins were dissected to the external iliac vessels. The two most caudal intercostal nerves were dissected out taking care to avoid excess traction on the nerves.

To determine which nerve innervated which part of the caudal segment, the two most caudal intercostal nerves were individually stimulated using a bipolar stimulating electrode cuff (model 4080, Medtronic, Inc., Minneapolis, MN). The part of the muscle that contracted when stimulating the most caudal nerve was tailored (4 cm width) into the final flap. The rectus abdominis muscle was then transected 12 cm from the pubic symphysis leaving the most caudal nerve and the deep inferior epigastric artery and veins intact. The rectus abdominis muscle flap was then dissected from the pubic bone incorporating a strip of periosteum.

The distal ileum was identified and transected, leaving two blind ends into which a rubber stent (diameter, 1.3 cm) was placed. The rectus abdominis muscle island flap was then snuggly wrapped around the end of the transected ileum and fixed to itself with two rows of 3-0 Dexon mattress sutures. Prior to electrical stimulation the stent was removed from the bowel lumen.

Sphincter Stimulation and Functional Measurements

Two stimulation electrodes (temporary myocardial pacing lead electrodes, model 6500, single lead, Medtronic, Fourmies, France) were placed 1 cm cranial and 1 cm caudal from the nerve entry into the flap and were connected to an electrical stimulator (A 310 Accupulser, World Precision Instruments, New Haven, CT).

The intensity of stimulation was normalized to motor threshold (MT) for all sphincters. MT was defined as that stimulus intensity which induces minimal muscle contraction as determined by visual inspection. The stimulator was then set at 4, 6 and 8 times motor threshold to determine the optimal current for maximal force contraction. All further muscle stimulation was performed at the optimal current, with a 270 μsec pulse duration. The resting time between stimulations was 10 min. or until the muscle's bloodflow reached it's resting value.

To determine rectus abdominis muscle sphincter function, the peak pressure, fatigue rate and continence time were measured. All measurements were performed using a microtransducer catheter (Millar®, Millar Instruments, Houston, TX, 1.67 mm diameter) placed into the lumen of the bowel wrapped by the rectus abdominis muscle sphincter. The microtransducer catheter was connected to a computer-based data acquisition system (CED 1401 PLUS interface and a 1902 signal amplifier, Cambridge Electronic Devices, U.K.).

Peak Pressure, Fatigue Rate, Continence Time & Blood Flow Measurements

Peak pressure in the stomal lumen (encircled by the rectus abdominis sphincter) and fatigue were measured at stimulation frequencies of 20, 30, 40 and 50 Hz. Peak pressure was defined as the maximal pressure generated (in the stoma lumen) by the sphincter during stimulation. Fatigue rate was defined as the time required for the maximal sphincter pressure generated during stimulation, to decline by half.

Continence time was defined as the amount of time (seconds) the rectus abdominis muscle sphincter could retain saline at different intraluminal bowel pressures. The continence time started with stimulation of the rectus abdominis muscle sphincter and ended at the instant when saline started leaking out of the stoma. The rectus abdominis muscle sphincter was stimulated at a frequency of 30 Hz at a pulse duration of 270 μsec at different (30, 65 and 100 mm Hg) intraluminal bowel pressures. Pressures were altered by varying the height of an infusion bag of saline. To prevent the retrograde flow of saline, away from the sphincter, a clamp was placed on the ileum 20 cm proximal to the sphincter. During filling intraluminal bowel pressure was monitored using a microtransducer catheter placed between the sphincter and the clamp (Fig. 1).

To measure blood flow to the rectus abdominis muscle sphincter, a blood flow probe (1.5RB; T206, Transonic Systems Inc., Ithaca, NY) was placed on the deep inferior epigastric artery. Measurements were performed before and during stimulation at the predetermined stimulation frequencies (see above). The change in the mean arterial blood flow over baseline was determined and recorded during stimulation.

Statistical Analysis

Results are presented as mean ± standard error of the mean (SEM). We used a one-way repeated measures analysis of variance (ANOVA) and the Tukey post-hoc test. A value of $p<0.05$ was considered to be significant.

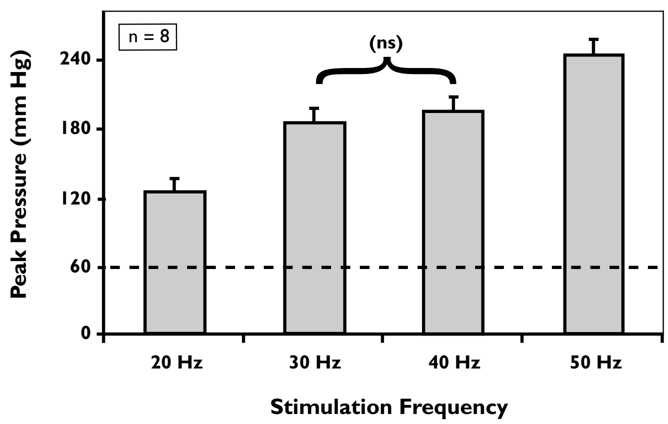
Results

Sphincter Peak Pressure and Fatigue

The peak pressures at 20, 30, 40 and 50 Hz were 124.2 ± 11.8 mm Hg, 183.0 ± 14.6 mm Hg, 192.5 ± 14.5 mm Hg, and 238.8 ± 16.7 mm Hg, respectively (Fig. 2). The increase in peak pressure rate was significant ($p<0.05$) when comparing 20 with 30 Hz, 20 with 40 Hz, 20 with 50 Hz, 30 with 50 Hz and 40 with 50 Hz. Fatigue rates at 20, 30, 40 and 50 Hz were 92.5 ± 10.6

Figure 2

Rectus abdominis muscle sphincter peak pressure (mm Hg) generation in the stomal lumen. Data (*n* = eight sphincters) are presented as mean ± SEM. All the peak pressures between the stimulation frequencies are significant (*p < 0.05* by Tukey posthoc test), except the comparison indicated by the bracket. ns, non significant.



seconds, 41.0 ± 4.1 seconds, 27.8 ± 1.8 seconds, and 20.4 ± 1.8 seconds, respectively (Fig. 3). A significant decrease in fatigue rate was observed when comparing stimulation frequencies of 20 with 30 Hz ($p < 0.001$), 20 with 40 Hz ($p < 0.001$) and 30 with 50 Hz ($p < 0.04$).

Sphincter Continence Time

The rectus abdominis muscle sphincter (stimulated at 270 µsec and 30 Hz) was able to maintain continence of saline at pressures of 30, 65 and 100 mm Hg for durations of 165.5 ± 15.8 sec, 62.7 ± 5.2 sec, and 37.1 ± 2.4 sec respectively (Fig. 4). Continence times decreased significantly at intraluminal bowel pressures of between 30 and 65 mm Hg ($p < 0.001$) and 30 and 100 mm Hg ($p < 0.001$).

Blood Flow to Sphincter

The decrease in the mean arterial blood flow to the rectus abdominis muscle flap over baseline during different stimulation frequencies is shown in figure 5. At the start of stimulation the bloodflow decreased at all tested stimulation frequencies, the speed of which depended on the stimulation frequency used. At a stimulation frequency of more then 20 Hz there was a larger drop in bloodflow. Although not statistically significant there was a tendency for bloodflow to recover faster towards baseline when using higher stimulation frequencies.

Figure 3

Rectus abdominis muscle sphincter fatigue rate (seconds). Data (*n* = eight sphincters) are presented as mean ± SEM. All of the fatigue rates between the stimulation frequencies are significant (*p < 0.05* by Tukey posthoc test), except the comparisons indicated by the brackets. ns, non significant.

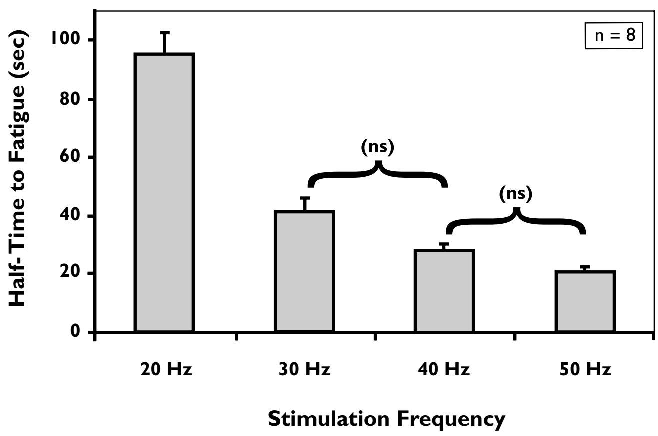


Figure 4
Rectus abdominis muscle sphincter continence time (seconds). Data (*n* = eight sphincters) are presented as mean ± SEM. All of the continence times between the different intraluminal bowel pressures tested are significant ($p < 0.05$ by Tukey posthoc test), except the comparison indicated by the bracket. ns, non significant.

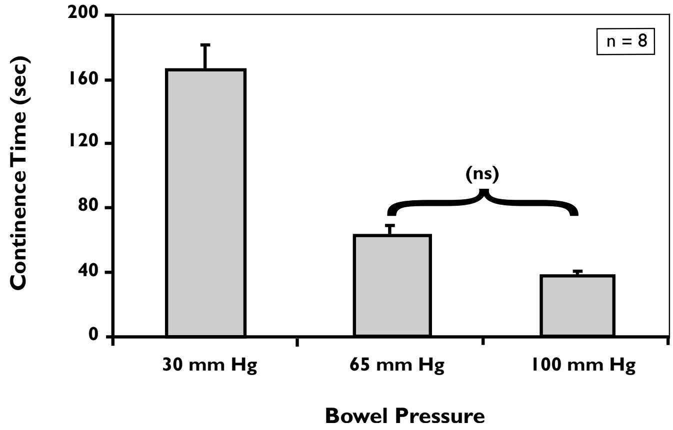
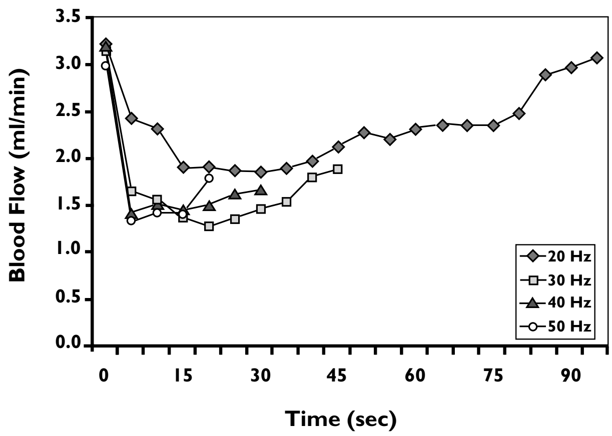


Figure 5
Mean arterial blood flow (ml/min) to the rectus abdominis muscle sphincters (*n* = eight sphincters) during stimulation using different stimulation frequencies. The *x*-axis represents the time (seconds) after the start of stimulation.



Discussion

There is no muscle or structure in the human body that has a more keenly developed sense of differentiation and accommodation than the anal sphincter. It can discriminate between solid, fluid and gas stool consistencies as well as standing, sitting or reclining postures all the time maintaining varying pressures consistent with continence. The normal anal sphincter contains an internal smooth muscle component and an external striated muscle component. The former allows it to contract involuntarily while the latter is voluntarily controlled. The interplay between these two is complex and controlled by feedback mechanisms through reflex neural pathways that result in reflex contraction of the anal sphincter. An ideal stomal sphincter would incorporate as many of the above qualities and functions as possible.

Recent technological advances in the field of electronics have made available electrical stimulation devices that are small, implantable, have long battery lives and can be programmed to respond to the body's own feedback stimuli. The latest technology utilizes sensors that sense pressures, electrical impulses, movement etc. and according to preset parameters use these to control the degree of stimulation and thus create closed feedback loop mechanisms. These advances have given rise to a whole new field known as dynamic myoplasty. Dynamic myoplasty is a term given to the use of electrical stimulation devices to stimulate skeletal muscle in situ or as surgically elevated muscle flaps. Using these new electrical devices and skeletal muscle flaps dynamic myoplasty could be used to provide many of the characteristics of an anal sphincter. In cardiomyoplasty the latissimus dorsi muscle flap is wrapped around the myocardium and made to contract in synchrony with the beating heart. This is accomplished using a closed loop feedback mechanism whereby the electrical stimulating device utilizes ventricular electrical activity as a stimulus to drive its stimulation pattern.[3] In graciloplasty for anal[4] and urinary[5,6] incontinence gracilis muscle flaps are constructed into the shape of sphincters. Using an electrical stimulation device the gracilis muscle is made to contract to generate average pressures of 60 cm H_2O for maintaining anal continence and 40 cm H_2O for maintaining urinary continence.

To avoid fatigue in all these applications, the skeletal muscle used must be trained prior to being asked to perform its definitive function. An electrical stimulation protocol lasting eight weeks is used to transform the muscle into a fatigue resistant fiber type. During this period the muscle is stimulated using a graded incremental training regimen until continuous stimulation is achieved.[7]

In creating a stomal sphincter using dynamic myoplasty techniques the goal is to create a stomal sphincter that simulates an anal sphincter. Such a sphincter would be located in the lower abdominal quadrant (where most stomas are placed), be able to generate sphincter pressures that are consistent with stomal continence, be fatigue resistant (to sustain elevated pressures for prolonged periods) and that could be regulated by stomal pressures. Proven technology is available to provide all these features.

The purpose of this study was to take a step toward achieving the above. In previous anatomical studies in human cadavers our group determined that a rectus abdominis muscle island flap was an ideal muscle flap design based on location, innervation and vascularity.[8] In the present study we wanted to determine if the rectus abdominis muscle island flap, constructed into the shape of a sphincter could generate pressures consistent with those needed to maintain stomal continence. In humans anal sphincter pressures sufficient to maintain continence range between 40 to 60 mm Hg.[9,10] In a clinical study Akwari *et al*. found that continence was maintained in a continent ileostomy and a conventional ileostomy at intraluminal peak pressures of approximately 50 cm H_2O and 60 cm H_2O respectively.[11] Based on this information 60 mm Hg was set as the target pressure needed to achieve continence in our rectus abdominis stomal sphincter design. We found that in all cases the canine rectus abdominis stoma sphincter generated peak pressures well above this 60 mm Hg mark. As anticipated we found that there was a drop in the bloodflow after the start of electrical stimulation followed by a recovery in bloodflow. The speed of recovery towards baseline was dependent on the stimulation frequencies used.

The best function of the stoma sphincter would be achieved if the rectus abdominis muscle contracted in a smooth fashion without rhythmic excursions in generated pressure, since this would result in immediate incontinence. To obtain such a contraction the fusion frequency of the muscle must be found. The fusion frequency is the minimum stimulation frequency that results in a smooth fused plateau in the pressure signals, implying a tetanic contraction. Stimulating the rectus abdominis muscle sphincter using 20 Hz did not yield a tetanic contraction in all the tested sphincters. However, 30 Hz gave the desired tetanic response. Using 30 Hz as stimulation frequency our rectus abdominis muscle sphincter was able to occlude the stomal lumen completely and maintain it continent for all the three intraluminal bowel pressures (30, 65 and 100 mm Hg) measured.

Based on our findings from the initial anatomical study and this present acute functional study we will conduct chronic functional studies to determine if this sphincter design with the stimulation parameters tested here are capable of providing a non-fatiguing stomal sphincter. In these studies we will test our ability to train the rectus abdominis stomal sphincter to achieve prolonged continence. These future studies will bring us closer to establishing a stomal sphincter with capabilities similar to that of an anal sphincter.

In conclusion, this study describes the acute functional characteristics of an electrically stimulated rectus abdominis muscle island flap wrapped around a stoma in a canine model. We demonstrated that by electrically stimulating the rectus abdominis muscle island flap stomal sphincter, sufficient contraction pressures could be generated to provide stomal continence. These findings contribute to the goal of using dynamic myoplasty as an alternative treatment for millions of patients with incontinent ileostomies or colostomies.

Acknowledgements

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Chapter 7

Fatigue Resistance in Rectus Abdominis Stomal Sphincters: Functional Results of Two Chronic Studies

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Introduction

Muscle Fatigue: The Critical Issue

Only a few attempts have been made in applying dynamic myoplasty to the problem of stomal incontinence. In 1982 Cavina *et al*. did the first clinical attempt of using an internal oblique muscle flap for stomal sphincter construction.[1] Later this was followed by two other attempts by Merrel *et al*.[2] and Konsten *et al*.[3] in animal experimental studies. All of these attempts failed. Muscle denervation atrophy and muscle fatigue were cited as the major reasons for failure. Based on the cause of these failures we performed a human cadaver study aimed at designing a stomal sphincter from a rectus abdominis muscle (RAM) island flap, taking special care not to dennervate the muscle.[4] After accomplishing our goal in this anatomical study we then performed an acute functional study in a dog model. In this study we demonstrated that, when electrically stimulated the RAM stomal sphincter was capable of generating pressures sufficient to maintain stomal continence.[5] Our final set of experiments were designed to investigate methods of minimizing muscle fatigue.

Past and Current Strategies for Minimizing Muscle Fatigue

Skeletal muscle is incapable of maintaining a long-term, sustained contraction consistent with stomal continence, without becoming fatigued. In the early days of anal graciloplasty Pickrell *et al*. introduced a technique that consisted of wrapping the gracilis muscle around the anal canal and relying on voluntarily adduction of the leg to contract the muscle and provide continence.[6] These attempts failed due to gracilis muscle fatigue and resulted in anal incontinence.

In 1981, Salmons *et al*. demonstrated that chronic low frequency electrical stimulation causes normally fatigable skeletal muscle to undergo a series of morphologic, physiologic, and biochemical changes, resulting in its transformation into nonfatigable muscle.[7] Following Salmons crucial work, a number of investigators in Europe rejuvenated the anal graciloplasty operation by Pickrell *et al*.[8], specifically, Hallan *et al*.[9] and Williams and colleagues[10] in England, Baeten and coworkers[11,12] in The Netherlands and Cavina *et al*.[13] in Italy. They introduced training regimens for the neo-sphincters with the goal of minimizing muscle fatigue. The results between the different centers vary,[14,15] however, the addition of electrical stimulation training protocols significantly improved the overall outcomes. Good results were reported in up to 78 percent of patients who have undergone dynamic graciloplasty with continence for both liquid and solid stool.[12,16,17] More recently, a multicenter trial (128 graciloplasty patients) showed that overall, 66% of the patients achieved and maintained a successful outcome over the follow-up period.[18] By etiology, these proportions were 71%, 50% and 66% for patients with acquired fecal incontinence, congenital incontinence, and total anal reconstruction, respectively. Experienced centers had better outcomes and lower complication rates than inexperienced centers. The most common complications described were technical problems with the muscle wrap and with muscle stimulation, perineal infection and infection of the stimulator and leads.

Both in anal and urinary dynamic graciloplasty the ultimate goal is continence. Of the various methods proposed for minimizing muscle fatigue in anal dynamic graciloplasty procedures (training, sequential stimulation and feedback-control), to date only muscle training has been used clinically. Since training the gracilis muscle in these procedures seemed to work for treating anal incontinence, we designed two chronic studies to test whether training would effectively minimize rectus abdominis muscle fatigue in our stomal sphincter application. We tested whether training the RAM sphincter would render it resistant to fatigue and thus provide long-term stomal continence.

Training Protocols in Other FES Applications

Like in dynamic myoplasty the importance of stimulation frequency and stimulation amount for the transformation of fatigue prone muscle to fatigue resistant muscle is a fast-twitch muscle fibers into slow-twitch muscle fibers has been a matter of discussion in other FES (Functional Electrical Stimulation) applications as described in Chapter 3. Pette *et al*. compared the effect of continuous low-frequency stimulation (10 Hz) and low-frequency stimulation for only 8 hours a day (intermittent stimulation) of the tibialis anterior and extensor digitorum longus muscle in a rabbit model.[19] Changes in fiber type were observed after intermittent stimulation periods exceeding 40 days or continuous stimulation periods longer than 20 days. It was evident that the changes in contraction properties toward slow-twitch muscle fiber type are found both in intermittent and continuous stimulated fast muscles, although the changes proceed faster during continuous stimulation. Hudlicka *et al*. used an equal number of stimuli per minute, as in low-frequency continuous stimulation experiments, but delivered them in short bursts of high frequency (40 Hz).[20] Although there were some quantitative differences between the contractile properties of the fast muscles subjected to these bursts of high-frequency stimulation and those subjected to conventional low frequency stimulation, the principle outcome was the same, that is, a conversion to slow-twitch characteristics.

There is evidence that the transformation resulting from stimulation at higher frequencies within the physiological range is similar if the same aggregate number of impulses is delivered to the muscle.[21-23] On the other hand, burst stimulation of this type tends to be more effective in preserving muscle mass and force-generating capacity.[24-26] The latter is very important for sphincter function. However, burst stimulation can't be used for the problem of stomal incontinence since sustained contraction is needed.

Training Protocols used in Dynamic Graciloplasty

Different training protocols for anal dynamic graciloplasty have been described in the literature. Williams *et al*. not only used a protocol with an intermittent pattern of stimulation (10-25 Hz, on-time 4-10 sec, off-time 1-24 sec) but also a protocol with a continuous pattern of stimulation (2 Hz).[10] Seccia *et al*. did the same but used a stimulation frequency of 20 Hz and an on-off ratio of 2:4 for the intermittent stimulation.[27] For their continuous stimulation protocol (training protocol for eight weeks, with increasing duty cycle every two weeks) they used a frequency of 25 Hz. Besides these differences with Williams *et al*., Seccia uses direct nerve stimulation in their intermittent stimulated group and intramuscular electrodes in their continuously stimulated group. Williams *et al*. mention in their study that it was impossible from their study to say whether continuous or intermittent stimulation is the best way to convert the muscle because there were too many variables between the two groups.[10] Seccia *et al*. should have mentioned this as well since they have at least two substantially different variables (different electrodes with different training protocols). Konsten *et al*.[28] and Janknegt *et al*.[29] used an intermittent stimulation protocol for their gracilis neo-sphincter for anal and urinary incontinence respectively. The only difference between their protocols was the duty cycle (percentage of time that the sphincter is on). Although most of the training protocols for dynamic graciloplasty last 8 weeks or longer, shorter training protocols have been investigated. Rosen *et al*.[30] demonstrated in an animal model that the functional efficiency of a training protocol for a sartorius muscle lasting 5 weeks was as good as the one lasting 8 weeks when using a stimulation frequency of 20 Hz. From all these studies we may conclude that of the different training protocols tested, all seem to work for both the gracilis and sartorius muscle.

One of the many factors that influence the training of muscle is the type and placement of the electrode being used. In the past, both intramuscular and perineural placement of the electrodes have been used by the pioneer centers of anal dynamic graciloplasty with equally good results.[12,31] In spite of this, the tendency nowadays is to use intramuscular rather than perineural placement of the electrodes.[18] Therefore we initially have used intramuscular electrodes in the acute functional study (Chapter 6) and accordingly in the subsequent chronic study (Part I. Intramuscular stimulation). However, the question rose which training protocol would work for our application.

Part I. Intramuscular Stimulation

Clinically Used Dynamic Graciloplasty Protocol for Training of the RAM Stomal Sphincter

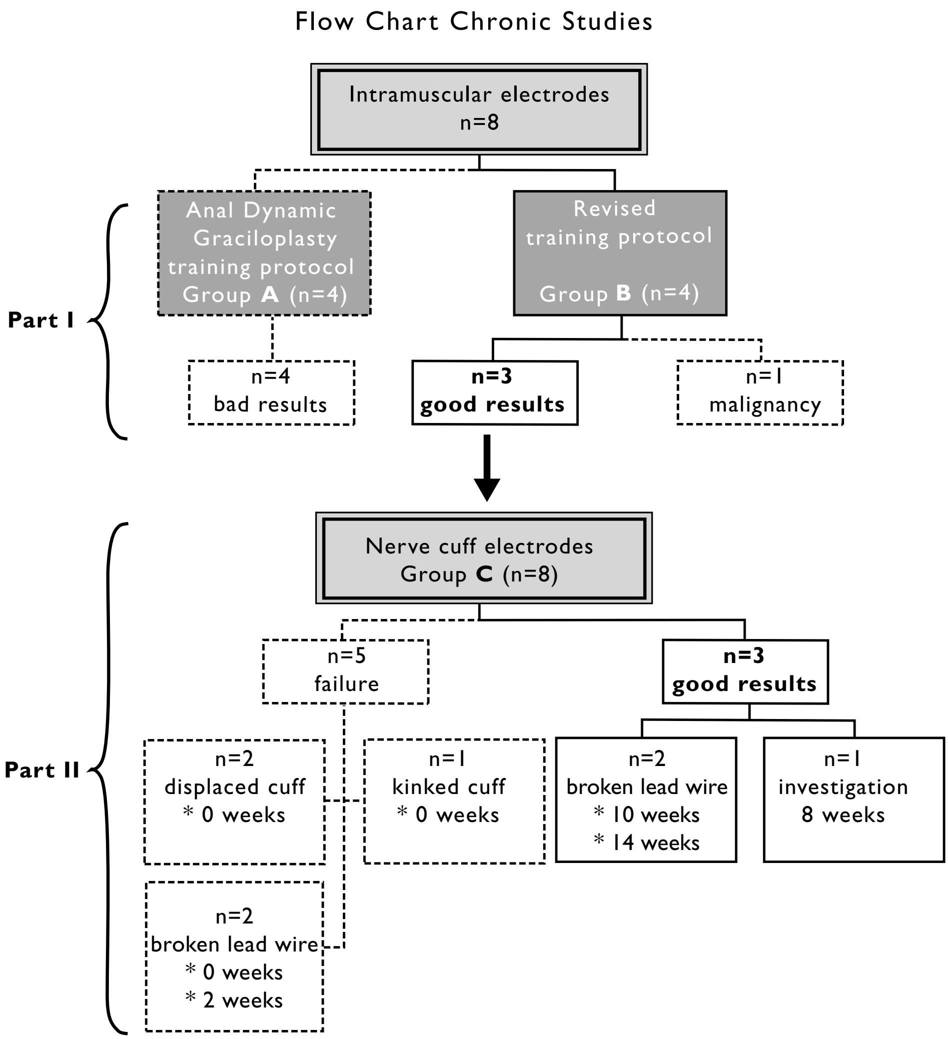
While reviewing the literature a specific training protocol for dynamic myoplasty for stomal incontinence has not been outlined. Cavina *et al*. only described the electrical stimulation parameters they used but did not describe how long they trained their muscle sphincter and which training protocol they used.[1] Merrel *et al*. did not train their different stomal sphincter designs. Instead, five months after sphincter creation they simply measured sphincter function.[2] Konsten *et al*. reproduced the same training protocol used for anal dynamic graciloplasty.[3] Since this training protocol specified by the FDA for clinical anal dynamic graciloplasty proved to work, we felt justified to use this training protocol for our rectus abdominis island flap stomal sphincter with a slight modification in the pulsewidth. Our pilot studies showed us that a pulsewidth of 270 μsec generated a better contraction (higher magnitude of force while using a lower voltage) in our rectus abdominis muscle sphincter. The purpose of the first chronic study (Part I, Fig. 1) was to define a training protocol that could generate 4 hours of stomal continence for an intraluminal bowel pressure of 60 mm Hg. The first training protocol that was tested was the same protocol used clinically in anal dynamic graciloplasty. In case it was found to be inadequate another protocol had to be designed and tested.

Materials & Methods

Animal Care

Eight Mongrel dogs weighing approximately 25 kg were used in this study. The animals were fed commercial dog diet and provided water ad libitum. This study was performed in the American Association of Laboratory Animal Care (AALAC) approved Research and Resource Center at the University of Louisville Health Science Center. Prior to the experiment, animals were housed in separate cages at a controlled temperature (22^0 C) and with a 12-hour light/dark cycle daily. They were given Enrofloxacin (5.0 mg/kg body weight, intramuscular, Baytril®, Bayer, Kansas) 30 min before and daily for 5 days after surgery. Animals were preoperatively medicated with Atropine (subcutaneously, 1 ml/10 kg) and anesthetized with intravenous Pentothal (6-12 mg/kg). Following anesthesia these animals were intubated and ventilated with a 2% Isoflurane/ 94% oxygen/ 4% nitrous oxide gas mixture (1 liter/min/kg) to maintain a surgical plain of anesthesia. Dogs were euthanized with an overdose (10 ml, intravenous) of Beuthanasia (390 mg pentobarbital sodium and 50 mg phenytoin sodium per ml) at the end of the study period.

Figure 1
In the first chronic studie (Part I) two different training protocols, Anal Dynamic Graciloplasty (Group A) vs. Revised (Group B), were tested while using intramuscular electrodes. This study revealed that the revised training protocol was far superior. Since fiber recruitment is 100% and stimulation voltage is lower when using nerve cuff electrodes we tested the revised training protocol in combination with nerve cuff electrodes in a second study (Part II).



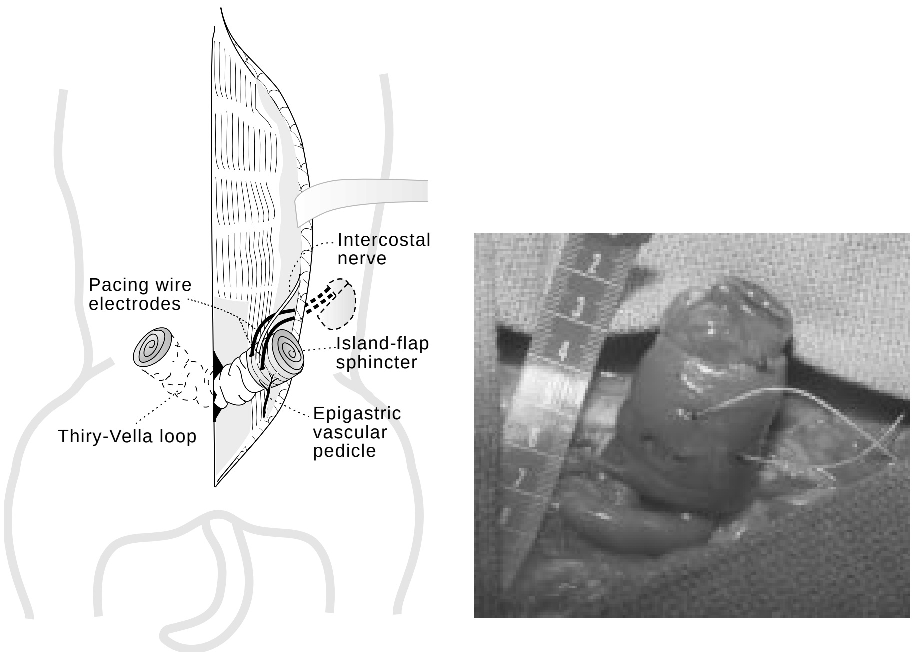
The studies were performed under Xylazine (intravenous, 2-3ml/20kg body weight) sedation.

Surgical Procedure

All surgical procedures were performed with accurate maintenance of fluid balance (Lactated Ringer's, 5% Dextrose 5 ml/h/kg), heart rate and temperature and a sterile surgical technique was used.
With the dog in the supine position, a longitudinal median abdominal incision was made to locate the left RAM. The anterior rectus fascia was incised paramedian. The rectus abdominis muscle was elevated while preserving the integrity of the posterior fascial sheath. Marking sutures were placed at the tendinous insertion and most caudal intersection, so that the muscle could be extended to its original length after detaching it from its distal insertion. The two most caudal nerves and the vascular pedicle were dissected free.
These two nerves were stimulated directly by a bipolar stimulating electrode cuff (model 4080, Medtronic, Inc., Minneapolis, MN). The part of the muscle that contracted when stimulating the most caudal nerve was tailored (4 cm width) into the final flap. The RAM was then transected 13 cm from the pubic symphysis leaving the most caudal nerve and the deep inferior epigastric artery and veins intact. Finally the RAM flap was made into an island flap by dissecting it from its insertion on the pubic symphysis.
Two intramuscular stimulation electrodes (temporary myocardial pacing lead electrodes, model 6500, single lead, Medtronic, Fourmies, France) were used for electrical stimulation of the sphincter. The leads of these electrodes were insulated with silicone tubing filled with silicone (Factor II Inc., Lakeside, AZ) in order to get a watertight seal. Before implantation these electrodes together with a pulse generator (Itrel III, Medtronic Inc., Minneapolis, MN) were immersed for at least 10 minutes in a saline antibiotic solution (Gentamycin 10ml/0.2l). Thereafter the electrodes were placed 1 cm cranial and 1 cm caudal from the nerve entry into the muscle flap after having determined the optimal electrode placement with EMG-electrodes.
The peritoneum was opened to gain access to the distal ileum. An approximately 20-cm segment of distal ileum, Thiry-Vella loop (TV-loop), was isolated. Intestinal continuity was restored by a hand sewn double layer end-to-end anastomosis using 3-0 Vicryl for the mucosa and 4-0 silk for the submucosa and serosa. Thereafter, the RAM island flap was snuggly wrapped around the distal end of the TV-loop in which a rubber stent (diameter, 1.0 cm) was placed. The ventral side of the flap became the interior surface of the sphincter. The flap was sutured with Dexon (3-0) mattress sutures to create a sphincter (Fig. 2).
A stoma of the distal end of the TV-loop including the sphincter was matured in the left lower quadrant of the abdominal wall. In the right lower quadrant a conventional stoma of the proximal end of the TV-loop through the RAM was

made (Fig. 2). A Marlex mesh (Davol Inc., Cranston, RI) was tethered over the suture line and around the stoma sphincter to reinforce the abdominal wall. The insulated stimulation electrodes were tunneled to the left flank and connected to a subcutaneously placed pulse generator as previously described. After positioning the stimulator in the subcutaneous tissue, all wounds were closed in layers.

Figure 2
Rectus abdominis canine island-flap sphincter design, Thiry-Vella loop and contralateral (control) stoma. (*Left*) Line drawing representation. The island-flap is created by wrapping the RAM around a blind loop of distal ileum while preserving the deep inferior epigastric pedicle and the most caudal intercostal nerve. (*Right*) Intraoperative photo of the dynamic RAM island-flap stomal sphincter. The sphincter's intramuscular electrodes are depicted protruding from the muscle; the vascular pedicle is preserved near het inferior border of the flap.



Training Protocols

A) Training Protocol as Used in Anal Dynamic Graciloplasty

Sphincter Training and Functional Measurements

To allow time for postoperative edema to subside, allow the muscle to become fixed in its new position and the wounds to heal, training was not begun for two weeks after surgery. Initially in 4 dogs (group A) a training protocol (protocol A) was applied as is clinically used in anal dynamic graciloplasty in our hospital (Table 1).

Sphincter function was evaluated every two weeks up to 14 weeks after surgery. During the training period of eight weeks the stimulation voltage was increased, if required, until an intraluminal stomal pressure of 80 mm Hg was measured. The intraluminal stomal sphincter pressure was measured using a microtransducer catheter (Millar®, Millar Instruments, Houston, TX), connected to a computer-based data acquisition system (CED 1401 PLUS interface and a 1902 signal amplifier, Cambridge Electronic Devices, U.K.).

The function of the sphincter was investigated by its ability to stop the flow of saline through the TV-loop while stimulated at a frequency of 25 Hz and a pulsewidth of 270 μsec. The proximal (right sided) conventional stoma of the TV-loop was intubated with a latex 22 Fr. Foley® catheter (Bard Urological Co., Covington, GA) and the balloon was inflated to achieve a watertight seal. A y-connector was attached to the Foley catheter. Through one branch of the y-connector the microtransducer catheter was entered to monitor the intraluminal TV-loop pressure. The other branch was connected to a saline infusion system (Fig. 3). The TV-loop was perfused with saline by gravity-induced flow up to a loop pressure of 60 mm Hg. The time from the commencement of stimulation to the return of flow of saline through the TV-

Table 1 Training Protocol A

Period (weeks)	0-2	2-4	4-6	6-8	>8
On time (sec)	0.1	0.2	0.4	1.0	4 hours
Off time (sec)	1.2	1.0	0.7	0.5	15 min
Frequency (Hz)	25	25	25	25	15
Duty cycle* (%)	8	17	36	67	100
Pulse width (msec)	270	270	270	270	270

* Duty cycle is the % of time over 24 hours during which the muscle is stimulated.

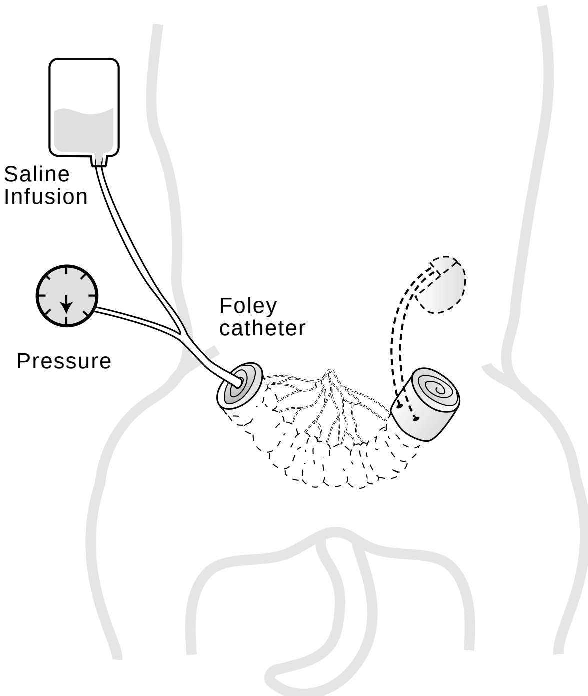
loop by visual control and by registration of a drop in pressure on the computer screen was defined as the continence time.

Results

The results after 8 weeks of training were disappointing with a maximal continence time of only 5 min and 56 sec in one dog after two weeks of electrical stimulation. In the three other dogs of group A, continence times were less at different time-points. The mean continence times ± SEM of group A at 0, 2, 4, 6, 8 and 10 weeks of electrical stimulation were 1.2 ± 0.6 min, 3.6 ± 0.9 min, 2.4 ± 0.6 min, 1.5 ± 0.3 min, 1.6 ± 0.6 min, and 1.3 ± 0.5 min, respectively. Because of these unacceptable results we reduced the

Figure 3

Experimental set-up. The contralateral stoma is intubated with a latex Foley® catheter. With gravity induced flow the stomal sphincter is able to retard flow through its lumen by generating a pressure gradient of greater than 60 mm Hg.



follow-up time from the initially 14 weeks after the operation to 12 weeks (= 10 weeks after start of stimulation).

Discussion

Although the training regimen as used in anal dynamic graciloplasty worked for that application, it did not work for our application. Failure, however, of our stomal sphincter to maintain long-term stomal continence could be attributed to other factors. Malfunctioning could be caused by the stimulation equipment (electrodes, pulse generator) used or related to the muscle sphincter itself (rectus abdominis muscle instead of gracilis muscle). The latter could be a possibility since so far training of a rectus abdominis muscle by means of electrical stimulation has not been attempted clinically. Therefore we chose first to test another stimulation protocol since if that one would work the other causes of failure could be ruled out.

B) Revised Training Protocol

Requirements Training Protocol for Stomal Continence

A stomal sphincter should be able to sustain a contraction for at least 4 hours for an intraluminal pressure of 60 mm Hg. It is not known how much the force will decrease by training a muscle. Maintaining its contraction force is possible by adjusting the stimulation voltage or current, within the limits of what the stimulated tissue can sustain. However, that can't be done unlimited because at a certain stage it will lead to muscle or nerve damage. Therefore the balance has to be found between the stimulation frequency and the stimulation voltage or current. Another aspect of stimulation that has to be considered is stimulating the muscle for a part of the day or during the whole day. Relaxation of the muscle for a part of the day is less damaging[32] and more physiologic, being comparable with what is done by athletes in endurance training. In addition it is known from stimulation experiments that a regimen in which periods of activity alternate with periods of rest generates a response, which differs in the time course of its component changes from that elicited by continuous activity. For example, after 4 weeks of low-frequency stimulation applied for only 8 hours per day, metabolic changes are well advanced, whereas changes in myosin synthesis, which would be evident after a similar period, are not detectable until a much later stage.[33]

Considering the above-mentioned requirements for a stomal sphincter, a more physiologic training protocol (Table 2) was developed through a collaborative effort with the Cleveland Functional Electrical Stimulation (FES) group.[34] This revised training protocol (protocol B) was applied in four other dogs (group B). The differences between this revised training protocol and the one clinically used in anal dynamic graciloplasty is that the 'on' and 'off' time of the sphincter is longer (seconds instead of tenths of a second), that in the beginning of the training protocol the sphincter is stimulated for a certain amount of hours during the day (12 hours (week 0-2) followed by 18 hours (week 2-4) instead of 24 hours) and that the sphincter is trained at a lower stimulation frequency (14 Hz instead of 25 Hz).

Statistical Analysis

Analysis of continence time between groups of animals in protocol A and B were assessed using analysis of variance (ANOVA) for repeated measurements followed by post-hoc-t-tests to determine differences at various time intervals. Results are represented as mean ± SEM. Significance was attributed to p values < 0.05.

Results

After several weeks of training the sphincters with the revised training protocol encouraging data were obtained. In three dogs of group B a continence time of 4 hours with an intraluminal bowel pressure of 60 mm Hg was reached after 8-10 weeks of electrical stimulation (Fig. 4). One of these three dogs was followed for a longer time. After 16 weeks of stimulation a continence time of 5 hours and 34 minutes was reached. One dog in group B had to be withdrawn from the study after 6 weeks due to the discovery of a visceral sarcoma. Although the numbers in the groups were low, a statistical significant difference in continence time between group A and B at 8 and 10 weeks after electrical stimulation was found (Fig. 4).

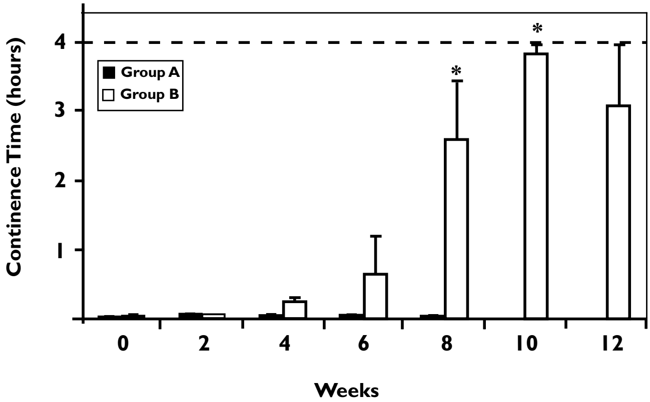
Table 2 Training Protocol B

Period (weeks)	0-2	2-4	4-6	6-8	>8
On time (sec)	10	10	10	30	4 hours
Off time (sec)	10	10	10	10	15 min
Frequency (Hz)	14	14	14	14	14
Duty cycle* (%)	12	18	24	24	-
Pulse width (msec)	270	270	270	270	270

* Duty cycle is the amount of hours during which the muscle is stimulated.

Figure 4

Comparison of rectus abdominis muscle sphincter Continence Time (hours) beween Group A and B at different time points (weeks) after start of electrical stimulation. Data are presented as mean ± SEM (*p < 0.05* vs. Group A). The dashed line represents the goal of 4 hours of stomal continence.



Discussion

After a thorough literature search we found that different training regimens were used in anal dynamic graciloplasty that reached the same endpoint and that seemed to be equally good.[10-18, 28-30] In dynamic graciloplasty no animal experimental studies in which different protocols have been tested and compared in the same study have been performed. However, in dynamic cardiomyoplasty this research has been done. Badylak *et al*. compared the effectiveness of 3 different methods of electrical stimulation for creating fatigue resistance while monitoring the pumping ability of the latissimus dorsi muscle in dogs. They found that one of the training protocols was better in terms of speed of fiber conversion and increased fatigue resistance without the loss of muscle strength[35] It must be taken into account that this was a relatively short study (6 weeks) and that data that are obtained from clinical studies in general last more then 3 months. The question rises why different training protocols seem to work equally well for anal dynamic graciloplasty and not for dynamic myoplasty for stomal continence? In none of the anal dynamic graciloplasty articles a clear reason is given why they use different protocols.

Since the stomal sphincter has to maintain a pressure that is able to withhold an intraluminal bowel pressure of 60 mm Hg it is required to adjust the stimulation voltage to a higher level during the training period. This is justified since it is known that the peakforce decreases by training a muscle. However, after the training period we still had to adjust the voltage in order to reach the goal pressure. We attribute this to the fact that prolonged stimulation results in fibrosis. This finding is found by other investigators too.[36]

Another way of stimulating the muscle is by direct nerve stimulation using nerve-based electrodes. In general a lower stimulation voltage is needed to elicit a muscle contraction and all the muscle fibers that are innervated by the nerve can be recruited. Besides, the use of a lower stimulation voltage lengthens the life span of the implanted pulse generator. Thus, direct nerve stimulation is theoretically a more efficient way of stimulation. Another advantage of direct nerve stimulation is that placement of a nerve cuff electrode is less complicated than an intramuscular electrode and consequently shortens the operation time. Therefore the next logical step was to test the effect of direct nerve stimulation in combination with the revised training protocol and evaluate if this would render even more favorable results.

Part II. Direct Nerve Stimulation

The long-term effects of using direct nerve stimulation in applications as diaphragm pacing,[37] dynamic cardiomyoplasty[38] and sacral nerve stimulation in the treatment of patients with bladder dysfunction[39] have been promising. By electrical stimulation of the phrenic nerves full-time ventilatory support was accomplished in 13 patients.[37] The average follow-up time was 26 months and nerve damage from prolonged electrical stimulation has not been a problem. In an animal model Malek *et al*. compared direct nerve (bi-polar nerve cuff electrodes) stimulation with intramuscular stimulation.[38] Following electrode implantation the latissimus dorsi muscle was chronically stimulated for two months. Their results indicated a tradeoff between the nerve cuff electrode's lower threshold, higher recruitment, and lower energy consumption at saturation, and the intramuscular electrode's greater mechanical stability and better long-term reproducibility. In a clinical study Bosch *et al*. continuously stimulated the sacral (S3) nerve as a treatment for urge incontinence.[39] Immediately after implantation they started to stimulate with 210 μsec, 10-15 Hz and 2.7 ± 0.4 volts. In the 18 patients with an average follow-up of 29 months they reported significant improvement in several urodynamics parameters. They didn't have any clinical evidence of nerve damage.

In the acute functional study (Chapter 6)[5] and previous chronic study[40] (Part I. Intramuscular stimulation) we used temporary myocardial pacing lead electrodes (model 6500, single lead, Medtronic, Fourmies, France, surface area: 8 mm^2). We used these electrodes in an attempt to overcome the problem of partial contraction of the sphincter that we saw in a pilot study in which we used the same wire electrodes used clinically in anal dynamic graciloplasty (model 4300, Medtronic, MN, adjustable length up to 4 cm). This was done by placing these temporary pacing electrodes into the muscle flap near the entry zone of the intercostal nerve. While we could recruit a greater part of the muscle flap with these small electrodes, we still were not able to recruit the entire muscle. Partial muscle flap contraction was evidenced by partial contraction of the sphincter during peroperative stimulation. Even though we were able to achieve our goal of 4 hours of stomal continence when using the intramuscular electrodes, the fact we did not achieve full muscle contraction was less favorable. As described in the last paragraph of Part I, we decided therefore to run an additional chronic functional study and switch to direct nerve stimulation. The main purpose of this chronic study (Part II. Direct nerve stimulation, Fig. 1) was to investigate the ability of nerve cuff electrodes to make the stomal sphincter fatigue-resistant in combination with training while using a lower stimulation voltage.

The final objective of this study was as in the former chronic study: 4 hours of stomal continence for an intraluminal bowel pressure of 60 mm Hg.

Materials & Methods

Surgical Procedure

In another group of 8 dogs (Group C), the RAM sphincter was created as detailed previously with the difference in type of electrode being used. After the sphincter was made a tripolar spiral nerve cuff electrode (Axon Engineering, Cleveland, OH) was carefully placed around the intercostal nerve that innervated the sphincter.

Training Protocol

To allow time for postoperative edema to subside, stimulation of the nerve was not begun for two weeks after implantation. After determining the fusion frequency (minimal frequency that results in a fused tetanic contraction), the required voltage in order to maintain continence for 60 mm Hg of bowel (TV-loop) pressure (80 mm Hg of sphincter pressure) and the continence time of an untrained stomal sphincter, the revised training protocol as previously described (Table 2) was started.

Assessment of Stoma Sphincter Function

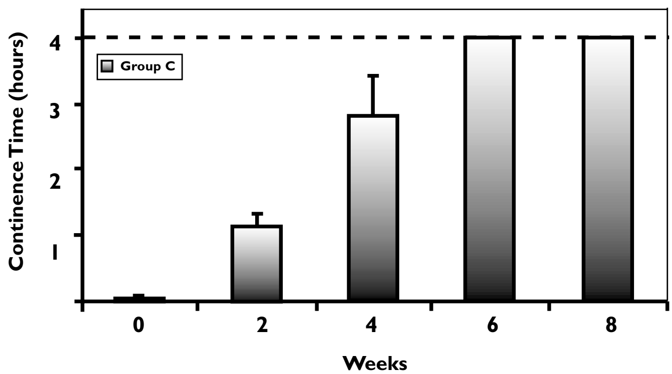
Sphincter function (continence time) was evaluated every two weeks after surgery, using the fusion frequency. This was done to prevent overstimulation of the nerve. Every two weeks the fusion frequency had to be determined. During the training period of eight weeks the stimulation voltage was increased until an intraluminal stomal pressure of 80 mm Hg or more was measured and continence was achieved for 60 mm Hg of TV-loop pressure.

Results

The sphincters of 4 of the 8 dogs tested did not contract at all at the start of stimulation (0 weeks). The reasons for failure were two nerve cuffs that were displaced from the nerve, one dead nerve because of kinking caused by the nerve cuff electrode, and one broken lead wire of the nerve cuff electrode (Fig. 1). The sphincters of three of the four remaining animals stopped working after 2, 10 and 14 weeks of electrical stimulation (Fig. 1). An autopsy study revealed that the reasons for failure were lead wire breakage of the electrode in all three animals. These results were supported by the fact that all the three nerves of these animals were found to be viable after histological assessment (H&E staining, light microscopy), although there was evidence of

nerve degeneration (vacuolar changes, granulation tissue formation, and compression of the perineural sheet).
The sphincter of the dog that was still working after 8 weeks of electrical stimulation was used for investigational purposes. In this dog we found that there was an increase in voltage as a result of increase in resistance. Impedance measurements showed that the increased resistance was a consequence of fibrosis at the level of the contact points of the nerve-cuff electrode and of fibrosis of the nerve.
Functional results could only be obtained from the sphincters of the dogs that were at least working for 8 weeks (n = 3). The mean continence times ± SEM of these three dogs at 0, 2, 4, 6 and 8 weeks of stimulation were 1.3 ± 0.4 min, 68.3 ± 10.1 min, 169.6 ± 35.4 min, 240 min, and 240 min, respectively (Fig. 5). One dog of group C reached a continence time of 4 hours (240 min) with an intraluminal bowel pressure of 60 mm Hg after 4 weeks of electrical stimulation while the remaining two reached this point after 6 weeks of electrical stimulation.

Figure 5
Rectus abdominis muscle sphincter Continance Time (hours) of Group C (n = 3) at different time points (weeks) after start of electrical stimulation. Data are presented as mean ± SEM. The dashed line represents the goal of 4 hours of stomal continance.



Discussion

The functional results of the sphincters of the three dogs that worked for eight weeks or more were promising, leaving the electrode failure aside. However it was not possible to compare the functional results of the study in which we used intramuscular stimulation (Part I.) and this study using direct nerve stimulation due to the fact there were too many differences between the two studies. Nevertheless we did observe that in the direct nerve stimulation study muscle training took a lot less time as evidenced by the fact that 4 hours of sphincter continence was achieved earlier than in the intramuscular stimulation study.

Others have demonstrated that different designs of nerve cuff electrodes resulted in varying stimulation outcomes. A comparative study of 5 different designs of nerve cuff electrodes was undertaken by Loeb *et al*. to determine their relative merits for stimulating and recording whole nerve activity over extended periods of chronic implantation on peripheral nerves in cats.[41] They found various advantages and shortcomings of the different designs. Only one of these electrodes, when properly installed, showed stable impedances and recruitment thresholds for the duration of 9 weeks. The effect of long-term implantation (307 days) of tripolar split cuff electrodes around peripheral nerves of spinal cord injured patient was investigated by Slot *et al*. They proved there was no influence on the electrophysiological properties of the nerve.[42]

From our chronic functional study using direct nerve stimulation in combination with the revised training protocol we may conclude that the RAM stomal sphincters are trained faster as opposed to intramuscular stimulation. However, technical difficulties of electrode displacement and lead fracture of the nerve cuff electrode caused poor long-term outcomes. In addition, we may conclude that the results of our two chronic studies indicate a trade-off between the nerve cuff electrode's higher recruitment, and lower voltage, and the intramuscular electrode's greater mechanical stability. It is expected that future studies using more sturdy electrode designs will give better functional outcomes in these chronic studies.

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Chapter 8

Analysis of Fiber Type Transformation and Morphologic Changes of Small Bowel in Chronic Electrically Stimulated Canine Rectus Abdominis Muscle Stomal Sphincters

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Introduction

Present day research examining the transformation of skeletal muscle through electrical stimulation uses similar concepts to those observed by Salmons *et al.*[1], who in 1981 used electrical stimulation to transform the metabolic characteristics of skeletal muscle, enabling it to perform more work over longer periods through aerobic metabolism. They showed that skeletal muscle fibers could be transformed from fast twitch (type II) fatigue-prone fibers to slow twitch (type I) fatigue-resistant fibers through training with low-frequency electrical stimulation. Applications involving the training of the graciloplasty and gluteoplasty muscular flaps with low frequency stimulation have improved upon their original design by prolonging the mechanical circumferential force generated by these skeletal muscle flaps making them more clinically useful.[2-8]

The majority of research dedicated to the functional, metabolic and histologic changes which take place in skeletal muscle has been observed in in-vivo skeletal muscle experiments in small animals.[9-11] In these models, the skeletal muscle remains at its optimal resting length allowing the actin and myosin filaments to fully interact, generating the most effective amount of force per square area, and thus maximizing the work capacity of the muscle. Additionally, the vascular supply to these skeletal muscle flaps is usually undisturbed with preservation of the muscles main vascular pedicle and its perforators. Understandably, the ability to maintain the optimal resting length of the skeletal muscle may influence the fiber type transformation process. Experimental cardiomyoplasty animal models and human cardiomyoplasty cadaver studies have shown that the complications associated with this procedure may be attributed to the inability to maintain the resting length of the latissimus dorsi muscle after it is wrapped around the heart, along with secondary ischemic muscular changes and the loss of flap innervation.[12,13] Other animal models using the graciloplasty have experienced similar problems with respect to disruption of the muscles resting length and distal muscular flap necrosis.[14-16]

One of the potential problems encountered with a functional dynamic skeletal muscle stomal sphincter is the formation of ischemic strictures within the bowel encircled by the muscle flap. Chung *et al.*,[17] have shown in a chronic dog model that ischemia of the bowel around colostomies leads to ischemic bowel strictures. Other investigators have shown that acute ischemic influences on the bowel result in morphologic changes in the bowel layers including loss of the mucosa and a decrement in the muscular layers.[18]

In-situ dynamic flap models such as our island-flap stomal sphincter offer insight in the chronic adaptive changes of the muscle fiber type transformation process caused by chronic electrical stimulation and into potential problems, which may arise from the dynamic physiologic changes, which take place in the small bowel, encircled by the sphincter. Therefore the purpose of this study was to: 1) determine if fiber type transformation from fatigue-prone (type II) muscle fibers to fatigue-resistant (type I) muscle fibers could be demonstrated in our chronic canine stomal sphincter model where the rectus abdominis muscle (RAM) was used to create a functional stomal sphincter, 2) assess if there was any relationship between the degree of muscle fiber type transformation and the continence times among the two different training protocols as used in Chapter 7, Part I. Intramuscular stimulation, 3) examine the long-term effects of the training regimens on the skeletal muscle fibers through histologic and volume-metric analysis over a flap stimulation period of 12 weeks, and 4) to examine the morphologic characteristics which could take place in the layers of the small bowel wall encircled by our dynamic sphincter.

Materials & Methods

In the eight male mongrel dogs (23-25 kg), as used in Chapter 7, Part I. Intramuscular stimulation, a RAM island-flap stomal sphincter was created, as previously described, by wrapping the left RAM flap around a blind loop of distal ileum (TV-loop), which was no longer in continuity with the rest of the small bowel. Both ends of the blind loop of distal ileum were matured as ileostomies on either side of the animal's abdominal wall. The island-flap sphincter remained on the left side of the abdomen and was stimulated with two intramuscular electrodes placed around the flap's intercostal nerve entry point. The sphincters were trained over 12 weeks using two different training protocols as previously described in Chapter 7, Part I. Intramuscular stimulation (Table 1, 2). Muscle biopsies were obtained pre- and post-training from the RAM sphincter. Fiber types within the RAM were assessed with monoclonal antibodies directed against the fast isoforms of myosin. Fiber volume-metric data were obtained after immunohistochemical analysis of the stained fibers with computer scanning software. Fiber histology was examined after staining with Eosin & Hematoxylin and Mason Trichrome stains. Every two weeks sphincter function (continence time) was assessed by its ability to stop the flow of saline (duration of time (minutes)) at an intraluminal TV-loop pressure of 60 mm Hg. At the completion of the study, the right control stoma, the left RAM sphincter-stoma complex and a mid portion of the small bowel wall within the TV-loop were harvested for histologic assessment.

Quantification of Fiber Types and Histology of Skeletal Muscle

Preoperative biopsies were obtained from the untrained RAM for histology and histochemical analysis. The study was terminated at 14 weeks, which was felt to be an adequate time frame to permit fiber type transformation to take place. Post-mortem biopsy samples were collected from the skeletal muscle sphincter 1 cm from the electrode entry point. The untrained and trained RAM biopsy samples for histochemical analysis were frozen in liquid nitrogen and stored at -70° C. At the time of processing, samples were cut in 10 μm sections in a cryostat and incubated with a monoclonal antibody MY-32 (Sigma Chemical Co., St Louis, MO) against the mouse major histocompatibility complex type II. Specimen cross sections were photographed under an Olympus CKZ inverted microscope (Jacob Instrument Corp., Shawnee Mission, KS) at high magnification (100x). A clear plastic grid (5 x 15) cm was placed over the microphotograph prints and the fiber types were counted by two independent examiners. Fibers which fell on the outer grid marks were included as part of the specimen. At least 450 fibers were counted per specimen.

Specimens for histological analysis were fixed in 4% phosphate buffered paraformaldehyde (pH 7.4), paraffin embedded cross sections of 6 μm thickness were cut on a microtome in a cryostat. Specimens were then placed on cover slips and stained with Hematoxylin & Eosin and Mason Trichrome stains.

Volume-metric measurements were obtained after scanning the histochemical fiber prints stained with the monoclonal antibody MY-32 against the fast isoform of myosin into a computer. Sigma Scan Pro Software® Version 5.0 (SPSS Science Co., Chicago, IL) was used to calculate the area within individual muscle fibers.

Histology/Morphometric Measurements of Small Bowel

The island-flap stomal sphincter complex, mid-portion of the small bowel within the Thiry-Vella loop and contralateral (control) stoma were obtained after the training protocol was completed at the time of sacrifice. The tissue specimens were fixed in formalin and paraffin embedded cross sections of 6 μm thickness were cut on a microtome in a cryostat then placed on a glass slide, cover-slipped and stained with Hematoxylin & Eosin and Trichrome stains. Histologic specimens were examined under the supervision of a Board certified pathologist (DA) to determine if architectural changes were present in the specimens. An ocular micrometer was used to quantitate the thickness of the intestinal wall components: mucosa, muscularis mucosa, submucosa, circular and longitudinal muscularis propria.

Statistical Analysis

Study design was implemented with a pair of groups. A paired t test was used to compare the fiber-type transformation, fiber volume and bowel layer thickness morphology between untrained and trained skeletal muscle. Data are represented as mean ± SEM. Significance was attributed to P values < 0.05.

Results

The percentage of type I and II muscle fiber types was determined immunohistochemically (Fig. 1). After continuous training over 12 weeks using training protocol A, the percentage of type I muscle fibers increased from a mean of 30.8 % ± 1.8 to 73.8 % ± 10.4, while the type II fibers decreased from 69.3 % ± 1.8 to 26.3 % ± 10.4. Training protocol B resulted in an increase of type I muscle fiber transformation from a mean of 39.3 % ± 2.3 to 77.3 % ± 6.8 with a concomitant decrement of type II muscle fibers from 60.8 % ± 2.3 to 22.8 % ± 6.8 (Table 1). Fiber diameters and volume were reduced after the skeletal muscle was trained. Continuous stimulation using training protocol A and B resulted in a decrement of 32% of the total

Table 1 Percent Fiber Type Transformation in Untrained and Trained RAM Island-Flap Stomal Sphincters

	Protocol A		Protocol B	
	Untrained RAM (n=4)	Trained RAM (n=4)	Untrained RAM (n=4)	Trained RAM (n=4)
% Type I Fibers	30.8 ± 1.8*	73.8 ± 10.4*	39.3 ± 2.3*	77.3 ± 6.8*
% Type II Fibers	69.3 ± 1.8*	7.3 ± 10.4*	60.8 ± 2.3*	22.8 ± 6.8*

* p < 0.05 (untrained vs. trained); Data are expressed as percentage of specimen fiber types ± SEM.

Table 2 Volume-metric Measurements of Untrained and Trained RAM Island-Flap Stomal Sphincters

	Untrained RAM	Trained RAM
Fiber Volume *(Pixel units)*	758.6 ± 17.6*	519.1 ± 20.6*

* p < 0.01 (untrained vs. trained); Data are presented as mean ± SEM.

fiber area as shown in Table 2. There was a statistically significant difference between the fiber volumes in pixel units between the untrained and trained muscle fibers ($P < .001$).
The fiber morphology between the untrained and trained skeletal muscle is depicted in Figure 2. In the untrained skeletal muscle specimens, the fibers are polygonal in shape with very little connective tissue or fat in between the fibers. After training, the fiber size (diameter) decreased, the general appearance of the fibers varied little without structural changes and there was

Figure 1

Immunohistochemistry of untrained and trained skeletal muscle fibers stained with an antibody against the fast forms of myosin. **A)** Untrained RAM fibers, fibers are predominately of the fast fiber type. **B)** Trained RAM fibers obtained from the island-flap sphincter after 3 months of training, the majority of fibers are of the slow fiber type.

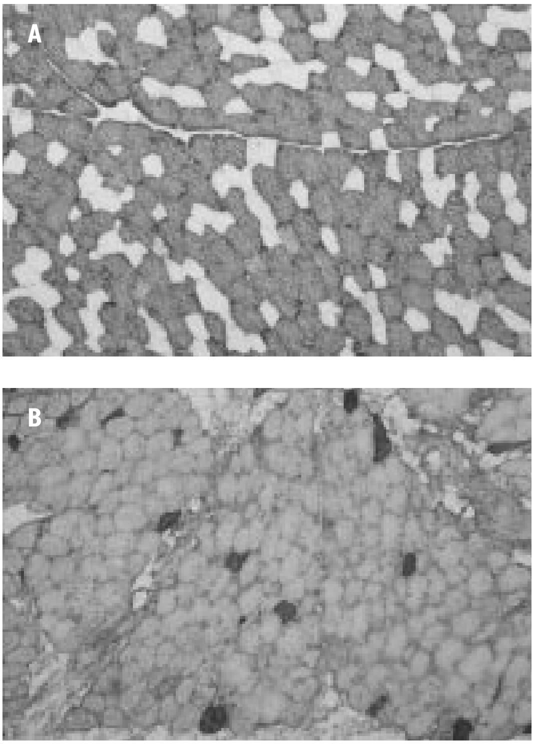


Figure 2
Histology of skeletal muscle fibers (magnification 100x, Bar 0.05 mm). **A)** H&E stain of untrained rectus abdominis skeletal muscle, note large fiber diameter with peripheral cell body nuclei. **B)** H&E stain of rectus abdominis skeletal muscle sphincter biopsy after 3 months of training, fiber diameter is smaller than untrained muscle, nuclei appear crowded due to smaller fiber diameter. **C)** Trichrome stain of trained rectus abdominis muscle sphincter wrap around small bowel, note minimal fibro-fatty deposition between atrophied skeletal muscle fibers.

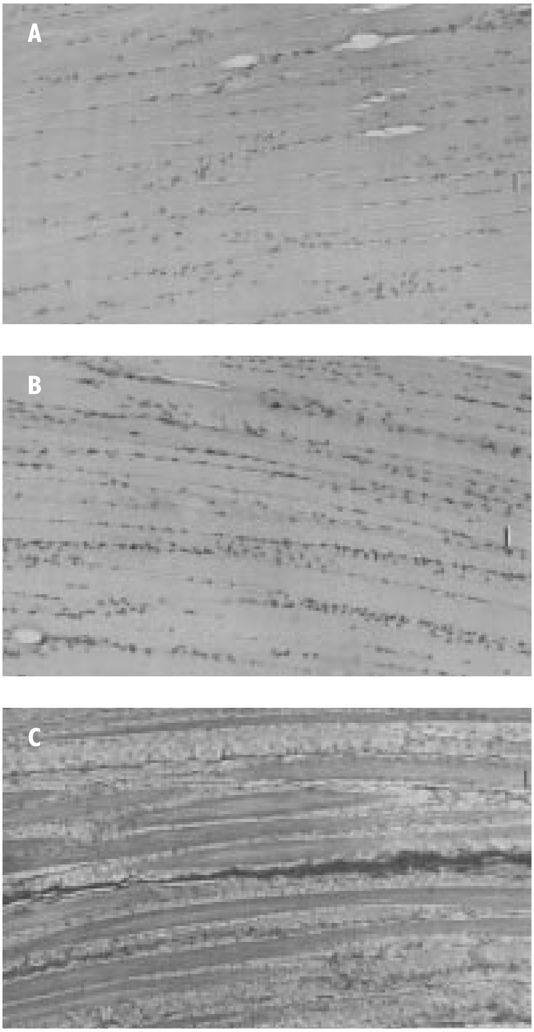
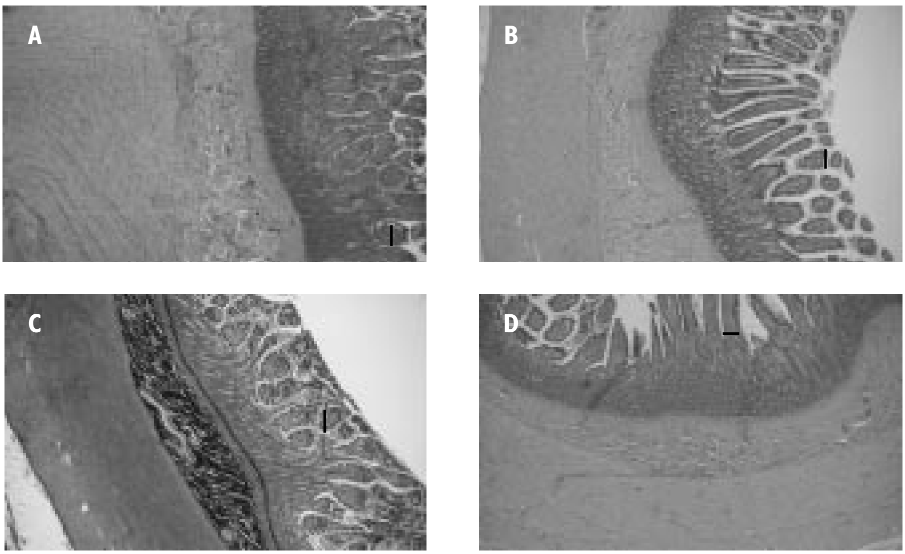


Table 3 Morphometric Measurements of Bowel Layers

	Stoma	Stomal Sphincter
Mucosa	1.04 ± .09	1.16 ± .14
Muscularis Mucosa	.08 ± .01	.08 ± .01
Submucosa	.43 ± .08	.30 ± .06
Circular Muscle	.63 ± .09	.57 ± .07
Longitudinal Muscle	.25 ± .03	.25 ± .04

* Data are expressed as mean thickness of bowel layers (mm) ± SEM, *n* = 7.

Figure 3
Small bowel canine biopsies, (magnification x100, Bar 0.10 mm).
A) H&E stain of small bowel biopsy from mid-portion of Thiry-Vella loop with undisturbed bowel layers. **B)** H&E stain of small bowel biopsy encircled by dynamic sphincter with healthy mucosa and unimpressive changes in the remaining bowel layers. **C)** Trichrome stain of small bowel encircled by dynamic sphincter without evidence of gross fibrosis of the small bowel layers. **D)** H&E stain of contra-lateral stoma small bowel layers.



a minor increase in the endomysial tissue between the fibers. Microscopically there was no evidence of damage to the fibers or degenerative changes.

The continence time for the skeletal muscle sphincters measured in minutes (mean ± SEM) for training protocol A averaged 1.3 ± 0.5 minutes at 10 weeks in contrast to the revised training protocol B which averaged 229 ± 10 minutes over the same time period, ($P < 0.05$). In Figure 4, Chapter 7, a comparison of RAM sphincter continence time (hours) between Group A and Group B at different time-points (weeks) after start of electrical stimulation are depicted. Data are presented as mean ± SEM. (* $p < 0.05$ vs. Group A)

Morphometric analysis of the individual bowel layers within the Thiry-Vella loop and the sphincter were similar in thickness ($p > 0.05$) when measured with a micrometer (Table 3). Histologically, the layers of the bowel which were encircled by our dynamic stomal sphincter including the mucosa, muscularis mucosa, submucosa, and muscularis propria were without architectural changes including neither ulcerations nor necrosis. Trichrome stains did not reveal any evidence of fibrosis within the bowel layers (Fig. 3).

Discussion

The dynamic RAM island-flap sphincter designed in this experiment for stomal continence relies upon the fatigue-resistant properties associated with type I skeletal muscle fibers. These fibers have been shown in previous experiments to contain a greater percentage of mitochondria,[19] rely more heavily on oxidative metabolism,[11] contain a higher capillary density,[20] and have reduced glycolytic activity.[11] The above skeletal muscle properties are advantageous with respect to promoting fatigue-resistance when increased demands are placed on skeletal muscle. Our previous experimental work with our dynamic island-flap stomal sphincter created from the RAM showed that the RAM in the canine consists predominately of fatigue-prone (type II) fibers (approximately 65%) with the remaining fibers of the fatigue-resistant type (type I) in origin.[21]

After studying many other skeletal muscle dynamic flap designs we felt that the maximal work potential of our flap could be achieved by: 1. Maintaining the innervation of the flap enabling it to be adequately trained. Previous experiments using a free gracilis muscle flap to achieve stomal continence in a canine model were largely unsuccessful due to flap denervation atrophy which lead to poor flap performance.[22] This concept is also appreciated by other investigators who have attributed the variable results of the cardiomyoplasty to loss of the flap's innervation distally which impaired the work performance of such flaps.[23] 2. The maintenance of adequate flap perfusion by preservation of the arterial supply and venous drainage to all regions of the flap. Prior research on cardiomyoplasty and graciloplasty have shown that poor perfusion to the distal part of the flap has a detrimental effect on flap performance and fiber phenotypic changes.[23,24] 3. Achieving adequate stretch of the flap's muscular fibers to attain physiologic overlap of the actin and myosin filaments thus optimizing the skeletal muscle's contractile characteristics. Williams and associates have shown that muscle stretched to its optimal resting length along with physiologic stimulation results in the least amount of connective tissue deposition within the skeletal muscle and leads to improved muscular work capacity and performance.[25,26]

More recently, investigators have attempted to preserve the relative portion of type IIA intermediate muscle fibers (a subset of type II fibers) which have superior forceful contractile qualities when compared to type I fibers along with acceptable fatigue-resistance properties.[9,27] Although there was no appreciable difference between the amount of type I fibers transformed using the two different training regimens, the continence times were dramatically different between the two groups when the sphincter was stimulated to contract against an intraluminal bowel pressure of 60 mm Hg. Training protocol A with a mean continence time of 1.3 ± 0.5 minutes was inferior to protocol B's mean continence time of 229 ± 10 minutes after 10 weeks of training ($P < 0.05$). One possible explanation for the difference between the two protocol's continence times is that the relative proportion of type IIB and IIA fibers might have been different between the two training protocols with a higher percentage of type IIA fibers in the animals trained with protocol B. Our monoclonal antibody stain was unable to differentiate between these two types of fibers. Type IIA fibers which exhibit superior fatigue-resistance and adequate contractile properties when compared to type IIB fibers have been shown to be a stable inducible phenotype. The conversion and maintenance of type IIA fibers is highly dependent on the training protocol used.[9,27] Lower frequency stimulation was found to play a significant role in fiber type conversion and maintenance of type IIA fibers in a study by Sutherland et al.[27] In our experimental training protocol B we used an initial lower frequency of 14 Hz during the early stimulation period over 8 weeks when compared to training protocol A with its 25 Hz frequency. This may have influenced the relative proportion of type IIA fibers between the two groups. An additional explanation may be attributed to the relative amount of change and stability of the enzymatic cellular processes present in the muscular fibers oxidative metabolism. Kwong and associates have shown that the inducible enzymes necessary for aerobic metabolism are variable and may proceed the fiber transformation process in skeletal muscle fibers.[28] The ability of skeletal muscle to maintain a contraction in an efficient manner after transformation of the skeletal muscle's fiber type is complete, may depend on the relative proportion of key enzymes in the citric acid cycle, fatty acid oxidation pathway and respiratory chain.[11] Perhaps in our study, both stimulation

protocols were able to transform the phenotypic characteristics of the muscle through changes in the myosin filaments, while protocol B was superior at producing and maintaining a greater proportion of those enzymes needed to generate a more efficient contraction.
The volume-metric data suggests that training resulted in a decrement of muscle fiber size by 32%. The reduction in fiber size may be beneficial through the reduction in the diffusion distance between the capillaries and the cells mitochondria, thus potentially increasing the oxidative metabolic capacity of the muscle.[29] The training protocols used in this experiment were adequate at transforming the fibers from type II to type I fibers, but perhaps unable to maintain the relative percentage of the intermediate type IIA fibers which are generally larger in diameter when compared to type I fibers. Duan *et al.*,[9] have shown that fiber diameter may be influenced by the duration of stimulation and rest used in the training protocols. Intermittent stimulation with more frequent rest may result in fibers more characteristic of type IIA fibers which tend to retain their size and more closely resemble the fast-twitch muscle fibers in diameter, while preserving the oxidative fatigue-resistant properties of type I skeletal muscle.
Histologic analysis of the sphincters also correlates with the volume-metric data results both of which showed a decrease in the fiber diameter resulting in less distance between the fiber's nuclei. The Mason Trichrome stain did not show significant accumulation of fibrotic tissue between the skeletal muscle fibers. Atrophy was apparent without obvious damage to the skeletal muscle fibers. The lack of significant fibrosis between the skeletal muscle fibers may be attributed to the degree of stretch found within the island-flap's wrap and the generous blood supply provided by the deep inferior epigastric artery. Oakley *et al.*,[30] demonstrated in a latissimus dorsi muscle goat model that loss of the flap's resting tension alone seemed to contribute substantially to the degree of muscular flap damage and connective tissue infiltration. When the flap was subjected to a loss of its resting length along with partial devascularization and constant training, the added effect of all three parameters resulted in a higher degree of muscular flap damage with fat and connective tissue infiltration. Similar architectural characteristics have been observed in the latissimus dorsi muscles of cardiomyoplasty patients on post mortem exam with replacement of muscle fibers by fibrofatty tissue.[13] Our model allows the skeletal muscle fibers to remain stretched around the bowel circumferentially. This is unlike the graciloplasty in which the muscle is wrapped around the bowel in a twisted configuration, which may influence the contractile characteristic of the wrap and the degree of fiber stretch and ultimately the deposition of collagen between the fibers.

With prolonged external compression of an intestinal stoma it is reasonable to assume that the sphincter has the potential to cause ischemic trauma to the small bowel that it encircles. Several investigators have noted the influence of an ischemic insult on bowel. Cohen *et al.*,[31] has shown in a canine model early changes in the bowel layers including hemorrhage into the mucosa, congestion of the mucosa and submucosa with subsequent mucosal sloughing with balloon occlusion of the superior mesenteric artery over 3 hours. Chung and colleagues[17] have investigated and determined in a canine model that bowel ischemia is proportional to the length of bowel devascularized and this ischemic insult influences the anastomotic diameter of colostomies. In their model the ischemic event lead to changes in the architecture of the bowel including fibrosis of the muscularis and submucosal layers. In our stomal sphincter model the terminal ileal vascular arcade is ligated to accommodate the skeletal muscle wrap thus the bowel within our sphincter must be supplied by intramural collateral flow. Armstrong and associates[32] have shown in a canine model that ligating the vascular arcade over 4 cm of bowel (as in our model) results in a decrement of blood flow from 32.4 ml/100 gm/min to 15.6 ml/100 gm/min or intramural blood flow falls with the square root of the distance from the inflow source. We suspect that flow to the bowel in our model may be lessened initially. This influenced our decision to begin the stimulation protocol 2 weeks after the creation of our sphincter. However, with chronic flap stimulation we felt that our sphincter could potentially have an adverse effect on the bowel from prolonged compressive flap ischemia.
Morphometric and histologic data of the bowel layers did not identify any gross differences between the control bowel and bowel encircled in the stomal sphincters. The thickness of the bowel layers was similar between the two groups. The mucosal layer, which is the most susceptible to ischemic changes,[31] remained healthy in the sphincter group. Bonakdarpour and associates[33] have shown in a semi-chronic canine model that when the bowel was subject to an ischemic insult afflicting a 65-105 cm segment of bowel over a 2-3 week period varying degrees of mucosal ulceration and necrosis occurs. In our sphincter model the convoluted bowel architecture of the mucosa was preserved with the normal compliment of crypts and secretory (goblet) cells. There was no evidence of mucosal necrosis or ulceration. The muscularis mucosa was unchanged between the control and sphincter groups and there was no evidence of muscular atrophy within this layer. The submucosal layer which is naturally composed of connective tissue and has been shown in numerous studies to become fibrotic with chronic ischemic insults was also histologically unchanged between the two animal groups in our study.[17,33] The largest smooth muscle layer of the bowel, the muscularis propria includes the circular and longitudinal muscles. Previous studies in dogs have shown that the cross sectional surface area and thickness of the circular and longitudinal

muscles of the small bowel is parabolic with the greatest thickness of these layers occurring in the proximal and distal segments of the bowel.[34] We also were unable to detect any significant differences in the thickness within these layers between the control and sphincter groups. These layers may be more resistant to ischemic insults because of the relative thickness of these tissue layers and their close proximity to the mesenteric collateral blood flow. Also, the parallel orientation of the island-flap's muscular sphincter probably exerts a more even distribution of pressure over the bowel lessening the risk of ischemic damage to the bowel wall. This is unlike the gamma wrap of the conventional graciloplasty procedure for fecal incontinence which has been found to produce colonic fistulas from the force exerted by the gracilis tendon along the colonic wall and bowel ischemia.[35,36]

Conclusion

In conclusion, it is possible to achieve fiber type transformation from fatigue-prone (type II) muscle fibers to fatigue-resistant (type I) muscle fibers in this unique canine island-flap model using the RAM to construct a stomal sphincter. To achieve a successful functional sphincter it is critical to maintain the vascular perfusion and neuronal innervation of the flap, the loss of which may contribute to muscular atrophy and poor flap performance. The training protocol used to convert the skeletal muscle sphincter to more favorable fatigue-resistant properties may profoundly influence the contractile characteristics of the flap while minimally affecting the degree of fiber type transformation. Fiber atrophy, which was seen in this study, is common when skeletal muscle is transformed from type II to type I fibers. Histologically minimal fibro-fatty deposition between the muscle fibers was seen.

In addition, our dynamic island-flap sphincter constructed from the RAM and trained over a 3-month period does not result in ischemic damage to the bowel wall that it encircles. There were no significant architectural differences in the layers of the bowel wall encircled by the stomal sphincter, which suggests that the collateral intramural perfusion was sufficient to maintain the integrity of all the bowel layers.

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Chapter 9

Summary & Epilogue

Summary

The key elements to creating a continent fecal stoma are voluntary control and a dynamic muscle sphincter that is resistant to fatigue and that is able to generate contraction pressures great enough to prevent the inadvertent leakage of stool. Additionally, the design of the sphincter muscle must be relatively straightforward, require no special devices, and preferably would not involve microsurgical techniques. A few attempts at creating a continent stomal sphincter using dynamic myoplasty have been reported but to date this remains an illusive goal. Denervation atrophy and early muscle fatigue have plagued all reported attempts to make a continent stoma a reality. It was our goal to see if we could make an abdominal stoma continent using dynamic myoplasty. A multiphase project was undertaken that was designed to solve the critical issues of denervation atrophy and early muscle fatigue.

Before starting with the description of the experimental studies, background information was given on the three research fields relating to this thesis, to better understand and approach the problems encountered in the experimental studies. I. Intestinal stomas and their associated problems, with focus on stomal incontinence and its treatment options (Chapter 2). II. Dynamic myoplasty, its clinical applications and the former attempts in applying dynamic myoplasty to the problem of stomal incontinence (Chapter 3). III. Functional electrical stimulation (FES), including the basic knowledge of physiologic and electrical muscle stimulation and with focus on the problem of muscle fatigue and methods of approaching it (Chapter 4).

To solve the problem of denervation atrophy an anatomic feasibility study was undertaken in fresh human cadavers (Chapter 5). This first study was designed to determine which local muscle could serve as an innervated and well-perfused muscle flap. The rectus abdominis muscle (RAM) was found to be ideal. This muscle has a dominant vascular pedicle in the deep inferior epigastric vessels, its elevation can be performed without dividing the intercostal nerves, and the sphincter can be created without the need for a microsurgical anastomosis. Additionally, the muscle location makes creating a sphincter in the lower abdominal quadrants relatively straightforward. Of the two RAM stoma sphincter designs the island flap was found to be superior to the peninsula flap design.

The next phase of the study was to identify an animal suitable for the development of a model for stoma sphincter design. After reviewing several potential animal models and doing several pilot studies, the dog was found to be appropriate. In an acute canine study, it was determined that the RAM island flap sphincter design used in human cadavers could be applied to the dog (Chapter 6). In this study an end ileostomy was created around which the muscle flap was wrapped. Using an electrical stimulation device, the muscle

was able to be stimulated and to generate peak pressures well above 60 mm Hg (pressure needed to maintain fecal continence in humans). Muscle fatigue was found to be directly proportional to the stimulation frequency and continence was provided at all the tested bowel pressures (30, 65 and 100 mm Hg).

These promising acute functional study results paved the way for the initiation of chronic trials incorporating survival operations in dogs. In the first chronic study (Chapter 7, Part I. Intramuscular stimulation), it was revealed that the sphincter design was fatigue-resistant for 4 hours up to three months post-op with one of the two training protocols tested. Although preliminary, a continence time of up to five and one half-hours has been achieved with a pressure in excess of 60 mm Hg in one animal.

In addition, a second chronic study (Chapter 7, Part II. Direct nerve stimulation) was undertaken to test whether direct nerve stimulation, as opposed to intramuscular stimulation, would render more favorable results. Although the numbers were too small there was a tendency that the sphincter could be trained faster with direct nerve stimulation. However, electrode failure (displacement and lead fracture) led to a non-functioning sphincter in 63% of the cases when using direct nerve stimulation.

Analysis of fibertype transformation, as described in Chapter 8, revealed that a significant fiber type conversion was achieved in both training protocols (as used in Chapter 7, Part I. Intramuscular stimulation), with a greater than 50% conversion from fatigue-prone (type II) muscle fibers to fatigue-resistant (type I) muscle fibers without evidence of muscle fiber damage or significant fibrosis. The bowel wall within the functional dynamic stomal sphincter did not exhibit any significant architectural changes related to ischemic fibrosis or mucosal damage. This suggests that our anterior abdominal wall dynamic island-flap stomal sphincter, which generates a contractile force over the bowel wall capable of producing enough stomal pressure to achieve fecal continence, is not intrinsically harmful to the bowel that it encircles.

Epilogue

Fecal and urinary stomal continence remains an illusive goal for the hundreds of thousands of individuals who have to live with the loss of bowel and urinary continuity. The exciting results reported here bring us closer to achieving what has been an objective, stomal continence. By combining a local muscle flap design and dynamic myoplasty technology, impressive continence times have been achieved in our chronic dog model. What remains to be determined at this time is the durability of the design with focus on the stimulation electrodes, the ability of the design to function around a functioning end ostomy, what the potential complication rates may be, and who the best candidates are for this technique. These issues are currently being addressed with ongoing trials in our laboratory. By addressing the aforementioned issues, clinical trials in patients may be forthcoming in the near future.

Ultimately the introduction of a physiologic feedback loop would most closely simulate the anal sphincter. With a feedback system (using bowel pressure sensors to indicate the need to increase muscle tone), the sphincter would adjust the magnitude of its contraction according to the amount of backpressure exerted on the stoma. The sphincter would therefore only contract with a force sufficient to maintain continence at any given moment based on the physiologic demands placed on the stoma sphincter. With a feedback system, muscle work would be reduced and the rate of fatigue minimized. Currently there are commercial products for electrical stimulation with feedback capabilities as well as pressure sensors available.

Other options to prolong the durability are to use pulse generators in which one can change the stimulus waveforms to ones that are more favorable to use in terms of muscle fatigue and muscle and/or nerve damage. Taking into account that by training the muscle sphincter the time to relaxation increases, one could consider to introduce a resting period of 0.5 seconds every ten seconds of stimulation. The advantage of this is that the generated force will be still sufficient for maintaining continence but at the same time provides the muscle a period of relaxation. Simultaneously the charge built up at the level of the contact points of the electrodes can be reversed. Both proposals could not be investigated in our studies because of limitations of the pulse generator we used.

Samenvatting

De belangrijkste factoren in het creëren van een continent fecaal stoma zijn vrijwillige beheersing en een dynamische sluitspier die onvermoeibaar is en in staat is drukken te leveren die voldoende zijn om het lekken van ontlasting te voorkomen. Tevens moet het ontwerp van de sluitspier relatief eenvoudig zijn, geen extra attributen vereisen en er moeten bij voorkeur geen microchirurgische technieken voor nodig zijn. In het verleden zijn er een paar pogingen gedaan een continent stoma te creëren door middel van de dynamische myoplastiek, echter tot op heden heeft dit niet geleid tot klinische toepassingen. Spier denervatie atrofie en spiervermoeibaarheid worden beschreven als de oorzaken voor het falen. Het was ons doel om een continent stoma te ontwikkelen door gebruik te maken van de dynamische myoplastiek. Een onderzoeksproject met een reeks aan experimenten werd opgesteld om de problemen van denervatie atrofie en spiervermoeibaarheid te bestuderen en zo mogelijk op te lossen.

In het begin van dit proefschrift worden allereerst de studies beschreven die achtergrond informatie bevatten over de drie lijnen van onderzoek die in dit proefschrift aan de orde komen, om de problemen die in de experimentele studies naar voren kwamen, beter te begrijpen en te benaderen. I. Abdominale stomas en de daarmee gepaard gaande problemen waarbij dieper wordt ingegaan op stoma incontinentie en de behandelingsmogelijkheden ervan (Hoofdstuk 2). II. Dynamische myoplastiek, de klinische applicaties ervan en de pogingen die er gedaan zijn om de dynamische myoplastiek toe te passen op het probleem van de stoma incontinentie (Hoofdstuk 3). III. Functionele electrische stimulatie (FES) en tevens de basiskennis van fysiologische en electrische spierstimulatie, waarbij dieper ingegaan wordt op het probleem van de spiervermoeibaarheid en de manieren om dit te verminderen (Hoofdstuk 4).

Om het probleem van de spierdenervatie atrofie op te lossen werd er een anatomische studie verricht in menselijke cadavers (Hoofdstuk 5). Deze eerste studie werd gedaan om te onderzoeken welke plaatselijke geïnnerveerde en gevasculariseerde spierlap het meest geschikt was voor stoma sfincter constructie. De musculus rectus abdominis spier werd het meest optimaal bevonden. Deze spier heeft een dominante vaatsteel (arteria epigastrica inferior), de mobilisatie ervan kan worden gedaan zonder de intercostaal zenuwen te doorsnijden, en de sfincter kan zonder microchirurgische technieken gemaakt worden. Tevens maakt de localisatie van de spier het maken van de sfincter in de onderste buik kwadranten eenvoudiger. Van de twee onderzochte sfincter ontwerpen werd de eiland lap superieur bevonden boven de gesteelde lap.

De volgende fase van de studie was het identificeren van een diermodel voor het ontwikkelen van het stoma sfincter ontwerp. Na het onderzoeken van een aantal diermodellen en het doen van pilot studies werd de hond als diermodel het meest geschikt bevonden. In een acute studie bij honden werd getoond dat het musculus rectus abdominis spier eiland lap ontwerp dat in menselijke cadavers ontwikkeld was ook toegepast kon worden bij de hond (Hoofdstuk 6). In deze studie werd een eindstandig ileostoma gemaakt waaromheen de spierlap werd gewikkeld. Door gebruik te maken van een pacemaker was deze spierlap in staat maximum drukken te genereren ver boven 60 mm Hg (drukken die nodig zijn om continent voor ontlasting te zijn bij de mens). De spiervermoeibaarheid was direct proportioneel aan de stimulatie frequentie en leidde tot continentie bij alle geteste darmdrukken (30, 65 en 100 mm Hg).
De veelbelovende resultaten van de acute functionele studie baanden de weg vrij voor de start van chronische trials met overlevingsstudies in honden. In de eerste chronische studie (Hoofdstuk 7, Deel I. Intramusculaire stimulatie) werd bewezen dat de door ons ontwikkelde sfincter gedurende vier uur onvermoeibaar was bij een follow-up periode van drie maanden met 1 van de 2 geteste trainingsprotocollen. Hoewel het een voorlopig resultaat betreft, werd er in 1 dier een continentietijd van vijf-en-een-half uur gemeten bij een darmdruk van 60 mm Hg.
Aanvullend werd er een tweede chronische studie verricht (Hoofdstuk 7, Deel II. Directe zenuwstimulatie) om te testen of directe zenuwstimulatie, in tegenstelling tot intramusculaire stimulatie, betere resultaten zou geven. Hoewel er sprake was van kleine aantallen, werd er een trend gezien dat de sfincters sneller getraind konden worden. Echter, het falen van de electrode (verplaatsing en breuk) leiden tot een niet-functionerende sfincter in 63% van de gevallen waarbij gebruik werd gemaakt van de directe zenuwstimulatie.
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Samenvatting

De belangrijkste factoren in het creëren van een continent fecaal stoma zijn vrijwillige beheersing en een dynamische sluitspier die onvermoeibaar is en in staat is drukken te leveren die voldoende zijn om het lekken van ontlasting te voorkomen. Tevens moet het ontwerp van de sluitspier relatief eenvoudig zijn, geen extra attributen vereisen en er moeten bij voorkeur geen microchirurgische technieken voor nodig zijn. In het verleden zijn er een paar pogingen gedaan een continent stoma te creëren door middel van de dynamische myoplastiek, echter tot op heden heeft dit niet geleid tot klinische toepassingen. Spier denervatie atrofie en spiervermoeibaarheid worden beschreven als de oorzaken voor het falen. Het was ons doel om een continent stoma te ontwikkelen door gebruik te maken van de dynamische myoplastiek. Een onderzoeksproject met een reeks aan experimenten werd opgesteld om de problemen van denervatie atrofie en spiervermoeibaarheid te bestuderen en zo mogelijk op te lossen.

In het begin van dit proefschrift worden allereerst de studies beschreven die achtergrond informatie bevatten over de drie lijnen van onderzoek die in dit proefschrift aan de orde komen, om de problemen die in de experimentele studies naar voren kwamen, beter te begrijpen en te benaderen. I. Abdominale stomas en de daarmee gepaard gaande problemen waarbij dieper wordt ingegaan op stoma incontinentie en de behandelingsmogelijkheden ervan (Hoofdstuk 2). II. Dynamische myoplastiek, de klinische applicaties ervan en de pogingen die er gedaan zijn om de dynamische myoplastiek toe te passen op het probleem van de stoma incontinentie (Hoofdstuk 3). III. Functionele electrische stimulatie (FES) en tevens de basiskennis van fysiologische en electrische spierstimulatie, waarbij dieper ingegaan wordt op het probleem van de spiervermoeibaarheid en de manieren om dit te verminderen (Hoofdstuk 4).

Om het probleem van de spierdenervatie atrofie op te lossen werd er een anatomische studie verricht in menselijke cadavers (Hoofdstuk 5). Deze eerste studie werd gedaan om te onderzoeken welke plaatselijke geïnnerveerde en gevasculariseerde spierlap het meest geschikt was voor stoma sfincter constructie. De musculus rectus abdominis spier werd het meest optimaal bevonden. Deze spier heeft een dominante vaatsteel (arteria epigastrica inferior), de mobilisatie ervan kan worden gedaan zonder de intercostaal zenuwen te doorsnijden, en de sfincter kan zonder microchirurgische technieken gemaakt worden. Tevens maakt de localisatie van de spier het maken van de sfincter in de onderste buik kwadranten eenvoudiger. Van de twee onderzochte sfincter ontwerpen werd de eiland lap superieur bevonden boven de gesteelde lap.

De volgende fase van de studie was het identificeren van een diermodel voor het ontwikkelen van het stoma sfincter ontwerp. Na het onderzoeken van een aantal diermodellen en het doen van pilot studies werd de hond als diermodel het meest geschikt bevonden. In een acute studie bij honden werd getoond dat het musculus rectus abdominis spier eiland lap ontwerp dat in menselijke cadavers ontwikkeld was ook toegepast kon worden bij de hond (Hoofdstuk 6). In deze studie werd een eindstandig ileostoma gemaakt waaromheen de spierlap werd gewikkeld. Door gebruik te maken van een pacemaker was deze spierlap in staat maximum drukken te genereren ver boven 60 mm Hg (drukken die nodig zijn om continent voor ontlasting te zijn bij de mens). De spiervermoeibaarheid was direct proportioneel aan de stimulatie frequentie en leidde tot continentie bij alle geteste darmdrukken (30, 65 en 100 mm Hg).
De veelbelovende resultaten van de acute functionele studie baanden de weg vrij voor de start van chronische trials met overlevingsstudies in honden. In de eerste chronische studie (Hoofdstuk 7, Deel I. Intramusculaire stimulatie) werd bewezen dat de door ons ontwikkelde sfincter gedurende vier uur onvermoeibaar was bij een follow-up periode van drie maanden met 1 van de 2 geteste trainingsprotocollen. Hoewel het een voorlopig resultaat betreft, werd er in 1 dier een continentietijd van vijf-en-een-half uur gemeten bij een darmdruk van 60 mm Hg.
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