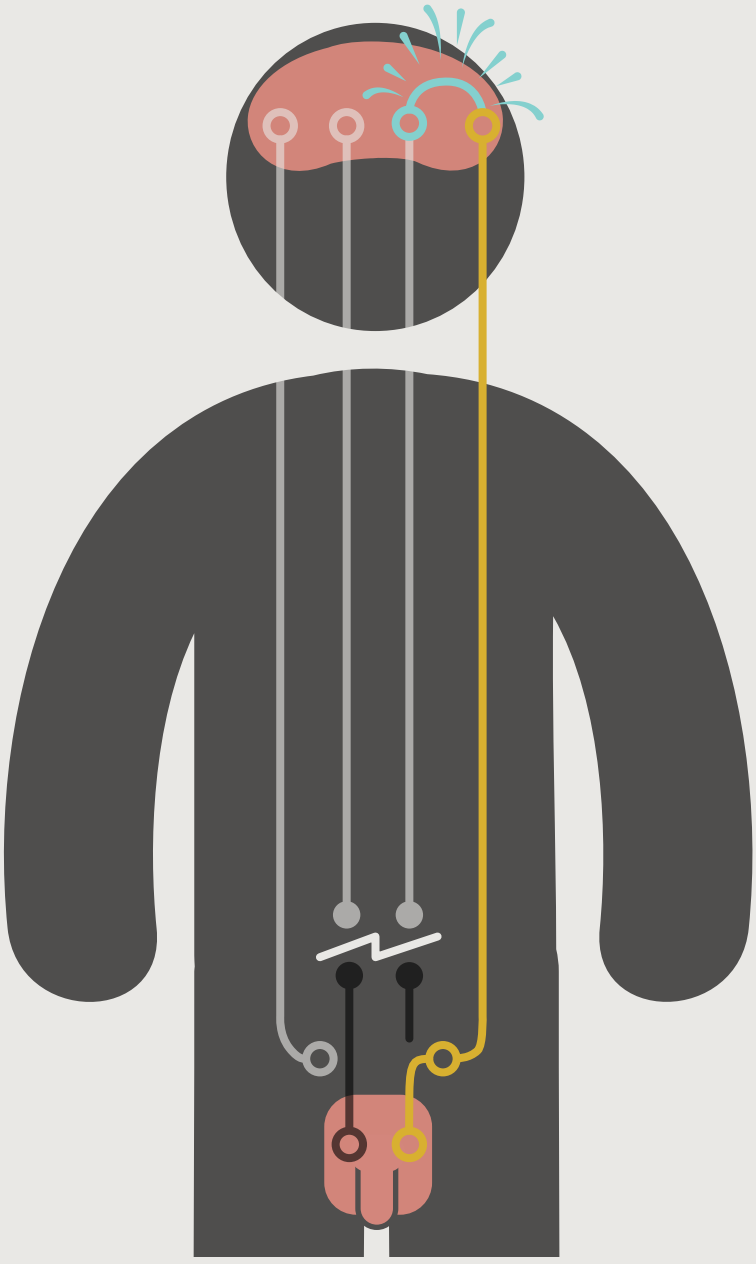

THE TOMAX PROCEDURE

Max L.E. Overgoor

Universiteit Utrecht

THE TOMAX-procedure

De TOMAX-procedure
(met een samenvatting in Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. G. J. van der Zwaan,
ingevolge het besluit van het College voor promoties
in het openbaar te verdedigen op
donderdag 29 januari 2015 des middags te 12:45 uur

door
Max Lucien Emile Overgoor
geboren op 14 november 1964
te De Steeg

ISBN 00000000000000

Illustrations: Ingrid Janssen, UMC Utrecht
Photography and Video on surgical technique: Jan de Witte, UMC Utrecht

Cover design and layout by Claudia Gonzalez Arevalo
argo1983@gmail.com
http://cmgonzalezarevalo.wix.com/layout

Promotores: Prof. dr. M. Kon
Prof. dr. T.P.V.M. de Jong

Paranimfen: Drs. Ralph J.P.M. Franken
Dr. Frank B. Niessen

Voor mijn vader en moeder

TABLE OF CONTENTS

Chapter 1

Introduction and outline
of this thesis

Introduction

Patients with a spinal lesion (SL) may have many neurological dysfunctions, such as walking difficulties due to paralyses, urinary and bowel dysfunction, and loss of sensation in the lower body and limbs. The severity and extent of these problems are related to the level- and the completeness of the lesion. Spinal lesions are most commonly seen in Spina Bifida (SB), a congenital disorder, and in traumatic and other spinal cord injuries (SCI) (acquired SL disorders).

Spina Bifida

Spina Bifida means "cleft spine" and is the result of an incomplete closure of the neural tube, causing incomplete, spinal cord and/or meninges.[1] There are multiple possible types of SB with varying severity of neurological symptoms. The exact cause is not known but genetic, nutritional and environmental factors may play a role. Although prenatal folic acid consumption has reduced the incidence of SB in the last few decades[2], it is still the most common permanently disabling birth defect, affecting 1.9 per 10,000 live births in the USA in 2005.[3] In 2010 there were 3.1 cases per 10,000 children and adolescents, aged 0 to 19 years[4] and around 166,000 individuals with SB are now living in the USA.[1] In the Netherlands about 110 new SB cases are born each year[5] with a prevalence of 1.7-2.7 per 10.000 between 2004 and 2008.[6]

There is no 'cure' for SB, but surgical interventions are frequently needed. If an 'open' SB is diagnosed, the spinal- and skin defect is closed within the first few days of life or earlier in utero, although this type of fetal surgery is still experimental. In hydrocephalus cases a shunt can be placed to drain cerebrospinal fluid into the abdomen. In a later phase additional orthopedic surgery might be needed to correct feet, hip and spine deformities. Urological problems due to the non-functioning of the urethral sphincter can be overcome by emptying the bladder 5-6 times daily by clean intermittent self-catheterization. This is done mostly by a transurethral route, but in some cases through a continent catheterizable stoma. Urological procedures are often necessary to tackle incontinence problems and safeguard kidney function. The neurological malfunctioning

of the rectum and anus is mostly treated with colonic wash-out enemas.

The range of eventual and permanent functional impairment varies between very little to severe, in both physical and mental disabilities. Most SB patients have a normal intelligence but this may depend on the presence or absence of a hydrocephalus.

Spinal Cord Injury

In Spinal Cord Injury the spinal cord and nerve roots have been damaged by a trauma due to an accident, tumor removal or other surgery, an infection, an intervertebral disc disease or vertebral vascular problems.[7] The incidence of SCI is estimated at 40 per million (approximately 12,000 new cases every year) in the USA[8] and the prevalence at 223-755 cases per million worldwide.[9] In the Netherlands the incidence of a survived, traumatic, complete SCI is about 150 new patients each year.[10] Similar numbers of new cases occur due to infection, benign tumor surgery, or vascular impairment.[10] The prevalence of SCI in the Netherlands is estimated at about 10.000 people.[10]

Depending on the level and severity of injury, the symptoms can vary from pain to paralysis to lower urinary tract dysfunction. Sensory and motor impairment can be classified using the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) from A to E.[11] This scale is based on the completeness of the SCI and the amount of motor and/or sensory loss below the neurological level of injury. More than 80% of SCI patients are male and the average age at injury is 42.6 years.[12] After the injury, stabilization and decompression surgery is important to limit the extent of neurological damage.

Level and completeness of spinal lesion

In incomplete lesions some sensory function and voluntary motor activity below the level of injury is retained, but in complete lesions there is a total lack of sensory- and motor function. Besides the completeness of the SL in SB and SCI, the level determines the extent of the neurological deficit. The cervical spinal nerves (C1-C8) control the back of the head, neck and shoulders, the arms and hands, and the diaphragm. The thoracic spinal nerves (T1-T12) involve chest and back muscles as well as many (abdominal)

organ systems. The lumbar spinal nerves (L1-L5) control signals to the lower abdomen *(including the inguinal area)* and back, the buttocks, some parts of the external genitalia and legs. The sacral spinal nerves (S1-S5) control signals to the thighs, lower parts of the legs, feet, *most of external genitals* and the anal area.[12]

In adults the spinal cord is shorter than the spinal column and ends at vertebral body level L1-L2. From below that point, the lumbar and sacral cord-nerves make-up a bundle called the cauda equina. In SB and SCI the neurological and physiological sequelae occur at and below the level of injury. This means that the higher the lesion, the more functional loss the patient suffers.

Penile sensation and sexual health

In the last few decades, the quality of life and sexual health have become important issues when dealing with SB and SCI patients. In the quality of life improvements desired by SL patients, regaining sexual function has the highest priority.[13,14] Most male patients with SB or SCI do not have any sensation in their penis, although most can achieve erections with ejaculations.[15-17] For example, the majority of SB patients (70%) can have an erection[15,17-19] with dribbling ejaculations in about 54%[18,19] and orgasms in 20%.[15] Many SB patients have normal sexual desires and fantasies and are actively interested in sex.[15] Their serum testosterone levels are normal.[18] When compared to high lesions, SB patients with low lesions (<L1) are in the majority, live a relatively normal life and have better sexual function as well as reproductive capacities.[15,18] Similar issues play a role in SCI patients but differ in that most of them did have relatively normal sexual experiences and sensations before their traumatic spinal lesion occurred.

In the low SL patients, the intact erectile function and active interest in sex,[15] combined with the absence of penile sensation, can lead to frustration. We increasingly encounter young and adolescent spina bifida patients and their parents, as well as SCI patients, at the outpatient department who have questions regarding their (future) sexual health. *"I do have a more or less usable erection but do not feel anything when touching my penis; can you do anything about it?"* Although many studies[14,20,21]

have reported decreased sexual health, surprisingly no study has dealt specifically with the role of penile sensation in SL patients.

Neuro-anatomy

In a normal situation, sensory impulses from the glans penis are transmitted through both the dorsal penile nerves (DNP) and the pudendal nerves, to the 2nd–4th sacral roots. They continue through the spinal cord to the sensory cortex **(Figure 1a)**, unless interrupted by a spinal lesion as in SB and SCI. **(Figure 1b)**

The cutaneous nerves responsible for the sensation in the lower abdominal- and inguinal/groin region around the genitals enter the spinal cord at the lumbar roots, and are thus cranial to the entrance of the DNP. These "groin" nerves are the iliohypogastric-(L1), ilioinguinal- (L1), the genitofemoral- (L1-2), and the lateral femoral cutaneous nerve (L2-3). They should function normally in SL patients with a lesion below their respective entrance levels in the spinal cord (L1-L3), **(Figure 2)**. Besides this, the groin nerves are anatomically in close proximity to the DNP **(Figure 3)**. In theory, if one of these functional sensory groin nerves could be transposed and connected to the non-functional DNP, sensory impulses from the penis might reach the sensory brain cortex and bypass the lesion in patients

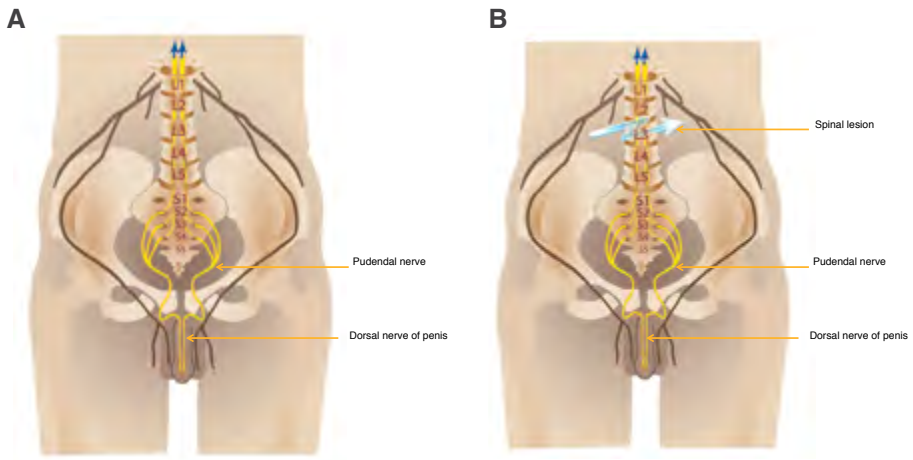

Figure 1A. In a normal situation, sensory impulses from the glans penis are transmitted through both the dorsal penile nerves and the pudendal nerves, to the 2nd–4th sacral roots. They continue through the spinal cord to the sensory cortex. **Figure 1B**.unless interrupted by a spinal lesion.

with a low SL. A restored sensation of the glans penis might be the result. **(Figure 4)**

Dissection study

To gain information on the anatomy, position, caliber, ease of dissection, and nerve transposition possibilities of the groin nerves and DNP, we used four fresh cadavers for anatomical dissections at the Department of Anatomy, (Prof R. Bleys, University Medical Centre Utrecht, the Netherlands).

The DNP runs bilaterally on the dorsum of the penis and was found to have a constant anatomy: it can be found under Buck's fascia, on top of the tunica albuginea and lateral to the centrally located dorsal vein and ipsilateral dorsal artery **(Figure 5,6)**. Both DNPs divide distally into a lateral- (to the ipsilateral shaft and urethra[22] and medial bundle (to the ipsilateral glans), merging proximally to one bundle at the base of the penis. At this base the nerve can be dissected off the tunica albuginea and cut as

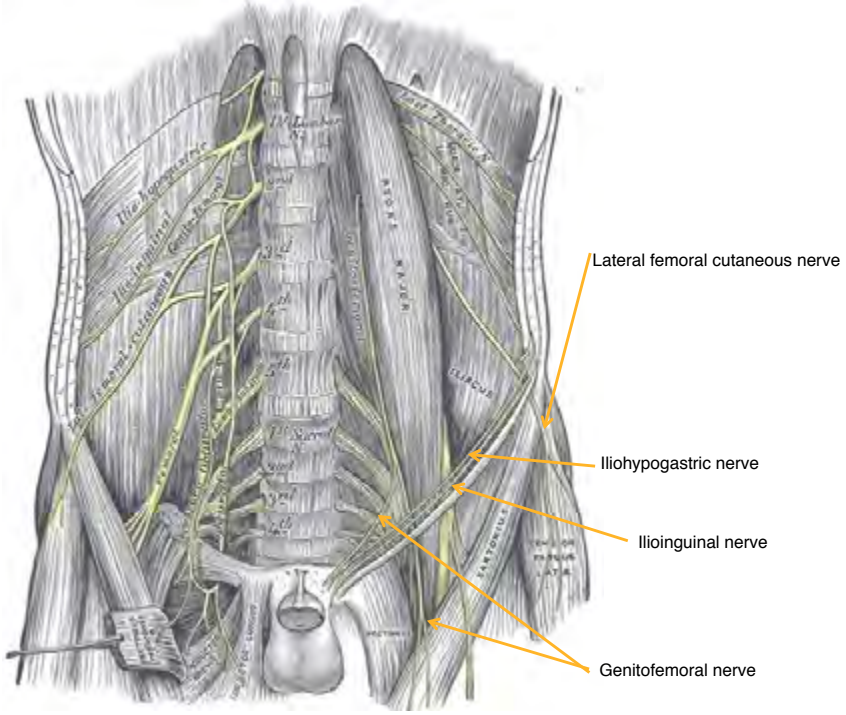

Figure 2. Cutaneous nerves responsible for the sensation in the lower abdominal- and inguinal/groin region around the genitals.

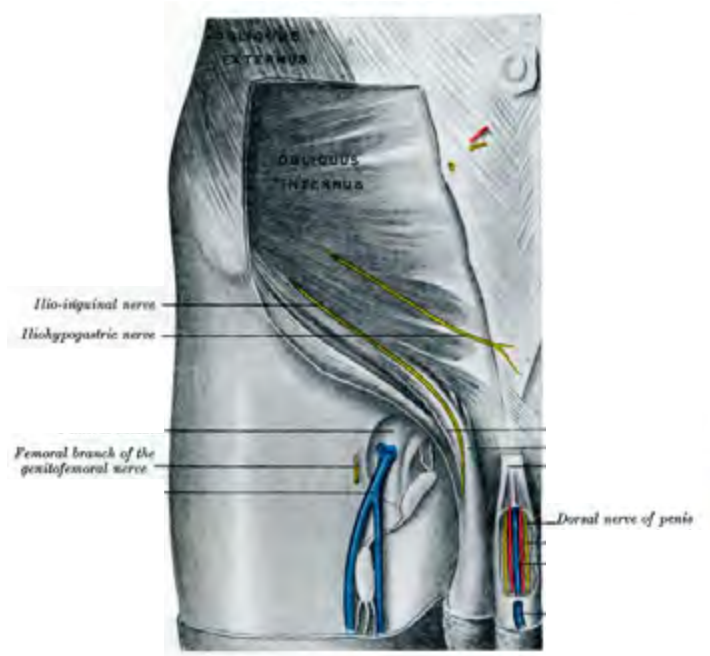

Figure 3. Groin nerves are anatomically in close proximity to the dorsal nerves of the penis

proximally as possible, resulting in 2-3 centimeters of lateral transposition for coaptation with a possible donor-groin nerve.

The lateral femoral cutaneous nerves and the iliohypogastric nerves were found to be too lateral- and too cranial, respectively, to reach the penile base. Both branches of the genito-femoral nerve were not easily found (inconsistent anatomy) and they are too thin and short for adequate nerve transposition.

The ilioinguinal nerve, however, was found just cranial to or at the spermatic cord, under the external oblique fascia, and with several distal branches going deep into the lateral scrotum/inner thigh or superficial to the pubic area and skin around the penile base **(Figure 5,6)**. When distally cut, the ilioinguinal nerve was long enough to reach the base of the penis for coaptation to the proximal cut end of the DNP. **(Figure 7)** Besides its favorable anatomical position, the ilioinguinal nerve had a good cross-sectional caliber-match (2-3 mm) with the DNP.

Based on these anatomical dissection studies, we were able to design a surgical procedure in which the ilioinguinal nerve is cut distally in the

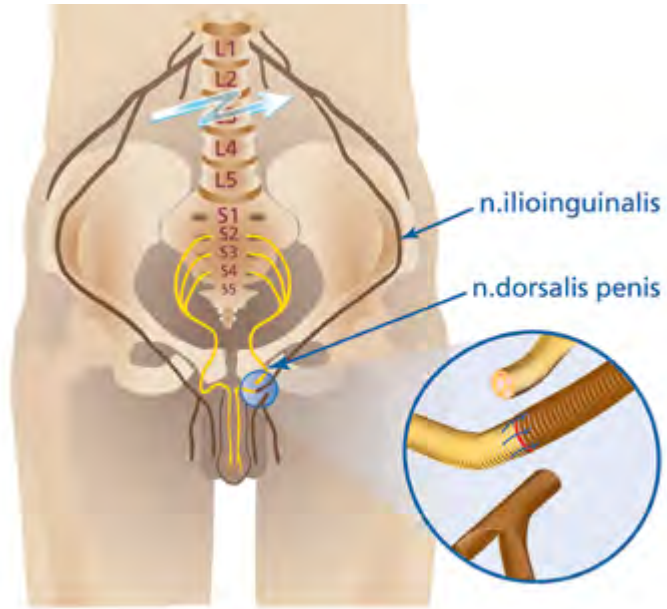

Figure 4. If a functional sensory groin nerve is connected to the non-functional dorsal nerve of the penis, sensory impulses from the penis might reach the sensory brain cortex and bypass the lesion in patients with a low SL.

groin and joined by microneurorraphy to the proximally divided DNP at the base of the penis on one side. This procedure is called TOMAX: TO MAX-imize sensation, sexuality and quality of life. **(Figure 4)**

Hypotheses

Triggered by the patients' wish to gain or regain penile sensation, we hypothesized that:

Penile sensation in low SL patients can be created by nerve transposition and this will contribute to their sexual health.

We performed five studies to test this hypothesis and answer the following five questions about the TOMAX procedure:

1. Is the procedure technically feasible in SB patients and does it lead to penile sensation?
2. Does it increase sexual health and satisfaction in SB and SCI patients?
3. Can it be safely done bilaterally and in which patients?

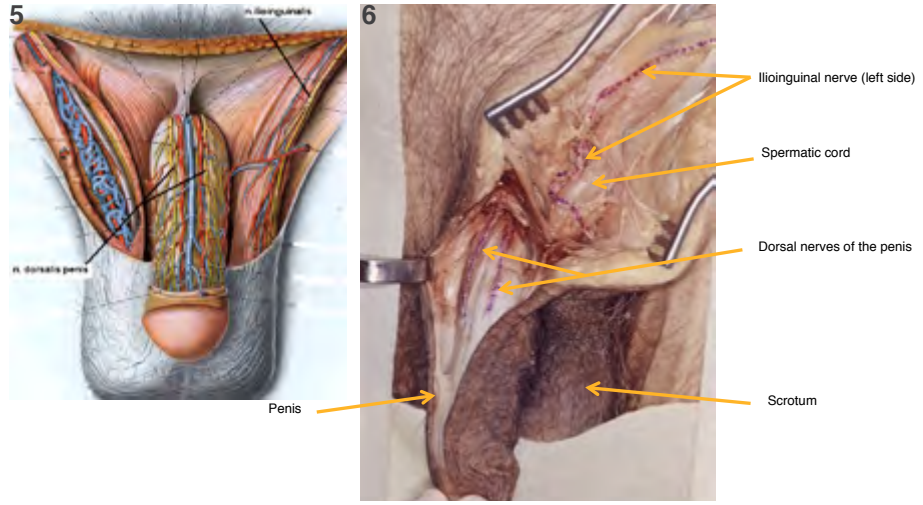

Figure 5 and Figure 6. The dorsal nerve of the penis runs bilaterally on the dorsum of the penis, lateral to the centrally located dorsal vein and ipsilateral dorsal artery. The ilioinguinal nerve is found just cranial to or at the spermatic cord with several distal branches around the penile base.

4. Can we describe the procedure in detail in order to teach other surgeons how to perform it?
5. Can we understand the possible changes in the brain due to the TOMAX procedure?

Study design/outline of this thesis

In **Chapter 2** we describe a pilot study of the TOMAX procedure in three low SB patients designed to answer the following questions:

- Is the TOMAX procedure technically feasible in SB patients?
- Does it restore (unilateral) penile sensation?
- What does the patient feel when touching the glans-penis: the groin (donor nerve area) or an actual glans-penis sensation?
- What is the nature of the sensations: tactile and/or erogenous?
- Do patients benefit from the surgery?
- Are there any negative aspects?

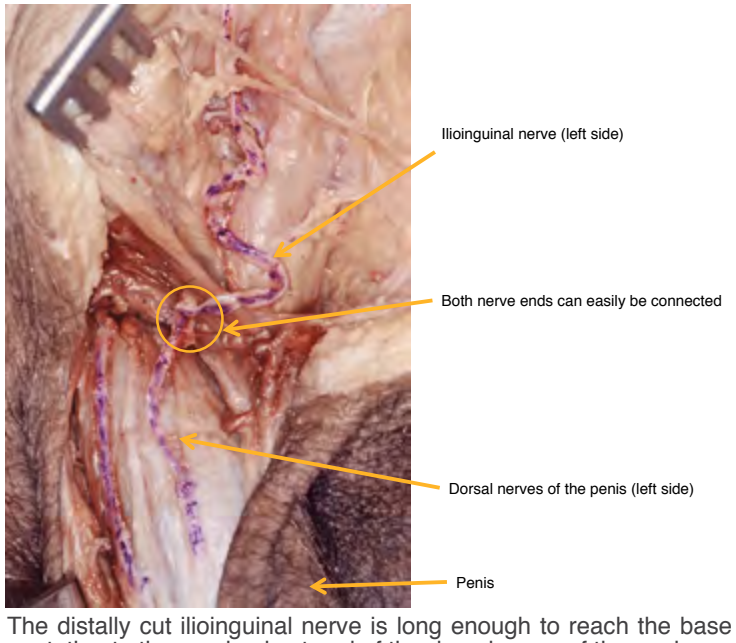

Figure 7. The distally cut ilioinguinal nerve is long enough to reach the base of the penis for coaptation to the proximal cut end of the dorsal nerve of the penis.

In Chapter 3 we describe a study in which the number of patients who had undergone TOMAX-surgery was expanded to 30, including both SB and SCI patients. This second study focused mainly on changes in sexual health and set out to answer the following questions:

- Can the results of the pilot study be confirmed?
- Can the TOMAX procedure be used in SB *and* SCI patients?
- Does (unilateral) restored penile sensation:
  -increase sexual health and satisfaction?
  -influence erectile capability?
  -influence incontinence management?

If *unilateral* sensory recovery is possible, we wondered if a *bilateral* procedure could safely be done to gain full glans sensation. With this in mind, it should be noted that besides transmitting penile sensory impulses to the brain, both DNPs play a crucial role in reflex erections (RE)[5,6] and (vibratory) ejaculations[4] through the sacral (S2-S4) reflex arc. If both DNPs are transected in a bilateral procedure, these vital functions might be at risk.

In **chapter 4** we describe a study focused on measuring signs of remaining DNP function, by using the bulbocavernosus reflex, and the preserved ability to have reflex erections. It set out to answer the following questions:

- How often are signs of DNP function still present in low SL patients?
- Can reflex erection ability or bulbocavernosus reflex measurements determine whether a unilateral- or bilateral procedure should be performed?
- Is it possible to design a selecting protocol for unilateral or bilateral surgery?
- Can we actually operate on patients bilaterally using this protocol?

In **chapter 5** the main focus lies on the procedural and technical aspects of the TOMAX procedure. Based on a series of 43 nerve transfers we aimed to teach others to select patients and perform the surgery. All the steps concerning patient selection, surgical history, pertinent anatomy of the ilioinguinal nerve and DNP, as well as uni-or bilateral surgery, surgical procedure (including a video), possible complications, and the patient briefing are described.

In chapter 6 we describe a functional MRI (fMRI) study aimed at demonstrating the cerebral networks involved in processing penile tactile stimulation. Three MRI-compatible post-TOMAX patients (with stimulation experienced as actual unilateral glans penis sensation) were enrolled and underwent fMRI scanning while penis, groin and finger were stimulated with a soft paint brush. This study aimed to determine whether cerebral reorganization due to activation differences between groin and penis occurs *in* the primary somatosensory cortex or if it becomes apparent *beyond* the somatosensory cortex. Any differences in brain activation between groin and penis could provide insight into the remapping process of the body scheme and could hint at areas that allow for development of erogeneity.

Literature

1) www.ninds.nih.gov/disorders/spina_bifida/detail_spina_bifida.htm

2) MRC Vitamin Study research group: Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. Lancet 1991; 338 (8760): p 131.

3) Centers for Disease Control and Prevention (CDC). Racial/ethnic differences in the birth prevalence of spina bifida - United States, 1995-2005. MMWR Morb Mortal Wkly Rep 2009; 57: 1409.

4) Shin M, Besser LM, Siffel C et al. Prevalence of spina bifida among children and adolescents in 10 regions in the United States. Pediatrics 2010; 126:274-279.

5) http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/aangeboren-afwijkingen/centrale-zenuwstelsel/hoe-vaak-komen-aangeboren-afwijkingen-voor

6) http://rug/research/genetics/eurocat/pdf/actuelecijfers/neuralebuisdefecten.pdf

7) van den Berg ME, Castellote JM, de Pedro-Cuesta J Mahillo-Fernandez I. Survival after spinal cord injury: a systematic review. J Neurotrauma 2010; 27 (8): 1517-28.

8) Jackson AB, Dijkers M, Devivo MJ, Poczatek RB. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. Arch Phys Med Rehabil. 2004; 85: 1740-1748.

9) Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? Spinal Cord. 2006; 44: 523-529.

10) Spek J. Zorg Standaard Dwarslaesie, Dwarslaesie Organisatie Nederland 2013; 18.

11) Marino, RJ et al. International standards for neurological classification of spinal cord injury, J Spinal Cord Med 2003; 26 (Suppl 1): S50-6.

12) http://www.ninds.nih.gov/disorders/sci/detail_sci.htm

13) Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 2004; 21: 1371.

14) McDonald JW, Sadowsky C. Spinal-cord injury. Lancet 2002; 359: 417-25.

15) Sandler AD, Worley G, Leroy EC, Stanley SD, Kalman S. Sexual function and erection capability among young men with spina bifida. Dev Med Child Neurol. 1996; 38(9):823.

16) Palmer JS, Kaplan WE, Firlit CF. Erectile dysfunction in spina bifida is treatable. Lancet 1999; 354: 125.

17) Dik P, Van Gool JD, De Jong TP. Urinary continence and erectile function after bladder neck sling suspension in male patients with spinal dysraphism. BJU Int 1999; 83: 971.

18) Decter RM, Furness PD, III, Nguyen TA, McGowan M, Laudermilch C, Telenko A. Reproductive understanding, sexual functioning and testosterone levels in men with spina bifida. J Urol 1997; 157(4):1466.

19) Perez-Marrero R, Young M, Stitzel D. A sexuality survey of young adults with spina bifida. J Urol 1984; 131(2):104A.

20) Lassmann J, Garibay Gonzalez F, Melchionni JB et al. Sexual function in adult patients with spina bifida and its impact on quality of life. J Urol 2007; 178: 1611.

21) Verhoef M, Barf HA, Vroege JA, et al. Sex education, relationships, and sexuality in young adults with spina bifida. Arch Phys Med Rehabil 2005; 86: 979.

22) Yang CC, Bradley WE. Neuroanatomy of the penile portion of the human dorsal nerve of the penis. Br J Urol 1998; 82: 109.

Chapter 2

The TOMAX-procedure in three low Spina Bifida patients: a pilot study

Overgoor ML
Kon M
Cohen-Kettenis PT
Strijbos SA
de Boer N
de Jong TP

Neurological bypass for sensory innervation of the penis in patients with spina bifida. *J Urol* 2006; **176:** 1086-1090

Abstract

Purpose

Most male spina bifida patients have normal sexual desires. During puberty they begin to realize that they can have erections and sexual intercourse, but without any sensation in the penis.

We hypothesized that a restored sensation in the penis would greatly contribute to their quality of life and sexual health. The aim of this prospective study was to investigate the outcome of a new operative neurological bypass procedure in spina bifida patients.

Materials and Methods

In three patients (17, 18 and 21 years old, spinal lesion at L5, L4 and L3-L4, respectively) the sensory ilioinguinal nerve (L1) was cut distally in the groin and joined by microneuroraphy to the divided ipsilateral dorsal nerve of the penis, (S2-4) at the base of the penis. All patients underwent pre and postoperative neurological and psychological evaluations.

Results

Fifteen months postoperatively, all patients gained excellent sensation on the operated side of the glans penis. They were unequivocally positive about the results and their penis had become more integrated in their body image. In two patients, masturbation became more meaningful and one patient became more sexually active with and without his partner.

Conclusions

The newly designed neurological bypass procedure in spina bifida patients resulted in excellent sensibility in the glans penis. The new sensation appeared to contribute to the quality of the patients' sexuality and sexual functioning, as well as the feeling of being a more 'normal' and 'complete' person who is more conscious of his penis. This new operation might become standard treatment for spina bifida patients in the future.

Introduction

The advances in medicine and multidisciplinary treatment have increased the life expectancy and quality of life for spina bifida patients. Most of them have normal sexual desires and fantasies and are actively interested in sex[1]. Normal serum testosterone levels have been found in male spina bifida patients[2]. The majority (70%) of these patients can have an erection[1-4] with dripping ejaculations in about 54%[2,3] and orgasms in 20%[1]. Spina bifida patients with low lesions (when compared to high lesions) have increased sexual function and reproductive capacities[1,2] and live a relatively normal life. Puberty is often highly frustrating since these patients begin to realize that they can have erections (and ejaculations) with possible sexual intercourse, but without any sensation in the penis. Surprisingly, no study in the literature has dealt specifically with the absence of penile sensation in spina bifida patients. In a non- pathological situation, sensory impulses are transmitted from the glans penis through both dorsal nerves of the penis (DNP) and pudendal nerves, to the sacral roots S2-S4 and, ultimately, to the sensory cortex. In spina bifida patients, this route is interrupted by the spinal lesion. We hypothesized that if this spinal lesion can be bypassed, a restored sensation in the penis would greatly contribute to their quality of life and sexual health.

To achieve this, we designed an operative procedure in which the sensory ilioinguinal nerve was cut distally, and joined by microneuroraphy to the divided DNP at the base of the penis (Figure 1).

The DNP was chosen (and not the perineal nerve to the anterior part of the schaft) because it is the most important sensory nerve to the (glans-)penis.The

Figure 1. Experimental design: the sensory ilioinguinal nerve (L1) is cut distally and joined by microneuroraphy to the divided dorsal nerve of the penis (S2-4) at the base of the penis.

ilioinguinal nerve was chosen for its length, its anatomical position, the high level of entrance into the spinal cord (L1), and the cross-sectional caliber-match with the DNP (S2-S4). Inguinal hernia surgery has shown that the ilioinguinal nerve can be cut without adverse effects for the patients. The aim of this prospective study was to investigate the outcome of this new surgical intervention in spina bifida patients.

Methods

Patient selection

We selected well-motivated patients, with no signs of psychopathology (as assessed by psychological tests, see below) or negative sexual experiences (except for frustration as a consequence of their condition), and with a spinal lesion between L1 (ilioinguinal nerve) and S2 (DNP). This level combines an absence of penile sensation with normal sensation in the groin.

The Medical Ethics Committee permitted performance of the procedure in 3 patients, 16-21 years old. This age was chosen because: 1) over the age of 16, no parental consent for joining the study was needed, 2) sexuality is very important for adolescents and young adults, and 3) the chances of nerve regeneration are significantly better in younger individuals[5,6].

Neurological assessment

We used simple non-quantitative neurological sensory tests for touch (pointed vs. blunt stimuli) and temperature (warm (37 °C) vs. cold (4 °C) stimuli). For testing purposes the groin area, penile shaft and glans penis were subdivided into smaller regions. After blindfolding the patient, each region was stimulated three times with random time intervals. If all three stimuli were correctly experienced, it was concluded that sensation was present in that particular region. The distal part of the urethra was tested separately using a soft cotton-wool stick. Besides the presence of sensation, we noted where the stimulus was experienced (groin, penile shaft or glans penis) and if the stimuli had been ever experienced erotically.

Psychological assessment

The patients were evaluated twice, once preoperatively and, once one year postoperatively, using a self-constructed, semi-structured interview to measure various aspects of sexuality[7]. Apart from this interview, the following questionnaires

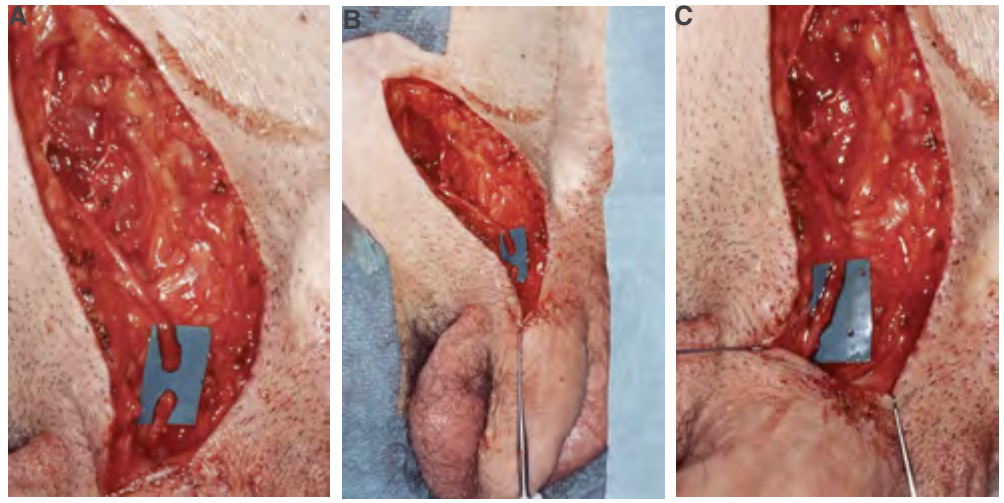

Figure 2. Surgical technique: a) incision over the course of the right ilioinguinal nerve to the base of the penis and exposure of the nerves; b) detail of the distally cut ilioinguinal nerve and proximally divided ipsilateral dorsal nerve of the penis; c) the two nerve-ends joined by microneuroraphy.

were used: the Dutch Personality Questionnaire[9], the Child Behavior CheckList (CBCL)[9], the Youth Self-Report version of the CBCL[10], the Hospital Anxiety and Depression Scale[11], and an adapted version of the Groningen Arousability Scale[12].

Surgical technique

Surgery was performed under general anesthesia. The incision was made over the course of the right or left ilioinguinal nerve to the base of the penis. After exposure, the ilioinguinal nerve was cut distally and the ipsilateral DNP proximally. The two nerve-ends were approximated at the base of the penis and joined by microneuroraphy (Figure 2) followed by closure of fascia and skin.

Study protocol

After selection of the patients and written informed consent, neurological and psychological evaluations were performed, followed by ilioinguinal nerve transposition to the DNP on one side of the penis. Postoperative neurological testing was carried out after 5-8 months and again after 12-15 months, while psychological assessment was repeated 12 months after the operation.

Results

Postoperatively, all patients gained excellent sensation in the glans penis on the operated side. The groin area, the medial mons pubic region and the lateral part of the scrotum had less or no sensation in comparison to the non-operated side. The patients did not experience any discomfort, pain, hyperesthesia or paresthesia. More detailed information on each patient is given below. See Table 1 for pre-surgical and post-surgical psychological evaluations**.**

Patient 1, age 18

The first patient had level L4 motor and sensory deficiencies. His sexual experiences were limited and he rarely masturbated due to lack of sensation.

In the eight months following surgery, the left side (i.e. the operated side) of the glans penis and the distal part of the urethra gained excellent sensation although no sensation was observed in the shaft. The stimuli were experienced as if the left groin was being touched and in a private environment qualified as tactile but not erogenous in nature. Fifteen months after the intervention, no new sensory changes had occurred.

Patient 1 reported to be happy with the gained sensation in his penis. He was more conscious of his penis making it a 'real' part of his body. He felt less handicapped. During self-catheterization he noticed the introduction of the catheter into the distal part of the urethra which was experienced as something positive. At the second psychological assessment session, patient 1 was still not very sexually active. (Table 1)

Patient 2, age 17

The second patient had level L5 motor and sensory deficiencies. Patient 2 had no sexual relationship and was not very sexually active. When masturbating, he could ejaculate (dripping) and have orgasms which gave him a vague sort of 'orgasmic-feeling' in his lower abdomen.

After five months, the left side (i.e. the operated side) of the glans penis and the distal part of the urethra had gained excellent sensation. The stimuli felt as if the left groin was being touched, but in some regions of the glans penis it felt as if the sensation was 'climbing up to the glans penis'. In the shaft, however, no sensation developed.

Twelve months after the intervention, stimulating the corona region was

Table 1. Preoperative and one year postoperative psychological evaluation.

	Patient 1		Patient 2		Patient 3	
	pre-op	post-op	pre-op	post-op	pre-op	post-op
masturbation [1)]	2	2	1	5	1	6
sexually active with partner [1)]	0	0	0	0	1	5
quality of erection [2)]	5	6	8	8	6	9
morning erections [1)]	2	2	0	1	3	15
ejaculation	no	no	dripping	dripping	dripping	dripping
orgasm	no	no	yes	yes	Yes	yes
sexual dreams [1)]	1	2	2	1	1	0
sexual thoughts [1)]	2	3	10	10	1	6
sexual desire [3)]	5	5	7	5	3	7
satisfaction sexual functioning[4)]	6	4	6	8	6	8
satisfaction sexual life [4)]	5	4	4	3	6	10
importance of sexuality [5)]	5	6	7	5	5	9

[1)]times per month, [2)]on a 10-point scale: flaccid-erect, [3)]on a 10-point scale: little-much desire, [4)]on a 10-point scale: not-very satisfied, [5)]on a 10-point scale: not-very important

experienced as a 'groin feeling,' whereas stimuli in the meatus region gave the impression that the glans penis was being touched. Also the distal shaft of the penis had gained some 'groin' sensation. The new sensations were qualified as tactile in nature.

Patient 2 was very happy with the new sensation in his penis. During self-catheterization he noticed the introduction of the catheter as a cold object, which was experienced as positive. The gained sensations had become totally integrated into his body perception and could be considered a step towards being a more 'normal' and 'complete' person. He masturbated slightly more because the sensations in his penis during masturbation were pleasant and orgasm had become more sexually exciting. Patient 2 reported having slightly less sexual desire, but about as many sexual thoughts. It was easier for him to become aroused. (Table 1)

Patient 3, age 21

The third patient had level L3-4 motor and sensory deficiencies. He reported feeling some sexual desire and arousal but he had no strong sexual motivation. The erections were of enough rigidity to enable him to be fully sexually active with his wheelchair-bound girlfriend, but obtaining an orgasm was difficult. Ejaculation gave him a 'tingling feeling inside'. Having an orgasm gave him a sense of relief and relaxation.

Five months after the operation, the right side (i.e. the operated side) of the glans penis and the distal part of the urethra had obtained excellent sensation. The stimuli were felt as if the right groin was being touched and were qualified as tactile in nature.

Twelve months after the intervention, stimulation of the corona region was experienced as if the glans penis was being touched, whereas the meatal area felt as if the groin area was being touched. In a private environment, the sensations were not only experienced as tactile, but also as an erogenous feeling. In the shaft, however, no sensation was recovered.

The new sensations made sexual activity more pleasurable for patient 3. Orgasm was experienced as very pleasant. He was very conscious about the new feelings and elicited them often. During masturbation, he felt sensations that might be considered as erogenous. Only after his treatment did he realize what he had been missing before surgery. He became sexually more active and the sexual relationship with his girlfriend improved significantly. His girlfriend reported that she had never realized how little he had felt before his operation. Both agreed that their sexual relationship had become more open and meaningful. (Table 1)

Discussion

The effects of a new procedure were studied in three spina bifida patients who had no penile sensation prior to surgery. By transposing the ilioinguinal nerve and connecting it to the ipsilateral DNP, excellent sensibility was gained in the glans penis. Sensation was present on the operated side of the glans-penis only, and not on the shaft or the contra-lateral side. This can be explained by the unilateral DNP's anatomy, which consists of one dorsal axonal bundle to the glans penis and distal urethra, and one lateral to the shaft. These axons, however, never cross the midline[13]. It is likely that the axonal growth from the ilioinguinal nerve only

traveled through the dorsal bundle, thus not reaching the shaft. This distal part of the DNP, which probably has been never functioning, can be used for conduction activity as long as the perineurium-"tube" is intact.

Besides gain of sensation there was also loss of sensation due to the division of the ilioinguinal nerve. This did not cause symptomatic sensory loss or chronic pain in our patients, a phenomenon which is described in the literature[14].

At first the stimuli of the glans penis were experienced as if the groin was being touched, but after 12 months two patients had 'remapped' sensibility to their glans penis. Detailed sensory testing revealed that in patient 2 the corona region gave a 'groin' sensation whereas the meatal area had developed a 'glans' sensation. The opposite was true for patient 3. These sensory changes might be the result of different stages of sensory reorganization due to the neural plasticity of the brain. This phenomenon of cortical reorganization is attributed to reinforcement or revelation of former relatively weak or ineffective connections. Ebner et al.[15] describe that the cumulative change of many synapses of the somatic sensory cortex leads to a change in their receptive field. This is interpreted as a reorganization of the map of the cortical representation of the body surface[15]. This capacity of the human brain to adapt to peripheral input seems to last a lifetime and is dependent on both the pattern and frequency of use[16]. This might explain the differences between the first and the other two patients: patient 1 was less motivated and less active in stimulating his penis, while masturbation was more frequent in the other two patients. Patient 3 was sexually active with a partner. These activities can be seen as sensory education programs in which visualization and motivation play a considerable role[17]. Age, however, is the most important factor in predicting sensory and functional recovery[5,6]. Transposing the nerve at an earlier age, preferably before the age of puberty, is likely to contribute to a more effective sensory re-education of the brain and make erogenous sensation more feasible.

Postoperatively, all patients retained their ability to have an erection, and their ejaculation, if present, was unchanged. The ability to have erections is dependent on the preservation of the psychogenic and/or reflexive pathways of erectile function. Psychogenic erections are regulated by a sympathetic spinal center at Th10-L2[18], and travel further along the hypogastric nerves to reach the penis by way of the pelvic plexuses. In our patients, psychogenic erections are likely to be

preserved because their spinal lesion was lower than Th10-L2.

Reflexive erections, on the other hand, are elicited by direct penile/genital stimulation through the somatic-afferent DNP and pudendal nerves. They are mediated in the sacral spinal segments S2-S4 and modulated by supra-spinal influences. Efferent parasympathetic and somatic fibers run to the penis and perineal musculature, producing a reflexive erection[19]. Due to the role of the DNP in reflexive erections (and ejaculation) and taking into account the fact that one has to retain the capacity of erection at all costs, it was decided not to operate bilaterally but to leave one DNP nerve intact.

In future patients, however, measurement of the bulbocavernous reflex (BCR) can predict whether or not one of the unilateral reflex pathways is intact. This may help to determine the risk of losing the reflexive pathway of erection by using one or both DNP's for sensibilisation of the penis. This risk will probably be low, since BCR in spina bifida patients is often negative[20].

All patients were unequivocally positive about the results of their operation: they felt sensations in an area where they had never had any sensation before; they felt less handicapped and their penis had become more integrated in their body image. Even the sensations during introduction of the catheter were contributed to the sense of being 'complete'. This is important since most spina bifida patients use intermittent self-catheterization to empty their bladder. In two patients, masturbation had become more meaningful. As it is difficult to measure, since these patients had never had erogenous feelings before, the new sensations were not really qualified as erotic. In patient 3, however, the new sensations stimulated him to be more sexually active, making the sexual relationship with his girlfriend more meaningful.

Conclusions

Since all patients have developed unilateral sensation in the glans penis, we can conclude that the operation was a technical success. Whether it will result in more satisfaction about their sexuality in general does not only depend on the technical success of the operation. For some patients, the frustration of not being able to have sexual feelings may spread to other life areas, such as not being able to find a (sexual) partner. Naturally, we cannot solve such problems by an operation. However, having increased (sexual) sensation in the penis may still contribute to the quality of life for this group of patients.

So far this novel surgical technique might be seen as experimental since it reports a small group. On the other hand the technique of nerve transpositions in hand surgery and neuroraphy in a free-flap reconstructed penis are well known.

To validate the new intervention we are treating at this moment a larger group of spina bifida- and traumatic spinal lesion patients starting at the age of 12, using a more detailed neurological evaluation. In the traumatic group the results will be interesting since they had previously sexual activity. These studies will answer the question whether this new operation should become standard treatment for spina bifida / spinal lesion patients in the future.

References

1) Sandler AD, Worley G, Leroy EC, Stanley SD, Kalman S. Sexual function and erection capability among young men with spina bifida. Dev Med Child Neurol. 1996; 38(9):823.

2) Decter RM, Furness PD, III, Nguyen TA, McGowan M, Laudermilch C, Telenko A. Reproductive understanding, sexual functioning and testosterone levels in men with spina bifida. J Urol. 1997; 157(4):1466.

3) Perez-Marrero R, Young M, Stitzel D. A sexuality survey of young adults with spina bifida. J Urol. 1984; 131(2):104A.

4) Dik P, Van Gool JD, De Jong TPVM. Urinary continence and erectile function after bladder neck sling suspension in male patients with spinal dysraphism. BJU Int. 1999; 83(9):971.

5) Imai H, Tajima T, Natsumi Y. Successful reeducation of functional sensibility after median nerve repair at the wrist. J Hand Surg [Am]. 1991; 16(1):60.

6) MacKinnon SE, Dellon AL. In: Surgery of the periferal nerve. New York: Thieme Medical Publishers; 1988.

7) HS Kaplan. The evaluation of sexual disorders; Psychological and medical aspects. New York, USA: Bruner/ Mazel, 1983.

8) Issued by: Luteijn F, Starren J, van Dijk H, editors. Manual of the Dutch Personality Questionnaire (NPV). Lisse, The Netherlands: Swetz en Zeitlinger; 1985.

9) Issued by: Verhulst FC, Van der Ende J, Koot H, editors. Manual of the Child Behaviour Checklist CBCL/4-18. Department of Children and Adolescent Psychiatry, AZ/Erasmus University. Rotterdam, The Netherlands; 1996.

10) Issued by: Verhulst FC, Van der Ende J, Koot H, editors. Manual of the Youth Self-Report. Department of Children and Adolescent Psychiatry, AZ/Erasmus University. Rotterdam, The Netherlands; 1997.

11) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67(6):361.

12) Van de Wiel HBM, Weijmar Schultz WCM, Molenaar IW, Vennix P, Beens H, Vessies D. Zelfbeoordeling van genitale sensaties en lichaamsperceptie bij vrouwen; de constructie van twee vragenlijsten. Tijdschrift voor Seksuologie. 1995; 19:119.

13) Yang CC, Bradley WE. Peripheral distribution of the human dorsal nerve of the penis. J Urol. 1998; 159(6):1912.

14) Ravichandran D, Kalambe BG, Pain JA. Pilot randomized controlled study of preservation or division of ilioinguinal nerve in open mesh repair of inguinal hernia. Br J Surg. 2000; 87(9):1166.

15) Ebner FF, Rema V, Sachdev R, Symons.F.J. Activity Dependant plasticity in adult somatic sensory cortex. Seminars in neuroscience. 1997; (9):47.

16) McAllister RM, Calder JS. Paradoxical clinical consequences of peripheral nerve injury: a review of anatomical, neurophysiological and psychological mechanisms. Br J Plast Surg. 1995; 48(6):384.

17) Gelberman RH, Operative nerve repair and reconstruction. Philadelphia: J.B. Lippincott Company; 1991.

18) Lue TF, Zeineh SJ, Schmidt RA, Tanagho EA. Neuroanatomy of penile erection: its relevance to iatrogenic impotence. J Urol. 1984; 131(2):273.

19) Giuliano FA, Rampin O, Benoit G, Jardin A. Neural control of penile erection. Urol Clin North Am. 1995; 22(4):747.

20) Sakakibara R, Hattori T, Uchiyama T, Kamura K, Yamanishi T. Uroneurological assessment of spina bifida cystica and occulta. Neurourol Urodyn. 2003; 22(4):328.

3

Chapter 3

Changes in sexual health following the TOMAX-procedure in 30 low Spina Bifida and Spinal Cord Injury patients

Overgoor ML
de Jong TP
Cohen-Kettenis PT
Edens MA
Kon M.

Increased sexual health after restored genital sensation in male patients with spina bifida or a spinal cord injury: The TOMAX procedure. *J Urol*. 2013; ***189***: 626-632.

Abstract

Purpose

This study prospectively investigated the contribution of restored penile sensation to sexual health in low spinal lesion patients.

Materials and Methods

In 30 patients (18 Spina Bifida, 12 Spinal Cord Injury, 13-42 years) with no penile- but good groin sensation the new TOMAX procedure was performed. This involves micro-surgically connecting the sensory ilioinguinal nerve to the dorsal nerve of the penis unilaterally. Extensive pre- and post-operative neurological- and psychological evaluations were made.

Results

Twenty-four patients (80%) gained unilateral glans-penis sensation. This was initially felt as 'groin-sensation' but transformed into real 'glans-sensation' in 11 patients (33%). They had better overall sexual function (p=0·022) and increased satisfaction (p=0·004). Although 13 patients (43%) maintained 'groin sensation', their satisfaction with their sexuality was only slightly less than that of those with glans sensation. Better sensations helped them manage their urine incontinence, improving personal hygiene and independence. Most patients felt more complete and less handicapped, with their penis now part of their body image. They reported having more open and meaningful sexual relationships with their partners.

Conclusions

Tactile- and erogenous-like sensibility was restored in the glans penis in patients with a low spinal lesion. This new sensation enhanced the quality of sexual functioning and satisfaction. The TOMAX procedure should become standard treatment for such patients.

Introduction

Most male patients with spina bifida (SB) or a spinal cord injury (SCI) do not have any sensation in the penis, although most can achieve erections with ejaculations.[1-3] Despite having erectile function and an active interest in sex[1], the absence of penile sensation leads to frustration. In the quality of life improvements desired by spinal lesion (SL) patients, regaining sexual function has highest priority.[4, 5] Many studies[5-7] have reported decreased sexual health, but no study has dealt specifically with the role of penile sensation in SL patients.

Normally, sensory impulses from the glans penis are transmitted through both dorsal penile- (DNP) and pudendal nerves, to the 2nd–4th sacral roots. They continue through the spinal cord to the sensory cortex, unless interrupted by a spinal lesion.

We hypothesized that restoring penile sensation in SL patients would contribute to their sexual satisfaction and health, and designed an operative procedure called TOMAX (TO MAX-imize sensation, sexuality and quality of life) to achieve this. Because of the high spinal entry level (L1) of the ilioinguinal nerve, we were able to use this nerve as a neurological-bypass to restore penile sensation in three low-lesion SB patients.[8] The sensory information from the glans was re-routed via the DNP and ilioinguinal nerve to the sensory cortex. Our first three patients claimed that their penis became more integrated in their body image; two found masturbation more meaningful and one became more sexually active. These promising results justified this study to test our hypothesis and investigate the outcome of the TOMAX procedure in 30 patients with a low spinal lesion.

Materials and Methods

Patient selection and procedure

With Ethics Committee permission, we selected 30 SL patients with no penile but normal groin sensation. They gave written consent, were assessed as psychologically stable, and had had no negative sexual experiences. We used our operative procedure called TOMAX[8], in which the sensory ilioinguinal nerve was cut distally in the groin, and joined by microneurorraphy to the divided DNP at the base of the penis. All interventions were performed by one plastic-surgeon (M.O.). The patients were evaluated pre-operatively and twice post-operatively, after a median time of 6 (5-10) months and 15 (11-24) months, when no further sensory improvement was expected.

Sensibility testing

The right and left halves of the shaft and glans of the penis and both groins were subdivided into three regions for testing. We used neurological sensory tests for touch (pointed vs. blunt stimuli) and temperature stimuli[9, 10] (at 37°C and 4°C) to determine what sensation was present. The patient was blindfolded and each region was stimulated three times at random intervals. If all the stimuli were correctly experienced all three times, we concluded they had sensation.

Quantitative fine-touch sensitivity was determined using Semmes-Weinstein monofilaments (North Coast Medical Supply Morgan Hill, CA, USA).[9, 11, 12] The monofilaments of ascending intensity (2·83–4·74, corresponding target force 0·07–6 g) were applied perpendicular to the skin of the groin and glans for about 1·5 seconds, with the threshold being the smallest stimulus identified correctly. The most sensitive region was taken to represent the amount of fine-touch sensibility for the groin and glans. Sensibility testing was repeated post-operatively. Apart from the presence of sensation, we noted where the stimulus on the glans was actually experienced: in the groin, penile shaft or on the glans itself.

Bulbocavernosus reflex

To preserve reflex erections, we decided not to operate bilaterally but to keep one DNP intact. We determined if the right or left DNP still played a role in erectile function, by studying the integrity of the reflex arc S2–S4 bilaterally using needle EMG-bulbocavernosus-reflex (BCR) measurements.[13] In this reflex the perineal bulbocavernosus muscle contracts to DNP stimulation. If the BCR was 'bilaterally positive or negative', we could operate on either side, but if it was 'unilaterally positive', we operated on the contralateral negative side.

Psychological functioning and sexuality

Psychological functioning and sexuality were measured by a clinical psychologist trained in sexology, using the Hospital Depression and Anxiety Scale (HADS)[14] questionnaire to determine the patients' level of distress, and the Symptom Check list-90-R (SCL90-R)[15] to measure psychoneuroticism. We used the Groninger Arousability Scale (GAS)[16] to assess their ability to experience the stages of the sexual response cycle. The psychologist also used a semi-structured interview to assess sexuality and sexual satisfaction.

The plastic-surgeon interviewed the patients to obtain a clinical perspective on their sexual- and genital functioning, and urine continence management.

Statistical analysis

Categorical data are presented as 'n' and were tested using Fisher's exact test (using SISA for more than two scoring categories, http://www.quantitativeskills.com/sisa) or McNemar test for unpaired or paired comparisons, respectively. Continuous data are presented as 'median (min-max)' and were tested using the Mann-Whitney U test, or the Wilcoxon signed ranks test for unpaired or paired comparisons, respectively. All analyses were performed two-tailed with alpha = 0·05 as significance level, using PASW version 18 (SPSS Inc., Chicago, IL, USA), unless stated otherwise.

Results

Patient characteristics

From 2001 to 2009 we operated on 30 SL patients. The ilioinguinal nerve could not be used in three SCI patients (median age 41(range 21–55 yrs), level of lesion L2 (L1–L5), median time since injury 5 years (range 5-12 yrs)): it was absent bilaterally in two patients, and both nerves were severely damaged in another patient. The other 27 patients were successfully operated on and followed-up (18 SB, median age 18.5 years (range 13–40 yrs), level of lesion L4 (L2–S1), and 9 SCI patients, median age 30 years (21–42 yrs), level of lesion L2 (T12–L4), median time since injury 5 years (range 2–15 yrs)). Based on the BCR measurements, we operated on16 left- and 11 right sides.

Sensation in glans penis

In many patients the first sign of unilateral penile sensation was being aware of the 'cold' urine-catheter being introduced into the urethra after 2–4 months. This was followed by an electrical/hypersensitive-, and later a tingling, sensation of the glans, experienced as if the *'groin'* was being touched. This glans penis sensation then changed into a non-painful, normalized sensation, which *'stayed in the groin'* or transformed to actual *'glans'* sensations experienced at the glans itself. No or only a little sensation was developed at the penile shaft. This resulted in unilateral glans penis sensation at the second post-operative visit in 24/30 (80%) of the patients, which was experienced as *'groin'* in 13/24 (54%) and as '*glans'* in 11/24 (46%). **Figure 1** shows the development of sensation with time.

Semmes-Weinstein

Reliable and reproducible Semmes-Weinstein monofilament glans- and groin sensory tests were performed in 13 and 15 patients, respectively. Post-operative glans sensation at the second visit increased from absence to having sensations in the range of 0·4–6 g (median 1 g) (**Figure 2a**). Donor groin sensibility was diminished in most patients compared to the pre-operative situation (**Figure 2b**), but none of them missed the groin sensation or experienced long-term discomfort or pain.

Sensory changes affecting management of urine continence

Of patients using self-intermittent catheterization, 14/22 felt a non-painful, cold sensation in the urethra when the catheter was introduced. Two patients noticed that their condom catheter/diaper became wet, while four could actually feel urine passing through the urethra. Two patients could partially empty their bladder.

Changes in mechanism of erection/ejaculations

All patients retained their pre-operative ability to have an erection and ejaculations. In five patients the mechanism of erection changed from a psychogenic-only pathway into a combined psychogenic-'reflex' pathway after the procedure (p=0·063) (**Table 1**). This change was seen significantly more in patients who developed actual '*glans*' sensations (p=0·036) (**Table 2**).

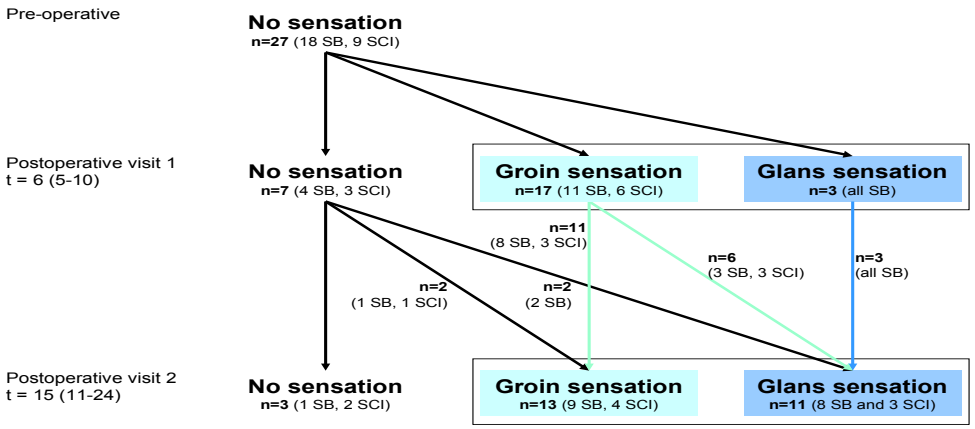

Figure 1 Development of sensation: SB, spina bifida; SCI, spinal cord injury; t, time in months (median with min-max). **Groin sensation:** touching the glans was experienced "as if the groin" was being touched **Glans sensation:** touching the glans was experienced "as if the glans itself" was being touched

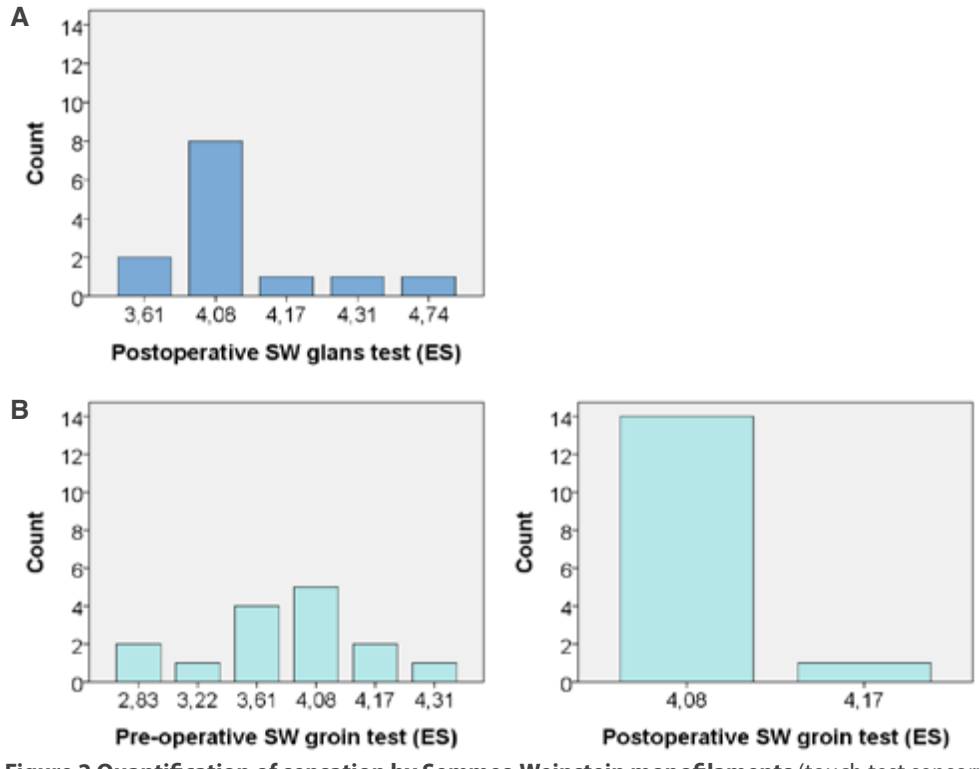

Figure 2 Quantification of sensation by Semmes-Weinstein monofilaments (touch test sensory evaluators) **2A.** Distribution of postoperative SW glans sensory test results at 2nd visit (n=13). **2B.** Distributions of pre-operative (n=15) and postoperative at 2nd visit (n=15) SW groin sensory tests. P = 0.135, by Wilcoxon signed ranks test.

ES, evaluator size; SW, Semmes-Weinstein SW evaluator size used (target force in g): 2.83 (0.07); 3.22 (0.16); 3.61 (0.4); 3.84 (0.6); 4.08 (1); 4.17 (1.4); 4.31 (2); 4.56 (4); 4.74 (6). Evaluator size is inversely related to the amount of sensation.

Psychological/sexological assessment

Post-operative psychosexual evaluations were performed in 19/27 patients. Of the eight who no longer participated, three developed no sensation, while four had tactile sensations but without real gain, and one developed erogenous sensations with similar results to those described below.

Psychological functioning: Pre-operatively, these 19 patients reported no significant distress or psychopathology (mean HADS-A score = 4·06; mean HADS-D score = 2·78; mean SCL-90-R score = 117), with scores comparable to the general population.[15, 17] After surgery, all the mean scores were even lower, but the changes were not significant (mean HADS-A = 2·8; mean HADS-D = 2·5; mean SCL-90-R = 111·8).

Sexuality: In general, all the patients were happy to have sensations instead of

being numb. Awareness of their penis contributed to their body image and they felt more complete (**Table 1**). Twelve patients were more strongly aroused and masturbated more frequently, while five patients started masturbating for the first time post-operatively. During masturbation patients reported a significant increase in stiffness (p=0·008) and satisfaction (p=0·016) with their erections. For eight patients it was easier to achieve an erection and orgasm while masturbating.

Many patients became more sexually active with a partner (frequency p=0·002 and with more satisfaction p=0·039). Three experienced orgasmic feelings for the first time. Eight patients felt introducing the penis into the vagina, which was new for them (p=0·008). However, one patient reported a decrease in some situations; the new sensations did not meet his high expectations.

The semi-structured interview led to three items measuring 'satisfaction with sexuality', which showed increased satisfaction with their sex life in general (p=0·004). (Cronbach's alpha for the 'satisfaction with sex' scale was 0·78 pre-operation and 0·85 post-operation.) The 19 patients also scored significantly higher on the GAS (p=0.022) after surgery, indicating better sexual functioning (see **Table 1**).

On comparing patients whose sensations matured to actual '*glans*' sensations to those whose sensations '*stayed in the groin*', we noted that the first group is more easily aroused (p=0·013), masturbate more frequently (p=0·013), and is more satisfied with their sexuality (**Table 2**).

Discussion

Using a new nerve re-routing procedure (TOMAX), we were able to restore unilateral glans penis sensation in 24/30 spinal lesion patients.

Sensation was restored on the operated side of the glans-penis only, due the unilateral DNP's anatomy.[18] The ilioinguinal nerve has a good cross-sectional calibre-match with the DNP and the distal part of the DNP functions as a conduit for in-growing axons of the ilioinguinal nerve. This axonal growth resulted in new penile sensations which developed in a sequence similar to that seen after traumatic nerve repair. The average amount of glans sensation obtained for 13 patients was 1·4±1·47 g, which was less than the pre-operative donor groin sensation (0·78±0·58 g) and the glans sensation in two healthy populations (0·96±0·15 g[12] and 0·83±1·00 g[9]). The differences are likely due to axonal loss at the nerve repair site and misdirection during re-growth.[19]

Table 1. Comparison of pre-operative and post-operative results

	Pre-operative	Post-operative (visit 2)	P-value
Data by clinician (n=27)			
Time from operation (months)		15 (11-24)	NA
Glans sensory test			
Sensation (no/yes)	27/0	3/24	NA
Sensation: yes			
- Localisation of sensation (groin/glans)	NA	13/11	NA
Penile function			
Erection (no/yes)	1/26	1/26	1.000
Erection: yes			
- Origin of erection (psychogenic/reflex)	21/5	16/10	0.063
Ejaculation (no/yes)	4/23	4/23	1.000
Partner			
Sexual partner (no/yes)	18/9	13/14	0.063
Sexual partner: yes			
- Introduction in vagina felt (no/yes)	9/0	6/8	NA
Data by psychologist (n=19)			
Arousal			
Strength of arousal (d/nc/i)		0/7/12	NA
Erection during arousal (d/nc/i)		1/18/0	NA
Masturbation			
Masturbation (no/yes)	7/12	2/17	0.125
Masturbation: yes			
- Orgasm (no/yes)	1/11	3/14	1.000
Masturbation frequency a month (d/nc/i)		0/7/12	NA
Ease of erection (d/nc/i)		0/11/8	NA
Ease of achieving orgasm (d/nc/i)		1/10/8	NA
Sensation of orgasm (d/nc/i)		1/10/8	NA
Partner			
Sexual partner (no/yes)	12/7	7/12	0.063
Intercourse (frequency a month)	0 (0-12)	2 (0-70)	**0.002**
Satisfaction (VAS score)	8 (6-9)	9 (4-10)	**0.039**
Stiffness erection			
Stiffness erection (VAS)	8 (1-10)	9 (4-10)	**0.008**
Satisfaction with sexuality			
Satisfaction with erection during masturbation (VAS)	6.5 (0-10)	8 (0-10)	**0.016**
Satisfaction with sexual function (VAS)	6 (1-9)	8 (2-10)	0.123
Satisfaction with sexual life (VAS)	4.5 (1-8)	6.5 (1-10)	**0.002**
Satisfaction sexual life in general (sum of the three VAS scores above)	17 (3-26)	24 (3-29)	**0.004**
Overall sexual functioning (total GAS score)	37 (28-50)	33 (24-46)	**0.022**

Groin, "groin sensation": touching the glans is experienced "as if the groin" was being touched;
Glans, "glans sensation": touching the glans is experienced "as if the glans itself" was being touched.
d, decreased; nc, no change; i, increased.
Psychogenic, psychogenic pathway; reflex, combined psychogenic and reflex pathway.
VAS, Visual Analogue Scale (0-10). GAS, Groninger Arousability Scale. NA, not applicable.
Bold values represent those that are statistically significant

Patients experienced sensory changes from *'groin'* to *'glans'* with development of 'pleasurable sensations'. Patients who had '*glans*' sensations were more likely to gain erogenous benefits than those with sensations '*in the groin*'.

These sensory changes could be attributed to brain plasticity. The human brain can adapt to new peripheral input but this depends on both the pattern and frequency of use.[20] This might explain why the sexually active patients all developed glans sensations and beneficial erogenous sensations. Their activities can be seen as sensory education programs in which visualization and motivation play a major role.[21, 22] Although age is the most important factor in predicting sensory and functional recovery,[19, 21, 22] we found no differences related to age nor the origin (SB or SCI) and level of the spinal lesion.

In four young spina bifida patients (13 & 14yrs) we could not rule out that some post-operative changes might also be related to their increasing sexual awareness in puberty. However, several spina bifida patients advised us that nerve transposition surgery should be performed before puberty to ensure the new sensations are incorporated and accepted as normal before sexual activity starts. It might also contribute to a more effective sensory re-education of the brain and make erogenous-like sensations even more likely. [22, 23]

Psychologically, the penis became a more real part of the body for most patients. Even the non-painful, cold sensation while introducing a catheter contributed to the sense of being 'complete' and less handicapped. This is important, since most SL patients use self-catheterization. Some patients became aware of urine passing through the urethra, which is hygienically and socially important for them.

Patients had more satisfaction with their erections during masturbation. The ability to have erections depends on preserving the psychogenic and/or reflex pathways of erectile function. Five 'psychogenic-only' patients reported postoperatively that direct stimulation of the penis could induce erections and that these could be maintained more easily. The neurological bypass did not reconstruct the reflex arc S2–S4, so they are more likely a *'sensory feedback-enhanced (psychogenic) erection*' rather than a 'real' reflex erection, but are still beneficial because maintaining erections is a recognised problem in SL patients.[24]

With patients being more strongly aroused and more conscious of their new feelings, they masturbated more frequently and had more pleasurable sensations and sometimes orgasms. Five patients, including two young spina bifida patients,

Table 2. Comparison of patients with "glans sensation" and "groin sensation", at second visit

	Groin sensation	Glans sensation	P-value
Data by clinician	(n=13)	(n=11)	
Condition (spina bifida/spinal cord injury)	9/4	8/3	1.000
Level of lesion	L3 (T12-S1)	L4 (T12-L5)	0.976
Time since operations (months)	15 (12-22)	13 (11-24)	0.220
Penile function			
Origin of erection (psychogenic/reflex)	10/2 (n=12)	4/7	**0.036**
Data by psychologist	(n= 8)	(n=10)	
Arousal			
Strength of arousal (d/nc/i)*	0/6/2	0/1/9	**0.013**
Erection during arousal (d/nc/i)*	1/7/0	0/10/0	0.444
Masturbation			
Masturbation (no/yes)	2/6	0/10	0.183
Masturbation frequency a month (d/nc/i)*	0/6/2	0/1/9	**0.013**
Ease of erection (d/nc/i)*	0/7/1	0/4/6	0.066
Ease of orgasm (d/nc/i)*	0/6/2	1/4/5	0.342
Sensation of orgasm (d/nc/i)*	0/6/2	1/3/6	0.153
Stiffness erection			
Stiffness erection (VAS)	7.5 (4-10)	9 (8-10)	0.067
Satisfaction with sexuality			
Satisfaction with erection during masturbation (VAS)	8 (0-10)	8 (7-10)	0.294
Satisfaction with sexual function (VAS)	5 (2-9)	8 (7-10)	**0.027**
Satisfaction with sexual life (VAS)	4.5 (1-9)	8 (3-10)	0.052
Satisfaction sexual life in general (sum of the three scores above)	17 (3-27)	24 (19-29)	0.055
Overall sexual functioning (GAS score)	36 (27-46)	31.50 (24-41)	0.196

*, compared to pre-operative.
Groin, "groin sensation": touching the glans is experienced "as if the groin" was being touched;
Glans, "glans sensation": touching the glans is experienced "as if the glans itself" was being touched.
Psych, psychogenic pathway; reflex, combined psychogenic and reflex pathway.
d, decreased; nc, no change; i, increased.
VAS, Visual Analogue Scale (0-10). GAS, Groninger Arousability Scale.
Bold values represent those that are statistically significant

masturbated for the first time ever, while three patients experienced their first orgasm.

Patients were more confident in their sexual activities, aware of their partner touching the penis and able to appreciate the moment of intromission. This led to more frequent and more satisfying sexual activities, and a more open and meaningful sexual relationship.

Four SCI patients had had sexual experiences before their trauma; three of them appreciated their improved situation. One very sexually active SCI patient

was pleased with the results and experienced satisfaction comparable to his pre-trauma period. At his request, we are planning a similar procedure on the contralateral side to introduce sensation to the entire glans.

Some limitations to this study: 1) the absence of a control group; 2) the use of questionnaires/interviews to measure psychological function although performed by an independent psychologist; 3) the sensory tests were only performed on the flaccid penis, so the outcomes might be 'underscored': several patients reported more sensitivity of the glans in erection at home and some experienced '*glans*' instead of '*groin*' sensations.

We have started to perform this procedure on patients with similar pathology due to a persistent cauda equine syndrome and are now transposing the nerves bilaterally if BCR measurements are negative on both sides. In cases of positive BCR, end-to-side neurotization unilaterally or bilaterally could also be considered.

In the future, we plan to operate on SB patients before the age of puberty. Post-operative sensory education programmes will be developed to make achieving erogenous sensation even more feasible.

The estimated incidence of SB is 1**.**9 per 10,000 new-borns[25] and of SCI is 40 per million in the USA alone,[26] so the new TOMAX procedure can be used to restore erogenous penile sensation and improve the quality of life and sexual health in large numbers of patients. The procedure is straightforward and can be performed by any surgeon trained in peripheral nerve- and microsurgery. Recently we introduced the technique in the USA resulting in the first two clinical cases outside the Netherlands.[27]

In conclusion, we show that restoring penile sensation can enhance sexual health and satisfaction in most male patients with a low spinal lesion. They felt more complete and less handicapped, discovered sexual activities for the first time or experienced them as more exciting and pleasurable. The development of a new 'reflex pathway' in patients with solely psychogenic erections helped them gain and maintain more rigid erections. Improvements in managing urine incontinence helped increase personal hygiene and independence, and therefore social participation. The TOMAX procedure should be offered to any spinal lesion patient with good sensation in the groin but no sensation in the glans, and it should become standard treatment for many patients in the future.

References

1) Sandler AD, Worley G, Leroy EC et al. Sexual function and erection capability among young men with spina bifida. *Dev Med Child Neurol* 1996; 38: 823.

2) Palmer JS, Kaplan WE, Firlit CF. Erectile dysfunction in spina bifida is treatable. *Lancet* 1999; 354: 125.

3) Dik P, Van Gool JD, De Jong TP. Urinary continence and erectile function after bladder neck sling suspension in male patients with spinal dysraphism. *BJU Int* 1999; 83: 971.

4) Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. *J Neurotrauma* 2004; 21: 1371.

5) McDonald JW, Sadowsky C. Spinal-cord injury. *Lancet* 2002; 359: 417-25.

6) Lassmann J, Garibay Gonzalez F, Melchionni JB et al. Sexual function in adult patients with spina bifida and its impact on quality of life. *J Urol* 2007; 178: 1611.

7) Verhoef M, Barf HA, Vroege JA, et al. Sex education, relationships, and sexuality in young adults with spina bifida. *Arch Phys Med Rehabil* 2005; 86: 979.

8) Overgoor ML, Kon M, Cohen-Kettenis PT et al. Neurological bypass for sensory innervation of the penis in patients with spina bifida. *J Urol* 2006; 176: 1086; discussion 1090.

9 Bleustein CB, Eckholdt H, Arezzo JC et al. Quantitative somatosensory testing of the penis: optimizing the clinical neurological examination. *J Urol* 2003; 169: 2266.

10) Yarnitsky D, Sprecher E, Vardi Y. Penile thermal sensation. *J Urol* 1996; 156: 391.

11) Bell-Krotoski J, Tomancik E. The repeatability of testing with Semmes-Weinstein monofilaments. *J Hand Surg Am* 1987; 12: 155.

12) Sorrells ML, Snyder JL, Reiss MD, et al. Fine-touch pressure thresholds in the adult penis. *BJU Int* 2007; 99: 864.

13) Amarenco G, Kerdraon J. Clinical value of ipsi- and contralateral sacral reflex latency measurement: a normative data study in man. *Neurourol Urodyn* 2000; 19: 565.

14) Bjelland I, Dahl AA, Haug TT et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; 52: 69.

15) Arrindell WA, Ettema JHM. SCL-90;Manual for a Multidimensional Indicator of Psychopathology. Lisse, The Netherlands: Swets Test Publishers; 2003.

16) Van de Wiel HBM, Weijmar Schultz WCM, Molenaar IW et al. Zelfbeoordeling van genitale sensaties en lichaamsperceptie bij vrouwen; de constructie van twee vragenlijsten. *Tijdschr Seksuol* 1995; 19: 119 [in Dutch with English abstract].

17) Crawford JR, Henry JD, Crombie C et al. Normative data for the HADS from a large non-clinical sample. *Br J Clin Psychol* 2001; 40: 429.

18) Yang CC, Bradley WE. Neuroanatomy of the penile portion of the human dorsal nerve of the penis. *Br J Urol* 1998; 82: 109.

19) Lundborg G, Rosen B. Sensory relearning after nerve repair. *Lancet* 2001; 358: 809.

20) McAllister RM, Calder JS. Paradoxical clinical consequences of peripheral nerve injury: a review of anatomical, neurophysiological and psychological mechanisms. *Br J Plast Surg* 1995; 48: 384.

21) Lundborg G, Rosen B. Hand function after nerve repair. *Acta Physiol (Oxf)* 2007; 189: 207.

22) Dellon AL. Somatosensory Testing & Rehabilitation. The American Occupational Therapy Association, Inc. 1997 Bethseda.

23) Lundborg G. Brain plasticity and hand surgery: an overview. *J Hand Surg Br* 2000; 25: 242.

24) Game X, Moscovici J, Game L et al. Evaluation of sexual function in young men with spina bifida and myelomeningocele using the International Index of Erectile Function. *Urology* 2006; 67: 566.

25) Centers for Disease Control and Prevention (CDC). Racial/ethnic differences in the birth prevalence of spina bifida - United States, 1995-2005. *MMWR Morb Mortal Wkly Rep* 2009; 57: 1409.
26) Jackson AB, Dijkers M, Devivo MJ, et al. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. *Arch Phys Med Rehabil* 2004; 85: 1740.
27) Jacobs M, Avellino AM, Shurtleff BD, et al. Ilioinguinal to penile neuro-neurorraphy in the myelomeningocele patient: presentation of 2 cases. *Podium presentation, Americal Urology Association Symposium*, May 19, 2012, Atlanta, Georgia, USA.

Chapter 4

Remaining signs of dorsal nerve of penis function in low spinal lesion patients in relation to a bilateral TOMAX-procedure

Overgoor ML
Braakhekke JP
Kon M
de Jong TP

Restoring penis sensation in patients with low spinal cord lesions: The role of the remaining function of the dorsal nerve in a unilateral or bilateral TOMAX procedure. *Neurourol Urodyn*. 2014; Jan 30. doi 10.1002/nau.22566

Abstract

Aims

The recently developed TOMAX-procedure restores unilateral genital sensation, improving sexual health in men with a low spinal lesion (LSL). It connects *one* dorsal nerve of the penis (DNP) to the intact ipsilateral ilioinguinal nerve. We proposed *bilateral* neurotization for full sensation of the glans but this entails cutting both DNPs, risking patients' erection/ejaculation ability.

The objective was to select patients for a bilateral TOMAX-procedure by measuring remaining DNP function and perform the first bilateral cases.

Methods

In 30 LSL patients with no penile- but normal groin sensation selected for a unilateral TOMAX-procedure the integrity of the sacral-reflex-arc and DNP function was tested pre-operatively using bilateral needle EMG-bulbocavernosus reflex measurements (BCR) and an interview about reflex erections (RE) ability.

Results

In 13 spina bifida- and 17 spinal cord injury patients [median age 29.5 years (range 13-59 yrs), spinal lesion T12(incomplete) to sacral], seven (23%) patients reported RE, four (57%) with intact BCR, and of nine (30%) patients with intact BCR, four reported RE (44%).

Conclusions

Even patients with a LSL and no penile sensation can have signs of remaining DNP function, but cutting both DNPs to restore full glans sensation in a bilateral TOMAX-procedure might interfere with their RE/ejaculation. To avoid this risk, we propose a selecting-protocol for a unilateral- or bilateral procedure using RE and BCR measurements.

Using this protocol, three patients were bilaterally operated with promising preliminary results. Full sensation of the glans could lead to further improvement in sexual function.

Introduction

We recently presented a new peripheral nerve re-routing procedure [1-3] to restore tactile and erogenous penile sensation in patients with low (<L1) spina bifida (SB) or spinal cord lesions (SCI). This so-called TOMAX-procedure (TO MAXimize sensation, sexuality and quality of life) involves cutting the functional sensory ilioinguinal nerve distally in the groin and joining it by microneurorraphy to the divided dorsal nerve of the penis (DNP) on one side. **(Figure 1)** Because of the high spinal entry level (L1) of the ilioinguinal nerve, excellent penile sensation was restored by this neurological-bypass in 24 out of 30 low spinal lesion (SL) patients with intact L1 dermatome.[1]

The unilateral glans-sensations were initially felt in the groin area but transferred to the glans penis-itself in about 50% of patients. This act of brain plasticity changed the initial tactile sensations even further into erogenous sensations in majority of patients, enhancing the quality of their sexual functioning and satisfaction.[1,3]

However, we foresaw possible problems in losing erectile and ejaculation[4] ability since the surgery involves dividing the DNP. Besides transmitting penile sensory impulses to the brain, both DNPs play a crucial role in reflex erections (RE)[5,6] and (vibratory) ejaculations[4] through the sacral (S2-S4) reflex arc. The

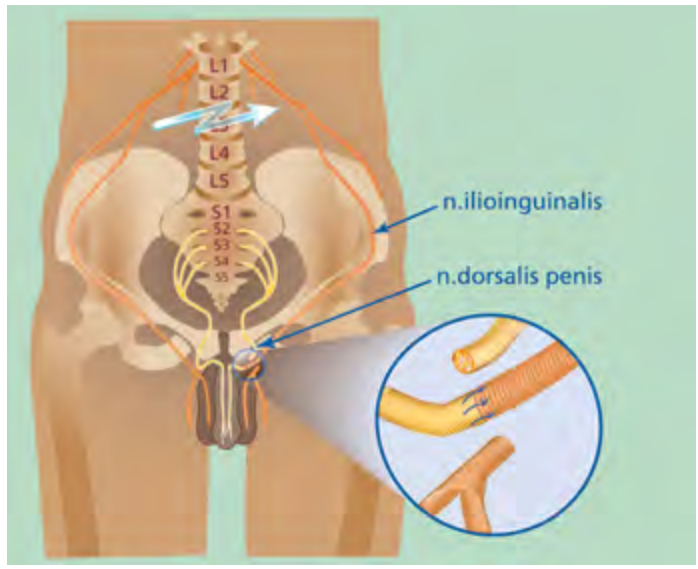

Figure 1. Schematic representation of the TOMAX-procedure to restore penile sensation in low spinal lesion patients: the sensory ilioinguinal nerve (L1) is cut distally and joined by microneurorraphy to the ipsilateral divided dorsal nerve of the penis (S2-4) at the base of the penis.

absence of penile sensation in low-lesion patients does not necessarily affect the sacral erectile reflex pathway.[7-10]

So far, we have only performed unilateral nerve transpositions, in order to be certain of retaining erection ability. Cutting only one of the DNPs still leaves the contralateral hemi-reflex arc intact to "protect" RE and ejaculations, if present. Indeed, such functions remained intact in all our patients following the unilateral TOMAX procedure.[1,2]

Our caution meant that sensations were developed only on one side of the glans penis (half the glans). Since our patients were happy with their new sensations, we wondered (and patients asked) if a *bilateral* procedure could be done safely, providing twice as many neurotising axons, with a chance of full glans sensation and even more erogenous sensations.

Selection criteria for the performance of a safe bilateral TOMAX procedure should focus on the signs of remaining DNP function. To investigate this, we used the bulbocavernosus reflex (BCR) combined with the preserved ability to have RE, since these reflect the integrity of the S2-4 reflex arc. We collected pre-operative data on RE and BCR from 30 patients already selected for a unilateral TOMAX procedure.

The aims of our prospective study were:

(1) to see how often signs of DNP function were still present,

(2) to see if RE ability or BCR could determine whether a unilateral or bilateral procedure should be performed,

(3) to design a protocol to help decide on unilateral or bilateral surgery and

(4) to operate patients bilaterally using this protocol.

Materials and Methods

Patients

With Ethics Committee permission and patients' written consent, 30 low SL patients with no penile but normal groin sensation were selected for the unilateral TOMAX procedure (13 SB patients, 17 with a SCI).

Erections/ejaculations

The plastic surgeon (M.O.) interviewed patients about their erections and ejaculations. Attention was paid to the presence of reflex erections (RE) (elicited by

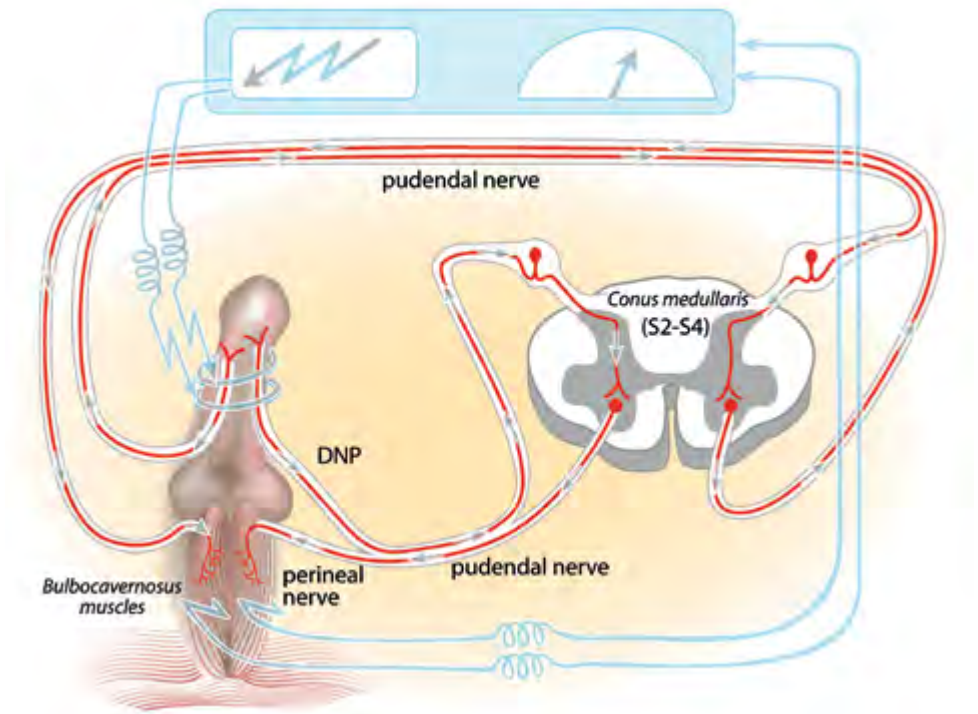

Figure 2. Diagrammatic representation of the bulbocavernosus reflex (BCR). In this reflex, the bulbocavernosus muscles contract on stimulating the dorsal nerve of the penis (DNP). It has an ipsilateral distribution.[12, 18]

direct penile stimulation) and/or psychogenic erections (PE) (resulting from any extrinsic (visual/auditory/chemosensory) stimuli or elicited by erotic thoughts/ fantasy/memory).[7,11]

Bulbocavernosus reflex (BCR)

We determined the integrity of the S2-4 reflex arc in our patients bilaterally using needle EMG-BCR measurements[12] while they were under general anaesthesia (no muscle relaxant used) and preceding the TOMAX surgical procedure. In this reflex, the perineal bulbocavernosus muscle contracts on stimulating the DNP. **(Figure 2)** Using two ring-electrodes around the shaft of the penis, both DNPs were stimulated simultaneously. Concentric needle electrodes were placed in the left and right bulbocavernosus muscles, to register left and right muscular responses separately. A ground electrode was placed on one thigh. Each stimulus consisted of a train of ten pulses (pulse duration 0.1 ms), delivered with a frequency of 1-2 Hz and intensity increasing to 50 mA (or three times the sensory threshold).

If no BCR was found, the stimulation was repeated up to three times, after replacing the needles. Unilateral or bilateral presence or absence of the reflex was registered.

Statistical analysis

Descriptive statistical analysis was used.

Results

Table 1a shows data on age, level of lesion, BCR, RE; **Table 1b** shows the association of BCR with RE for the combined SB and SCI group. The median age of the 30 patients was 29.5 years (range 13-59 yrs), with spinal lesions ranging from T12 (incomplete) to low sacral defined as the last intact segment of the spinal cord and determined by clinical neurological investigation and MRI.

According to patients' self-reporting, all had PE, seven (23%) had RE, of which four (57%) had a positive bilateral BCR, i.e. the positive predictive value (PPV) and negative predictive value (NPV) of RE testing for BCR was 57% and 78% respectively. There were nine (30%) patients with a positive BCR, of which four (44%) had RE, i.e. the PPV and NPV of BCR testing for RE was 44% and 86% respectively.

Discussion

We have shown that even patients with a low spinal lesion (including sacral involvement) can have signs of remaining DNP function (presence of RE and/or intact BCR). This means that a bilateral TOMAX procedure (involving cutting both DNPs) might be risky in some cases. The ability to have erections depends on preserving the psychogenic and/or reflex pathways of erectile function. PE is regulated by a centrally connected, sacral erection centre or, if the sacral region is damaged/disconnected, by a sympathetic spinal centre at T10–L2.[7] **(Figure 3)** In RE, however, the sacral region and DNP/pudendal nerves are mainly involved. Its mechanism can be described through two different sacral-reflexes **(Figure 3)**: (1) The somatic-autonomic *pudendo-cavernosal reflex loop* in which the DNP and perineal nerves send afferent sensory information to the lumbo-sacral dorsal horn. Together with supraspinal information, the efferent cavernosal nerves initiate arterial vasodilatation in the erectile tissues of the penis leading to tumescence. (2) The somatic *bulbocavernosus reflex loop* involves the pudendal

Table 1a. BCR measurements and self-reported reflex erectile mechanisms in Spina Bifida and Spinal Cord Injury patients for TOMAX procedure

Patient	Age	SB/SCI	Level	BCR	RE	RE post-TOMAX
1	18	SB	L2-L5	-/-	-	-
2	26	SB	L3	+/-	-	-
3	35	SB	L3	-/-	-	-
	29	SB	L3-(L4?)	-/-	-	-
5	14	SB	L3-L4	-/-	-	-
6	32	SB	L4	+/+	+	+
7	19	SB	L4	-/-	+	+
8	14	SB	L4-L5	+/-	-	-
9	17	SB	L5-S1	-/-	-	-
10	13	SB	L5-S1	-/-	-	-
11	21	SB	L5-S2	-/-	-	-
12	40	SB	L5-S2	-/-	-	-
13	21	SB	Sacral	+/+	+	+
14	29	SCI	T12 incompl	+/+	-	-
15	42	SCI	T12 incompl	-/-	-	-
16	36	SCI	T12/L1 incompl	-/-	-	-
17	30	SCI	T12-L1	-/-	+	+
18	30	SCI	L1 incompl	-/-	-	-
19	55	SCI	L1/L2	-/-	-	-
20	26	SCI	L1-L3	+/+	+	+
21	41	SCI	L1-L4	-/-	-	-
22	36	SCI	L2	+/+	-	-
23	29	SCI	L2	-/-	-	-
24	21	SCI	L2-L3	-/-	-	-
25	41	SCI	L3	+/+	+	?[1]
26	34	SCI	L3-L4	+/-	-	-
27	46	SCI	L4/L5	-/-	-	-
28	49	SCI	L4/L5	-/-	-	-
29	59	SCI	L4/L5	-/-	+	?[2]
30	55	SCI	L5	-/-	-	-

Table 1b. Association between BCR and self-reported RE in Spina Bifida and Spinal Cord Injury patients selected for TOMAX procedure

	RE +	RE-	Total
BCR +*	4	5	9
BCR -	3	18	21
Total	7	23	30

SB, spina bifida; SCI, spinal cord injury; BCR, bulbocavernosus reflex; RE, reflex erection; -, absent; +, present; -/-, BCR bilaterally absent; +/-, BCR unilaterally intact; +/+, BCR bilaterally intact; ?[1] Not yet operated; ?[2] operation failed due to absence ilioinguinal nerve; , sacral involvement. BCR+*, involves both unilateral (BCR+/-) and bilateral (BCR +/+)

nerve. The DNP and perineal nerves send afferent sensory information to S2-4, while efferent motor neurons travel via the pudendal nerve to the ischio- and bulbocavernosus muscles as well as to the external urethral and anal sphincters. A rhythmic contraction of the perineal musculature produces penile rigidity by enhancing pressures to supra-systolic levels.[13]

These reflexes imply that the level of spinal lesion influences erectile function in different ways **(Figure 4):** in high lesions (above T10-L2), PE will be lost but RE remains intact; in lesions between the thoraco-lumbar- and sacral centres both should be preserved; and low lesions in the sacral area result in losing RE but an intact PE.[7] This would be the case in 'pure' lesions, but in reality, spinal lesions range from incomplete to involving single/multiple levels.

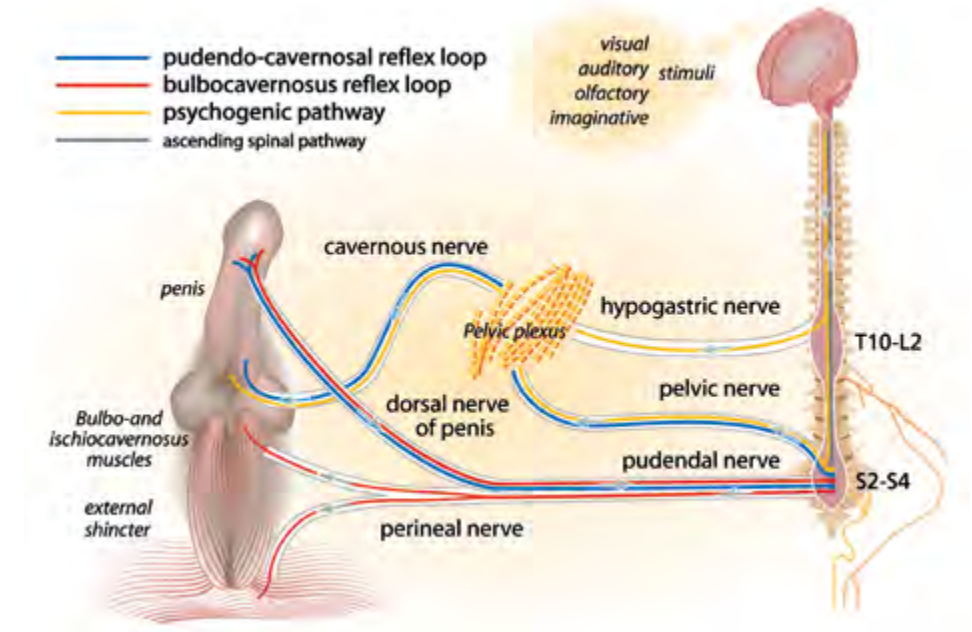

Figure 3. Diagrammatic representation of three different pathways controlling penile erection in a non-pathological situation[13,24]: 1) *Psychogenic erection* (PE) (orange line) is regulated by a centrally connected thoracolumbar (T10–L2) and sacral (S2-4) erection centre. Visual, auditory, olfactory and imaginative stimuli as well as sensory input from the penis (ascending spinal pathway; (grey line) are involved in the initiation of psychogenic erections through these thoracolumbar- and sacral centres and are conducted to the penis by the pelvic and/or hypogastric nerve, pelvic plexus and cavernous nerve. 2) *Reflex erections* (RE) involve two reflex loops: -the *pudendo-cavernosal reflex loop* (blue line) initiates RE: the dorsal nerve of the penis (DNP) send afferent sensory information to the sacral erection centre S2-4 and the efferent cavernous nerves (through the the pelvic nerve/ plexus) initiate arterial vasodilatation in the erectile tissues of the penis leading to tumescence. -in the *bulbocavernosus reflex loop* (red line) the DNP send afferent sensory information from the penis to the sacral erection centre S2-4, while efferent motor neurons travel via the pudendal nerve and perineal nerves to the ischio- and bulbocavernosus muscles and external sphincter. A rhythmic contraction of the perineal musculature produces penile rigidity by enhancing pressures to supra-systolic levels.

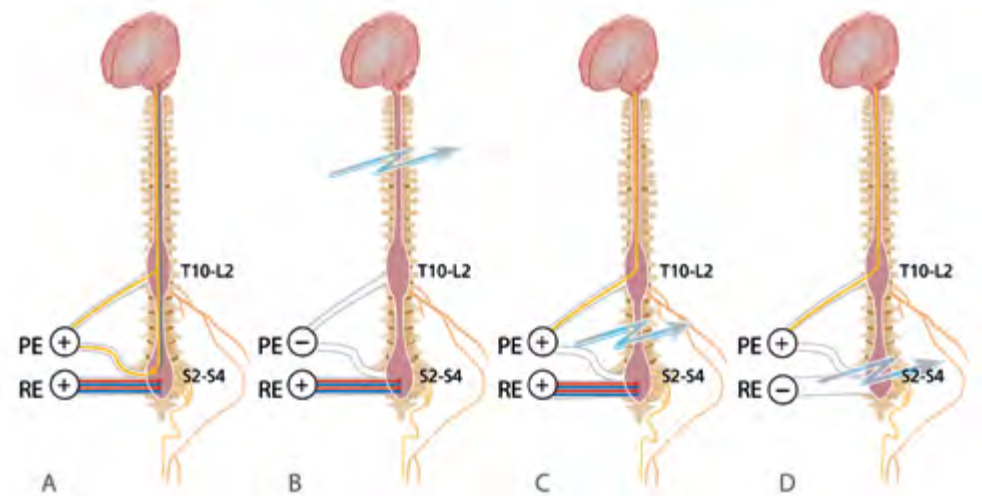

Figure 4. The influence of the spinal cord lesion level on reflex (RE)- and psychogenic (PE) erectile function: A) healthy subject; B) lesion above the thoracolumbar (T10–L2) and sacral (S2-4) erection centres; C) lesion between the thoracolumbar (T10–L2) and sacral (S2-4) erection centres; D) lesion at the level of the sacral (S2-4) erection centre. Orange line: psychogenic pathway. Blue and Red line: reflex pathway (pudendo-cavernosal and bulbocavernosus reflex loop)
(See also figure 2)

In candidates for the TOMAX procedure, good sensation of the groin (ilioinguinal nerve) implies that the "effective" lesion should be lower than L1 (intact L1 dermatome). In these cases, one might expect preserved PE with more or less no RE **(Figure 4)**, depending on the involvement of the sacral area. Studies[7,9] show a significant correlation between the presence of RE and BCR, which indicates an intact S2-4 reflex arc; they describe a mix of patients with high and low lesions. Generally, they state that high-lesion patients have both an intact RE and BCR, while low-lesion patients have no remaining RE or BCR.

We compared these studies[7,8,10] to our own after filtering out female patients[8] and patients with lesions above L1.[7] Schmid et al.[6] **(Table 2)** reported 44% (4/9) SCI patients still had a measurable BCR, while Sakakibara et al.'s study on SB patients[8] and Podnar's on SCI patients,[10] focussing on sacral level lesions, reported 21% (3/14) and 19% (10/53) with intact BCR, respectively. We found intact BCR in 30% (9/30) of our SB/SCI patients (**Table 1b**). RE was intact in 23% (7/30) of our cases compared to 56% (5/9 cases) in Schmidt et al.[7] (**Table 2)**

Accordingly, cutting the DNP in the TOMAX procedure might risk damaging the remaining S2-4 reflex arc connections in 19-56% of the cases.

On comparing our data to Schmid et al.'s **(Tables 1b and 2)**, 43% (3/7) and 20% (1/5) of the patients with reported RE had a negative BCR, i.e. these patients

did not have a measurable nerve circuit as a 'foundation' for their RE. In contrast, 55% (5/9) of our patients with measurable reflex arc (BCR+) did not have RE.

If we exclude the patients with sacral involvement in our study and Schmid et al.'s, 68% (17/25) and 83% (5/6) had lost BCR, while 76% (19/25) and 67% (4/6) had lost RE. Reversely, if we only look at sacral lesion patients, 20% (1/5) and 100% (3/3) of patients had both RE and intact BCR in these studies. This is surprising since the reflex arc S2-4 should theoretically be intact in the higher lesion patients and damaged in those with lower (sacral) lesions.

Although we found a low positive predictive value of BCR testing for RE (44%) and vice versa (57%), Schmid et al.'s study did show a higher association between BCR and RE. The differences might be due to the fact that in Schmid's study: (1) patients with sacral involvement all had incomplete lesions;(2) all patients had SCI (not SB) which means that sacral structures are more likely to be intact than in SB. These findings may warrant a different interpretation when comparing BCR only between low lesion (<L1) patients (as for the TOMAX procedure), opposed to studies comparing high (>L1) to low (<L1) lesions[7]: the low lesion group showed no reliable association between BCR and RE. But how can we explain signs of DNP function in low lesion patients?

Partial lesions?

Patients often have partial lesions with more intact nerve connections than expected from the lesion level alone. Schmid et al. described how incomplete sacral involvement can leave the BCR and RE intact.[7] Although in practice, the height of the spinal lesion is established by clinical tests and MRI, it seems that sometimes there is more intact or less damage than one would expect: complete lesions may be clinically incomplete and *vice versa*.

Unknown nerve connections?

Although the S2-4 reflex arc is well established as a basis for reflex erections through the bulbocavernosus and pudendo-cavernosal reflex loops **(Figure 3)**,[13] other mechanisms may also play a role. One study[5] reported erections in cats with a complete lesion of the lumbo-sacral spinal cord, and another found the pudendal and hypogastric genital nerve fibres to have connections with spinal levels from S1 to L2 in female mice.[14] A sacrolumbar inter-segmental reflex circuit related to DNP stimulation has also been established and may be related to the

ejaculatory process[15]. Two reports suggested the involvement of the perineal nerve in afferent input to the BCR thus not involving the DNP.[16,17] Re-routing via higher/other levels could explain the intact BCR in some sacral lesion patients or persistent RE in some patients with no BCR.

Is our method robust?

The BCR measurement used in this study is based on the fact that the BCR has an ipsilateral distribution.[12, 18] However in two elegant experimental studies on the somatic- and reflex innervation of the BC-muscle, the included drawings of the BCR-mechanisms do suggest crossed connections within the sacral conus medullaris.[16,17] Yet no substantiation can be found that actual stimulation of the DNP contracts the contralateral BC-muscle. These studies *do* suggest that the perineal nerve have sacral-medullary crossed connections since direct afferent stimulation of the perineal nerve contracts the contralateral BC-muscle. Bilateral distribution was also found in a study on the vaginocavernosus reflex in female rabbits after selective transection of the clitoral nerve[19]. It is difficult however to correlate these findings direct a cross-species/gender due to differences in anatomical arrangement of perineal muscles and nervous system organisation. Nevertheless, unilateral distribution of the BCR[12, 18], has been confirmed by stimulating both DNP's after unilateral selective anaesthetic block of one DNP[12] on which we based our BCR measurements. Future studies may be designed comparing pre- and post-op BCR-measurements in unilaterally operated TOMAX patients to gain more knowledge on BCR distribution.

Another objection to our method could be related to the stimulus protocol we used. Although our protocol is very similar to the one used in Schmid's study, stronger stimulation using longer stimuli and/or double or triple stimuli with higher intensity might elicit more reflexes not shown yet. In future patients, we plan to stimulate with stronger stimulation protocols to compare with the present outcome.

Table 2. Association between BCR and self-reported RE in male Spinal Cord Injury patients adapted from Schmid 2003[6]: only patients with lesion < T12/L

	RE +	RE-	Total
BCR +	4	0	4
BCR -	1	4	5
Total	5	4	9

BCR, bulbocavernosus reflex; RE, reflex erection; -, absent; +, present

Self-reported RE is a highly reliable tool to establish RE ability and results corresponded with clinically induced RE by vibro-stimulation in 29 spinal lesion patients.[7] We therefore assume that our numbers on RE are reliable.

Pre-operative selection protocol

We reveal that self-reported RE and BCR measurements, when used independently, do not provide strong enough evidence to confirm or rule out remaining DNP function. No significant association could be found between BCR and RE in patients with low lesions. If we consider remaining DNP function as 'intact RE and/or intact BCR', the sensitivity and specificity of the combined test is 100%. We therefore propose that both parameters should be used in the pre-operative work-up for the TOMAX procedure:

(1) Ask the patient (and his partner) if he has RE,

(2) Perform a bilateral needle EMG-BCR measurement in an outpatient setting pre-operatively.

If a patient has an RE+, a unilateral TOMAX procedure should be performed with BCR determining which side to use. If a patient has an RE-, BCR will determine whether a unilateral or bilateral procedure should be performed (**Table 3a**).

When we retrospectively applied this protocol on 30 patients who had a unilateral TOMAX procedure (we did not do bilateral procedures yet at that moment) (**Table 1**), signs of DNP function were found in 12 patients: four with both BCR+ and RE+, five with solely BCR+ (RE-) and three with solely RE+ (BCR-) (**Table 3b**). Thus, we could have offered 18 (60%) patients a bilateral procedure.

As the proposed protocol is designed for future patients, its safety on preserving RE in a unilateral procedure and the possible benefits of a bilateral procedure still have to be proven. Based on the current experience however, the following statements can be made.

Protocol preserves RE erection?

The question arises if unilateral surgery always preserves RE? In the 30 patients who had *unilateral* surgery and used in this study and also described previously,[2] the preoperative BCR measurement was still only used to decide which side to operate: if the BCR was 'bilaterally positive or negative', we could operate on either side (randomly chosen), but if the BCR was 'unilaterally positive', we operated on the contralateral negative side. Using this scheme, all five successfully operated

Table 3a. Pre-operative protocol to decide on a unilateral or bilateral TOMAX procedure

	RE +	RE-	Which side
BCR +/+	unilateral	unilateral	right or left
BCR +/-	unilateral	unilateral	the "BCR-"
BCR -/-	unilatera		right or left
BCR -/-		bilateral	right *and* left

Table 3b. Results of the protocol above (3a), applied retrospectively to 30 patients who had a unilateral TOMAX procedure

	RE +	RE-
BCR +/+	Unilateral 4	Unilateral 2
BCR +/-	Unilateral 0	Unilateral 3
BCR -/-	Unilateral 3	Bilateral 18

BCR, bulbocavernosus reflex; +/+, BCR bilaterally intact; +/-, BCR unilaterally intact; -/-, BCR bilaterally absent; RE, reflex erection; +, present; -, absent.

patients with preoperative ability to have RE (BCR +/+, n=3; BCR -/-, n=2) retained their RE ability postoperatively (**Table 1a** last column: RE post-TOMAX). Although small in numbers these results suggest that unilateral surgery using BCR measurement is safe for retaining RE.

Bilateral TOMAX-procedure

To address the proposed additional benefit of bilateral surgery, we recently operated three patients on both sides using the proposed protocol. *One* patient (SB, L3, 38 yrs, RE-, BCR -/-) was so happy with the gained sensations after unilateral TOMAX-procedure that he requested surgery on the other side as well. We performed a contralateral TOMAX-procedure three years later. He gained full "glans" sensation of the glans, reinforcing the already present erogenous sensations. A *second* patient (SB-occulta, sacral, 36 yrs, RE-, BCR-/-) was operated bilaterally and after 6 month he gained bilateral sensation, still experienced as if the groin is being touched. Recent email contact (9 month post op) revealed that the bilateral sensations were "moving into the direction of the glans" and were slowly adopted into a more erogenous context. A *third* patient (incomplete S2-3 following sacral-chordoma excision, 47 yrs, RE-, BCR-/- was operated recently (4 month ago). Results are not available yet.

Although based on only three patients we can say that a bilateral procedure is technically feasible and theoretically increases the chance of re-innervating the glans, with the possibility of full glans- and probably more erogenous sensation.

Long term follow-up with larger number of patients using the new protocol is needed to confirm preservation of RE in unilateral- and the additional benefits of bilateral surgery.

Conclusions

Even patients with a low spinal lesion and no sensation of the penis can have signs of remaining DNP function. Cutting both DNPs in the bilateral TOMAX procedure while there is still evidence that they might contribute to erection and ejaculation mechanisms is risky. We propose a protocol to select patients for a unilateral or bilateral procedure using self-reported RE combined with BCR measurements. A unilateral procedure will preserve RE and a still existing sacral reflex arc, while a bilateral operation increases the chances of (re-) innervation with the possibility of full glans sensation. Based on patients already operated on unilaterally, we expected to offer 60% of new patients a bilateral procedure. The preliminary results of the first three bilaterally operated patients are promising.

In the USA, the estimated birth-prevalence of spina bifida in 2005 was 1.9 per 10,000 per live births[20] and in 2010, 3.1 cases per 10,000 children and adolescents, aged 0 to19 years had spina bifida.[21] For Spinal Cord Injury the incidence is estimated at 40 per million in USA[22] and the prevalence at 223-755 per million worldwide.[23] This means that the TOMAX-procedure can be used to restore penile sensation in large numbers of patients with no penile but good groin sensation. Full sensation of the glans due to bilateral surgery, may enhance erogenous sensations even further, leading to better sexual function and satisfaction.

References

1) Overgoor ML, de Jong TP, Cohen-Kettenis PT et al. Increased sexual health after restored genital sensation in male patients with spina bifida or a spinal cord injury: the TOMAX procedure. J Urol 2013; 189: 626.

2) Overgoor ML, Kon M, Cohen-Kettenis PT et al. Neurological bypass for sensory innervation of the penis in patients with spina bifida. J Urol 2006; 176: 1086; discussion 1090.

3) Jacobs MA, Avellino AM, Shurtleff D et al. Reinnervating the Penis in Spina Bifida Patients in the United States: Ilioinguinal-to-dorsal-penile neurorrhaphy in two cases. J Sex Med 2013; Jul 11.doi.111/jsm.12255 [Epub ahead of print]

4) Wieder JA, Brackett NL, Lynne CM et al. Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. Urology 2000; 55: 915.

5) Giuliano F, Rampin O. Neural control of erection. Physiol Behav 2004; 83: 189.

6) Giuliano FA, Rampin O, Benoit G et al. Neural control of penile erection. Urol Clin North Am 1995; 22: 747.

7) Schmid DM, Curt A, Hauri D et al. Clinical value of combined electrophysiological and urodynamic recordings to assess sexual disorders in spinal cord injured men. Neurourol Urodyn 2003; 22: 314.

8) Sakakibara R, Hattori T, Uchiyama T et al. Uroneurological assessment of spina bifida cystica and occulta. Neurourol Urodyn 2003; 22: 328.

9) Tas I, Yagiz On A, Altay B, Ozdedeli K. Electrophysiological assessment of sexual dysfunction in spinal cord injured patients. Spinal Cord 2007; 45: 298.

10) Podnar S. Clinical and neurophysiologic testing of the penilo-cavernosus reflex. Neurourol Urodyn 2008; 27: 399.

11) Sachs BD. Placing erection in context: the reflexogenic-psychogenic dichotomy reconsidered. Neurosci Biobehav Rev 1995; 19: 211.

12) Amarenco G, Kerdraon J. Clinical value of ipsi- and contralateral sacral reflex latency measurement: a normative data study in man. Neurourol Urodyn 2000; 19: 565.

13) Tajkarimi K, Burnett AL. The role of genital nerve afferents in the physiology of the sexual response and pelvic floor function. J Sex Med 2011; 8: 1299.

14) Martin-Alguacil N, Schober JM, Sengelaub DR et al. Clitoral sexual arousal: neuronal tracing study from the clitoris through the spinal tracts. J Urol 2008; 180: 1241.

15) Ertekin C, Uysal H, Bademkiran F et al. Sacrolumbar intersegmental reflex circuit in men and its relation to the ejaculatory process. Clin Neurophysiol 2007; 118: 2368.

16) Yang CC, Bradley WE: Reflex innervation of the bulbocavernosus muscle. BJU Int 2000; 85: 857.

17) Yang CC, Bradley WE: Somatic innervation of the human bulbocavernosus muscle. Clin Neurophysiol 1999; 110: 412.

18) Deletis V, Vodusek DB. Intraoperative recording of the bulbocavernosus reflex. Neurosurgery 1997;40:88; discussion 92-3.

19) Cruz Y, Rodriguez-Antolin J, Nicolas L et al: Components of the neural circuitry of the vaginocavernosus reflex in rabbits. J Comp Neurol 2010; 518: 199.

20) Centers for Disease Control and Prevention (CDC). Racial/ethnic differences in the birth prevalence of spina bifida - United States, 1995-2005. MMWR Morb Mortal Wkly Rep 2009; 57: 1409.

21) Shin M, Besser LM, Siffel C et al. Prevalence of spina bifida among children and adolecents in 10 regions in the united states. Pediatrics 2010;126:274

22) Jackson AB, Dijkers M, Devivo MJ et al. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. Arch Phys Med Rehabil 2004; 85: 1740.

23) Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? Spinal Cord 2006; 44: 523.

24) Steers WD. Neural pathways and central sites involved in penile erection: Neuroanatomy and clinical implications. Neurosci Biobehav Rev 2000; 24:507.

Chapter 5

The procedural and technical aspects of the TOMAX procedure based on a series of 43 nerve transfers

Overgoor ML
de Jong TP
Kon M

Restoring tactile and erogenous penile sensation in low spinal lesion patients: procedural and technical aspect following 43 TOMAX-nerve transfer procedures. *Plast. Reconstr. Surg*. 2014;**134**: 294e-301e.

Video on surgical technique available at ***http://links.lww.com/PRS/B52***

Abstract

Background

The TOMAX-procedure restores genital sensation in men with a low spinal lesion improving sexual health as shown previously. It connects the dorsal nerve of the penis (DNP) to the intact ipsilateral ilioinguinal nerve, uni- or bilaterally. This study reports on the technical aspects based on 43 TOMAX-nerve transfers.

Methods

In 40 patients with no penile- but intact groin sensation, 43 nerve transfers were performed. All steps concerning, patient selection, surgical-history, anatomy of ilioinguinal nerve and DNP, uni-or bilateral surgery, surgical technique, complications and patient information, have been collected prospectively.

Results

No matter the origin, all patients with no penile- but good groin sensation are eligible for the procedure as long as the ilioinguinal nerve is not damaged due to former inguinal surgery or absent due to anatomical variations. Selection for a uni- or bilateral procedure depends on the presence/absence of reflex-erections and bulbocavernosus-reflex. Preliminary experience with the first three bilateral cases, show that it is technically feasible with encouraging results. The surgical technique has evolved (described in-detail, including video) to enhance outcome and reduce complications. Patients are better informed resulting in realistic expectations.

Conclusions

This manuscript is a synthesis of the procedural- and technical experience of 43 TOMAX-nerve transfers. This information might help anyone skilled in peripheral nerve- and microsurgery to adopt this concept and further develop it. The TOMAX procedure can then be used to restore erogenous penile sensation and improve the quality of sexual health in large numbers of patients with absent penile- but good groin sensation.

Introduction

Most patients with a low spinal lesion (LSL) due to spina bifida (SB) or a spinal cord injury (SCI) can have erections and sexual intercourse with ejaculation but do not have any sensation in the penis. This situation can result in frustration and a decrease in sexual health.[1-3]

In a normal situation penis sensations are transmitted through both dorsal penile- (DNP) and pudendal nerves, to the 2nd–4th sacral roots. From there, the sensory-impulses are send through the spinal cord to the sensory cortex, unless interrupted by a spinal lesion. **(Figure 1)**

Recently the TOMAX-procedure was presented to restore tactile and erogenous genital sensation in these LSL patients.[4-6] The procedure involves cutting the functional sensory ilioinguinal nerve distally in the groin and joining it by microneurorraphy to the 'non-functional' divided dorsal nerve of the penis (DNP) at the base of the penis on one side. **(Figure 1)** This neurological-bypass is indicated only in LSL patients (below L1) with no penile- (S2-4) but normal groin sensation (intact L1 dermatome) because of the high spinal entry level (L1) of the ilioinguinal nerve.

In the recently published functional- and sexological outcome study[5] ilioinguinal neurotization of the DNP, restored unilateral glans-penis sensation

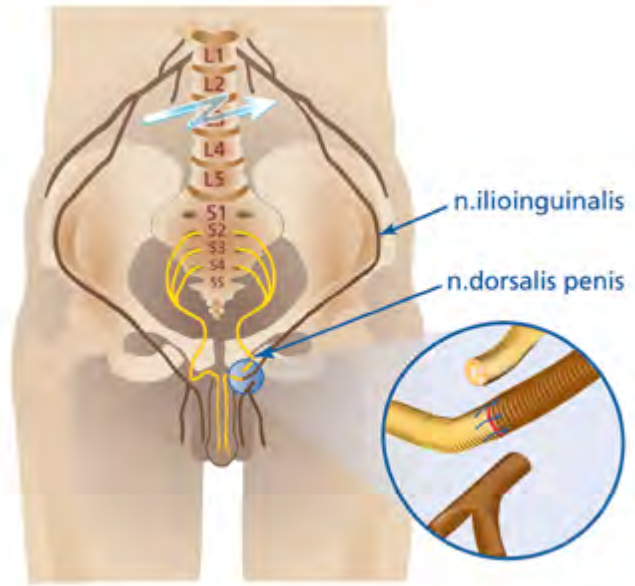

Figure 1. Schematic representation of the TOMAX-procedure. The sensory ilioinguinal nerve (L1) is cut distally and joined by microneurorraphy to the ipsilateral divided dorsal nerve of the penis (S2-4) at the base of the penis.

in 24 out of 30 (80%) of these LSL patients. Post-operatively, the initial unilateral sensations are felt in the groin area but after a mean follow-up of 15 months, are transferred to the glans penis in about 50% of patients through plasticity of the brain. Besides tactile sensations, the erogenous sensations can result in better erectile function and discovering (new) sexual activities as more pleasurable with and without a partner. Overall, the quality of their sexual functioning and satisfaction was significantly increased.[5] They felt more complete and less handicapped.

In the USA, the estimated birth-prevalence of spina bifida in 2005 was 1.9 per 10,000 per live births[7] and in 2010, 3.1 cases per 10,000 children and adolescents, aged 0 to 19 years had spina bifida.[8] For Spinal Cord Injury the incidence is estimated at 40 per million in USA[9] and the prevalence at 223-755 per million worldwide.[10] This means that the TOMAX procedure can be used to restore erogenous penile sensation and improve the quality of life and sexual health in large numbers of patients with no penile but good groin sensation.

In daily practice, SB and SCI patients with these neurological and sexual issues will be seen by urologists, rehabilitation doctors, neurologists, general practitioners and sexologists but should also be correctly referred to doctors skilled in peripheral nerve- and microsurgery. Results of the TOMAX-procedure are likely to be dependent on tissue handling and fine surgical technique. Plastic- and reconstructive surgeons are trained in these techniques so patients should also be referred to them.

The goal of this study is to share up-to-date information on technical issues involving the TOMAX-procedure which we came across after a series of 43 nerve transfers in 40 patients, with emphasis on a detailed description (and video) of the surgical technique.

Materials and Methods

The TOMAX-procedure has been performed in 40 LSL patients (the first 30 patients[5] with necessary ethics committee permission and written informed consent), with no penile sensation but normal groin sensation between 2001 and 2013. All the procedural steps concerning, patient selection, surgical history, absence of ilioinguinal nerve, anatomy of DNP, uni- or bilateral surgery, surgical technique, complications and patient information have been collected prospectively and

are described in the result section. The final functional and sexological outcome mean follow-up of 15 month) of the first 30 patients has been recently described in detail.[5]

Results

Patient selection

Absence of penile- but remaining groin sensation is not only seen in low-lesion SB (n=21) and SCI (n=13) patients but also in other low-lesion neurological disorders. We started to include three patients with a *conus-medullaris- or cauda-equina syndrome* due to failed hernia surgery: two patients gained excellent tactile (although not sexually beneficial) "groin" sensation while in the third patient, surgery failed due to absence of the ilioinguinal nerve. Similar 'nerve-absence' happened also in one *spondylodiscitis* case. In two other patients, following partial resection of the sacrum due to a *chordoma*, one developed erogenous "glans" sensation while the other did not gain sensation. Postoperative follow-up was more than 18 month in each case.

Although age is inversely related to sensory recovery, two older patients (aged 42 and 46) did develop erogenous-like glans sensations 2 years after the TOMAX-procedure.

Surgical history

Non-usable and damaged/scarified ilioinguinal nerves were encountered in all patients with prior groin/lower abdominal surgery involving scars over the course of the ilioinguinal nerve: inguinal hernia repair (n=2), orchidopexy- (n=1) and extensive hip surgery (n=1).

Absence of ilioinguinal nerve

In three patients the ilioinguinal nerve was absent bilaterally and in two- unilaterally. In the latter two patients the contralateral ilioinguinal nerve could also not be used due to damage by a former inguinal hernia repair (see above). However in one of patients with no ilioinguinal nerve on both sides, the iliohypogastric nerve was used instead on one side: subcutaneous dissection revealed that it was long enough for direct coaptation to the DNP. In most cases, this nerve will not to be long enough. Six month following this alternative nerve transposition the patients did not develop sensation yet.

Anatomy of DNP

The penile portion of the DNP consists of a medial bundle to the glans and a lateral bundle to the shaft and urethra bilaterally.[11] At the dorsal base these bundles join to become one, most of the time. In case the bundles run separately at the base of the penis, the medial 'glans' bundle is used for the connection with the ilioinguinal nerve.

Bilateral surgery

Until recently the TOMAX-procedure was performed unilaterally. Bilateral neurotization however might give full sensation to the glans but entails cutting both DNPs. Besides transmitting penile sensory impulses to the brain, both DNPs play a role in reflex erections (RE)[12,13] and (vibratory) ejaculations[14] through the sacral (S2-S4) reflex arc. We found that even patients with a low spinal lesion and no sensation of the penis still can have signs of remaining DNP 'function' in 12 out of 30 patients (40%).[15] Cutting both DNPs in these cases in a bilateral TOMAX procedure might be risky. Therefore a protocol was developed to safely select for a unilateral- or bilateral procedure using self-reported RE combined with bilateral needle-EMG- bulbocavernosus reflex (BCR) measurements[15]: if both RE and BCR are absent, bilateral surgery can be performed. This was done recently in three patients. *One* unilateral operated patient (SB, 38 yrs, L3, absent RE/BCR) had the same procedure on the other side on his own request since he was happy with the results but wanted full glans sensation. He finally (after 1 yr) gained sensations in the entire glans reinforcing the already present erogenous sensations. A *second* patient (SB-occulta, sacral, 36 yrs, absent RE/BCR) had primary bilateral surgery resulting in bilateral (full) glans-sensations after 12 month. The sensations were still experienced as if the groin was being touched, but were erotically beneficial to him. A *third* patient (incomplete S2-3 following sacral-chordoma excision, 47 yrs, absent RE/BCR) was operated recently (4 month ago). Results are not available yet. To decide for unilateral- or bilateral surgery, BCR is no longer performed preoperatively under anesthesia[5] prior to the TOMAX-procedure (n=35) but preoperatively in an outpatient setting (n=5).

Surgical Technique

Video on surgical technique available at *http://links.lww.com/PRS/B52*

All SB and SCI patients are routinely treated in Latex-free environment because of multiple surgical procedures. The patient is prepped and draped and a transurethral catheter is inserted in incontinent patients. An oblique incision is made over the course of the right and/or left ilioinguinal nerve and curved caudally to the ipsilateral base of the penis in unilateral cases **(Photo1)** and to the central penile base when operating on both sides. Careful dissection below Scarpa's fascia is necessary medially since in some cases (31%)[16] the essential cutaneous end-branches of the ilioinguinal nerve are encountered here. These branches are angulating at its exit behind the external inguinal ring area and should be left uninjured **(Photo 2).** After exposure of the external oblique muscle fascia, the fascia is opened from lateral to medial in line with the fascial-fibres in the area were the ilioinguinal nerve is to be expected **(Photo 2)**. In most cases, the ilioinguinal nerve is found at 1 cm cranial to the spermatic cord, but sometimes the nerve may run with or under the spermatic cord.[17] Anatomical variations are common and are often related to the course of the genitofemoral nerve[17] (in which the ilioinguinal nerve is incorporated) and/or the iliohypogastric nerve.[16] We have not really encountered problems to find the nerve as long as the ilioinguinal nerve is primary searched for lateral from the superficial inguinal ring. Sometimes a nerve is encountered more cranially. This is the iliohypogastric nerve which has been used once in absence of the ilioinguinal nerve (see above).

The ilioinguinal nerve is identified, grasped at its epineurium or surrounding tissue, circumferentially freed and dissected in a lateral to medial/distal direction

Photo 1 Oblique incision is made over the course of the (left) ilioinguinal nerve.

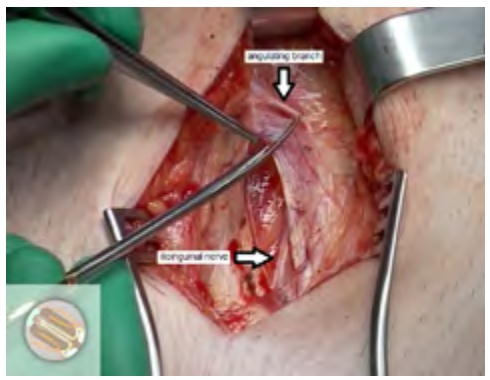

Photo 2 The external oblique muscle fascia is opened. Angulating branches of the ilioinguinal nerve exits behind the external inguinal ring.

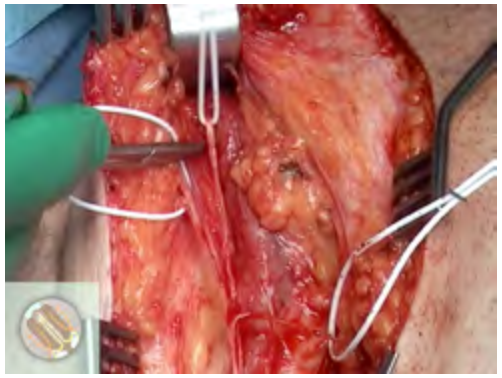

Photo 3 The ilioinguinal nerve divides often into 2-4 different branches (the scrotum or medial pubic skin).

Photo 4. At the ipsilateral (left) base of the penis, the many different fascia-like layers are opened until Buck's fascia.

using the vessel-loop for traction. The external oblique muscle fascia is now opened more medially including the external inguinal ring, to facilitate more medial dissection of the nerve **(Photo 2)**. One needs to be careful here since the ilioinguinal nerve divides here into 1-4 (sometimes more) different nerve branches. As mentioned above, one division is often a recurrent branch which angulates at its exit behind the external inguinal ring area to the subcutaneous tissue[16]. All branches of the ilioinguinal nerve are dissected as far as possible into the fatty tissue and spared. In most cases, there is one main branch which often runs in the direction of the scrotum or medial pubic skin **(Photo 3)**. Bleeding is controlled with (bipolar) coagulation throughout the procedure.

Next, the skin incision is deepened medially through fatty tissue up till the base of the penis**.** Large veins are spared if possible and retracted with vessel loops. At the base of the penis ipsilateral from the dorsal vein and artery, the many different fascia-like layers are lifted with forceps and opened with diathermy until Buck's fascia **(Photo 4).** The DNP runs in or under Buck's fascia. After opening Bucks fascia the ipsilateral DNP is identified. The DNP consists of many small zigzag-course nerve branches distally to the shaft (lateral bundle) or glans (medial bundle)[11] **(Photo 5).** More proximally at the penile base the two bundles become one bundle most of the time. Using blunt and sharp dissection on both sides of the DNP after careful bipolar coagulation of fascial-attachments, the nerve is now dissected off the tunica albuginea in a proximal direction. The DNP often has a tight connection to the underlying tunica albuginea and dissection can result in local blood-loss. Post-operative hematoma in the two patients needing reoperation was caused by bleeding from this dissection. As the assistant gives

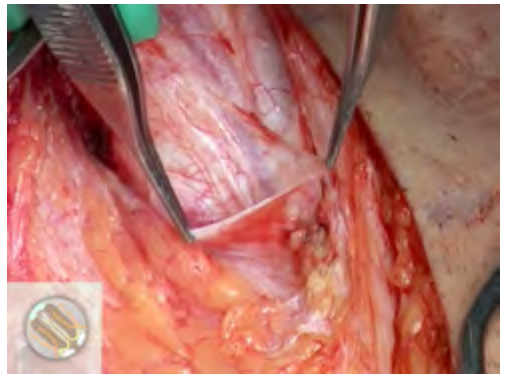

Photo 5 The DNP runs under Bucks fascia and consists of a lateral- and a medial nerve bundle running distally to the shaft and glans respectively.

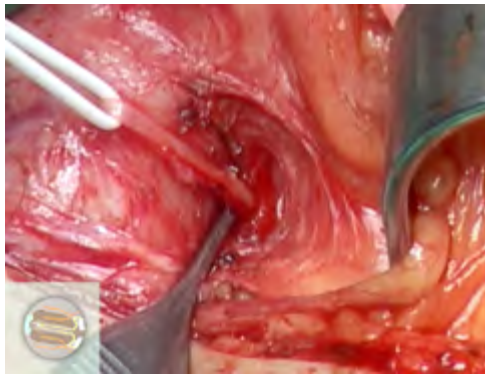

Photo 6 Detailed view to penile-base: the DNP is dissected off the tunica albuginea in a proximal direction as far as possible towards the penile base.

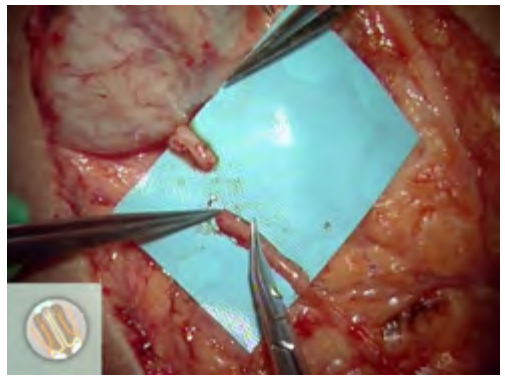

Photo 7 A tension free neurorraphy is done under the operating microscope.

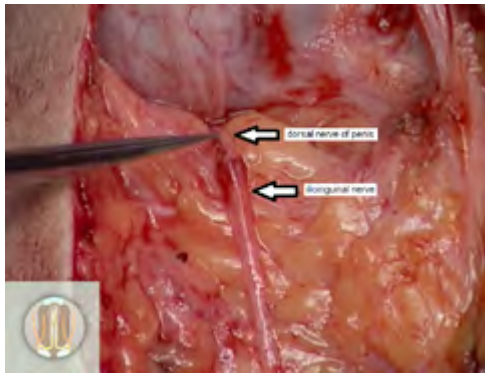

Photo 8 Ilioinguinal- and DNP- nerves connected at the medial-groin/penile-base junction.

traction on the penis to reveal more space at the penile base and with the use of retractors, the DNP can be dissected as proximal as possible using the vessel loop for nerve manipulation **(Photo 6)**. The nerve is than clamped as proximal as possible and cut distally (on the penis side) from the clamp. The proximal stump which has the clamp on it is coagulated. If more length is needed more distal DNP dissection over the tunica albuginea can be done.

The branches of the ilioinguinal nerve are cut as distally as possible (at a level where the branch still has a good caliber) to gain as much length as possible**.** All branches together (as if it is one branch), are brought in the direction of the DNP at the base of the penis. Sometimes interposing fatty tissue has to be cut to gain more space.

Using nylon 9.0 sutures a tension free neurorraphy is done under the operating microscope using standard a-traumatic microsurgical techniques **(Photo 7, 8)**

Photo 9 Final appearance after closure.

The external oblique muscle fascia is closed using absorbable 2.0 interrupted suturing starting from lateral to medial. Care is taken that the ilioinguinal nerve is not entrapped in these sutures. In most cases, the fascia is not completely closed medially. After closing Scarpa's fascia and placement of a suction catheter, deep dermal sutures are placed with vicryl 3.0. The skin is closed with intradermal monofilament absorbable 4.0 sutures. **(Photo 9)**

Postoperative care

Up till now, patients have been hospitalized in bed for 36-48 hrs and leaving their indwelling catheter in place until they are mobilized. Two days after surgery patients are dismissed from the hospital, and advised to minimize the use of their abdominal muscles during 4 weeks (no sports). Post-operative outpatient control is planned at two weeks, six- and 12 month. In future cases hospitalization might be reduced to daycare surgery.

Complications

In one patient the ilioinguinal nerve was accidentally cut and repaired by microneurorraphy; he developed good, but delayed, tactile sensations. In two out of three patients a post-operative hematoma led to disruption of the nerve repair necessitating a re-microneurorraphy. Eventually both patients developed excellent erogenous-like sensations.

Patient information

Pre-operatively patients are told that they have about 80% chance of regaining (unilateral/bilateral) sensation which will mature from groin- to glans sensation in about 46%. If this happens, erogenous sensations are more likely to be

developed.[5] First signs of sensation are to be expected at 4-6 months but this can extend to one year and first sensation can be experienced as somewhat painful but this always disappeared over time. Patients are advised to do "sensory (re-) educational-homework" as soon as the wounds are healed to promote neural remapping of the brain: look at their penis while touching, masturbating and fantasizing and if possible with a partner. After 1-2 years a definite outcome can be expected in most cases. Importantly, the new sensations are not to be compared with a normal non-spinal-lesion situation (ie before the SCI) but are to be seen as serious and positive step forwards.

Diminished sensation in the groin is noticeable but until now without any problems, neuroma or pain.

Discussion

Restoration of lost tactile- and sexual penile sensation due to spinal interruption of the sensory pathway to the brain in LSL-patients is feasible. It can lead to improved quality of sexual functioning and satisfaction. Because the TOMAX-procedure is new, this novel development might be of interest to surgeons involved in reconstructive nerve surgery. In this manuscript the procedural steps and surgical technique evolved in the last 12 years are described.

Ilioinguinal anatomy / inguinal surgery

Due to anatomical variations we now ensure that new patients are informed that the groin nerve may be (unilaterally) absent in 7-12% of cases[16,18] making contralateral exploration necessary in unilateral cases. Preoperative visualisation of the ilioinguinal nerve using high resolution ultrasound[19,20] or DTI-MRI[21] in the future might be valuable, but has to be studied in relation to the TOMAX procedure. Furthermore patients with prior surgery involving scars over the course of the ilioinguinal nerve are discouraged from TOMAX surgery on that particular side. Preoperative intact groin sensibility in these patients can be explained by the fact that the iliohypogastric- and genitofemoral nerves have taken over ilioinguinal nerve function. Using these groin nerves for transposition might seem an attractive alternative in these cases. A problem is that the sensory branch of the genitofemoral nerve is too thin and the iliohypogastric nerve is too short in most cases to reach the base of the penis. In one recent case described above we gained enough length of the iliohypogastric nerve by extended subcutaneous dissection, but we do not have long-term outcome yet.

Stretching the indication

Until now, the experience with this procedure revealed that all patients with no penile- but good sensation of the groin might be candidates. For example, patients who have a damaged non-functional pudendal nerve following unsuccessful decompression surgery might benefit from a unilateral nerve transfer, but this is still speculation. Likewise, more experience is needed with the bilateral TOMAX procedure. Theoretically, full glans sensations should be beneficial. Although the preliminary results are positive, the numbers are still limited.

Another point of discussion is the fact that older patients might not have good results for this type of surgery due to impaired nerve regeneration. However, two older patients (aged 42 and 46) did develop erogenous-like glans sensations. Therefore, the age of the patients has not been maximized yet and recently we included a 55 yrs old patient but we do not have outcome yet. Remapping of sensibility in the brain in case of the TOMAX procedure might be less dependent of age than thought. Besides this, a patient was selected recently with present but markedly decreased ilioinguinal-groin sensation due to an incomplete T12-lesion. The patient was informed that the outcome might be questionable.

Long term follow-up is needed to know if all these expanded indications have impact on the final results.

Future

As the experience with the TOMAX procedure is expanding future developments may be to offer young SB patients to be operated before puberty and restoring clitoral sensation in women with lower lesions. Patients with higher SL might benefit from the use of alternative (intercostal) nerves transfer to the DNP in combination with vascularised ilioinguinal- or non-vascularised sural nerve-grafts. Patients with intact BCR might be offered an end-to-side nerve coaptation technique if the ilioinguinal nerve is long enough.

Conclusion

This manuscript is a synthesis of the procedural- and technical experience of 43 TOMAX-nerve transfers in the last 12 years. This information might help medical healthcare professionals involved in the multidisciplinary care and quality of life issues of low spinal lesion patients to adopt this concept and further developing it. Plastic surgeons skilled in peripheral nerve- and microsurgery should know

about this concept and be part of the team treating patients with SB or SCI. To confirm the reliability of the procedure it might be advisable to have similar pre- and postoperative neurological and psycho-sexological evaluations in the first series of patients as presented in our functional- and sexological outcome study[5]. Besides this, reliable and realistic information should be given to the patients to avoid disappointment. Recently, two successful penile re-innervations were performed in the USA.[6,22]

The TOMAX procedure can be used by to restore erogenous penile sensation and improve the quality of life and sexual health in large numbers of patients with no penile but good groin sensation.

Acknowledgements

We thank Jan de Witte from Multimedia productions UMC Utrecht, for his excellent work in creating the video on Surgical Technique.

References

1) McDonald JW, Sadowsky C. Spinal-cord injury. *Lancet* 2002; 359: 417-425.

2) Lassmann J, Garibay Gonzalez F, Melchionni JB, Pasquariello PS, Snyder HM. Sexual function in adult patients with spina bifida and its impact on quality of life. *J Urol.* 2007; 178: 1611-1614.

3) Verhoef M, Barf HA, Vroege JA et al. Sex education, relationships, and sexuality in young adults with spina bifida. *Arch Phys Med Rehabil.* 2005; 86: 979-987.

4 Overgoor ML, Kon M, Cohen-Kettenis PT, Strijbos SA, de Boer N, de Jong TP. Neurological bypass for sensory innervation of the penis in patients with spina bifida. *J Urol.* 2006; 176: 1086-1090; discussion 1090.

5) Overgoor ML, de Jong TP, Cohen-Kettenis PT, Edens MA, Kon M. Increased sexual health after restored genital sensation in male patients with spina bifida or a spinal cord injury: The TOMAX procedure. *J Urol*. 2013; 189: 626-632.

6) Jacobs MA, Avellino AM, Shurtleff D, Lendvay TS. Reinnervating the Penis in Spina Bifida Patients in the United States: Ilioinguinal-to-dorsal-penile neurorrhaphy in two cases. *J Sex Med* 2013; Jul 11.doi.111/jsm.12255 [Epub ahead of print]

7) Centers for Disease Control and Prevention (CDC). Racial/ethnic differences in the birth prevalence of spina bifida - United States, 1995-2005. *MMWR Morb Mortal Wkly Rep*. 2009; 57: 1409-1413.

8) Shin M, Besser LM, Siffel C et al. Prevalence of spina bifida among children and adolecents in 10 regions in the united states. *Pediatrics*. 2010;126:274-279

9) Jackson AB, Dijkers M, Devivo MJ, Poczatek RB. A demographic profile of new traumatic spinal cord injuries: change and stability over 30 years. *Arch Phys Med Rehabil.* 2004; 85: 1740-1748.

10) Wyndaele M, Wyndaele JJ. Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? *Spinal Cord*. 2006; 44: 523-529.

11) Yang CC, Bradley WE. Peripheral distribution of the human dorsal nerve of the penis. *J Urol*. 1998; 159: 1912-6; discussion 1916-7.

12) Giuliano F, Rampin O. Neural control of erection. *Physiol Behav.* 2004; 83: 189-201.

13) Giuliano FA, Rampin O, Benoit G, Jardin A. Neural control of penile erection. *Urol Clin North Am*. 1995; 22: 747-766.

14) Wieder JA, Brackett NL, Lynne CM, Green JT, Aballa TC. Anesthetic block of the dorsal penile nerve inhibits vibratory-induced ejaculation in men with spinal cord injuries. *Urology*. 2000; 55: 915-917.

15) Overgoor ML, Braakhekke JP, Kon M, de Jong TP. Restoring penis sensation in patients with low spinal cord lesions: the role of the remaining function of the dorsal nerve in a unilateral or bilateral TOMAX procedure. *Neurourol. Urodynam.* 2014; DOI 10.1002/nau

16) Al-dabbagh AK. Anatomical variations of the inguinal nerves and risks of injury in 110 hernia repairs. *Surg Radiol Anat*. 2002; 24: 102-107.

17) Rab M, Ebmer And J, Dellon AL. Anatomic variability of the ilioinguinal and genitofemoral nerve: Implications for the treatment of groin pain. *Plast Reconstr Surg*. 2001; 108: 1618-1623.

18) Ndiaye A, Diop M, Ndoye JM et al. Anatomical basis of neuropathies and damage to the ilioinguinal nerve during repairs of groin hernias. (about 100 dissections*). Surg Radiol Anat*. 2007; 29: 675-681.

19) Eichenberger U, Greher M, Kirchmair L, Curatolo M, Moriggl B. Ultrasound-guided blocks of the ilioinguinal and iliohypogastric nerve: accuracy of a selective new technique confirmed by anatomical dissection. *Br J Anaesth.* 2006; 97: 238-243.

20) Willschke H, Marhofer P, Bosenberg A et al. Ultrasonography for ilioinguinal/iliohypogastric nerve blocks in children. *Br J Anaesth* 2005; 95: 226-230.

21) van der Jagt PK, Dik P, Froeling M et al. Architectural configuration and microstructural properties of the sacral plexus: A diffusion tensor MRI and fiber tractography study. *Neuroimage*. 2012; 62: 1792-1799.

22) Jacobs M, Avellino AM, Shurtleff BD, Lendvay TS. Ilioinguinal to penile neuro-neurorraphy in the myelomeningocele patient: presentation of 2 cases. Paper presented at: 2012 Annual Meeting of the American Urology Association; May 19, 2012; Atlanta, Georgia.

Chapter 6

Cerebral networks involved in processing penile tactile stimulation following the TOMAX-procedure

Kortekaas R
Overgoor ML
Nanetti L
de Jong BM
Georgiadis JR

Central somatosensory networks respond to a de novo innervated penis in spina bifida. *Submitted*

Abstract

Spina bifida (SB) causes low spinal lesions and patients often have absent genital sensation and a highly impaired sex life. A novel surgical procedure (TOMAX) entails transposing the ilioinguinal nerve from the groin onto the intact dorsal penile nerve. This results in a gradual shift from penile stimulation experienced as groin sensation to penis sensation.

We aimed to study cerebral networks involved in processing penile tactile stimulation and hypothesized that an unchanged groin area of the primary somatosensory cortex (SI) would respond in addition to higher order areas implicated in erogeneity.

We enrolled three MRI-compatible post-TOMAX human patients and scanned them while penis, groin and finger were stimulated with a soft paint brush. In addition to brain activations we used Granger Causality (GC) analysis to identify brain areas that were functionally connected with the identified SI.

Stimulation of the penis and groin resulted in similar robust and plausible SI activations. In addition we identified distinct functional networks for each stimulation site. The posterior part of the middle cingulate cortex (pMCC) and the parietal operculoinsular cortex (OIC) were more activated during penis stimulation than during groin stimulation in all three subjects.

The consistent activation of these regions supports the concept that pMCC and OIC are core areas underlying the altered body map in these patients. Moreover, given the role of pMCC and OIC in attributing meaning to sensory stimuli, the entrance of penile sensory information into cerebral networks that subserve sexual arousal and expectation apparently facilitates such body scheme remapping.

Introduction

SB concerns a malformed or absent sacral spinal cord resulting from incomplete closing of the caudal part of the neural tube at three to four weeks post-fertilization. Men with SB often have an ineffective erectile function and poor or absent genital sensation. This leads to high levels of frustration and low subjective sexual health [1,2] when young men with SB develop an active interest in sex [3,4,5].

Recently, Overgoor *et al.* [6,7] described a new surgical technique (see figure 1A) to newly innervate the penis in SB patients with a lesion below spinal cord level L1. This so-called *TOMAX-procedure* involves two nerves which are normally not connected: the sensory ilioinguinal nerve (IIN) and the dorsal nerve of the penis (DNP). The IIN originates from the medial inguinal area (hereafter called "groin") and enters the spinal cord in the intact spinal segment L1. The DNP innervates penile shaft and glans, but as a terminal branch of the sacral pudendal nerve its sensory inflow is disconnected in SB. The *TOMAX-procedure* entails cutting the intact IIN and joining it, at the base of the penis, by microneurorrhaphy to the intact DNP. This procedure results in excellent sensation in the glans penis [6,7] and the experience that the penis is a more normal part of patients' body image [7]. In the operated patients, penile sensory information now travels from the

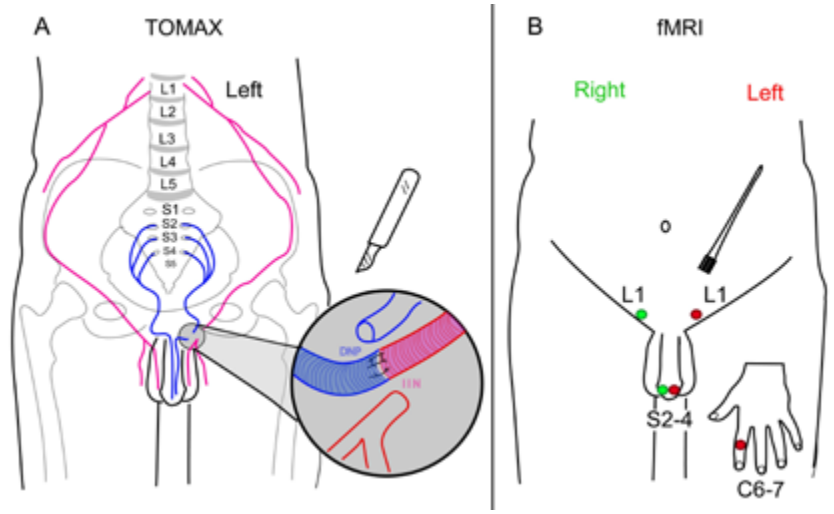

Figure 1: Surgical by-pass and stimulation sites. Panel A depicts the TOMAX procedure. The left ilioinguinal nerve (IIN, pink), a lumbar spinal nerve, was cut, transposed, and connected via neuroraphy to the left dorsal nerve of the penis (DNP, blue), a sacral spinal nerve. This connection bypasses the sacral defect in spina bifida, and enables genital feelings to develop. On the right side, INN and DNP were not connected. Panel B depicts the body sites that were stimulated during the fMRI experiment. The penile glans, as well as the skin overlying the medial aspect of Poupart's ligament ('groin'), were stimulated bilaterally. In addition, the radial aspect of the left index finger was stimulated. L1, first lumbar dermatome; S2-4, second to fourth sacral dermatome; C6-7, sixth and seventh cervical dermatome.

DNP onto the transposed IIN and enters the spinal cord at the unaffected level L1. Despite the different receptive properties of penile glans and inguinal skin, most men treated with TOMAX experience their new sensations from the glans as pleasant and, in the appropriate context, erotic [6,7] leading to increased sexual health and function.

The somatosensory plasticity that remaps groin sensation to penis sensation takes at least one year [7]. This course of events is interesting because normal development of erotic genital feelings typically occurs during early adolescence, which is difficult to study because of obvious ethical constraints. TOMAX-patients thus could provide an adult human model of sexual development.

We enrolled three MRI-compatible post-TOMAX patients and scanned them while penis, groin and finger were stimulated with a soft paint brush. We hypothesized that reorganization would not occur in SI, but that activation differences between groin and penis would become apparent beyond SI. Any differences in brain activation between groin and penis could provide insight into the remapping process of the body scheme and could hint at areas that allow for development of erogeneity.

Materials and methods

Ethics Statement

Because this fMRI study was not part of the patients' normal post-operative follow-up treatment regime we sought and obtained approval from the internal ethical committee of the University Medical Center Utrecht. Written informed consent was obtained from all subjects and this investigation was conducted according to the principles expressed in the Declaration of Helsinki. Operated patients were approached by their surgeon (MLO) with reassurance that the decision to participate in the fMRI study or not would have no consequences for the patients' treatment.

Surgical procedures

For detailed surgical procedures and full inclusion criteria of the initial TOMAX procedure we refer to Overgoor *et al.* [6,7]. Briefly, the left IIN was exposed to the base of the penis and cut distally. Through the same incision the ipsilateral DNP was exposed and cut proximally followed by microneurorraphy of the two nerve-ends.

Subjects

In order to be eligible for this study, patients had to have SB caudal to spinal vertebral level L1, had to be right handed and 18 years or older (see **Table 1** for detailed patient demographics). Also they had to have TOMAX-acquired sensation in their penis, as well as intact sensibility in the contralateral inguinal region. Patients with MRI-incompatible devices like pace-makers or electrical connectors were excluded from the study, as were patients with claustrophobia and epilepsy. We included three male SB patients (n3842, n3861, n3877) who were at least 2.5 years post-TOMAX.

Neurological, psychological and sexological evaluation

Pre- and post-operative psychological and sexual functioning was assessed by a clinical psychologist trained in sexology. The Groninger Arousability Scale (GAS) was used to gain an overall assessment of the ability to experience the various stages of the sexual response cycle. Besides questionnaires, the psychologist used a semi-structured interview. The surgeon also interviewed the patients to obtain a clinical perspective on their sexual- and genital functioning. Psychological and sexological assessments were repeated at the 11-13 month post-operative visit. Results are described elsewhere [7].

On the day of the fMRI experiment subjects neurological functions were clinically assessed by a neurologist (BMdJ). All subjects had intact spinal cord function of at least innervation level L3 and higher. Table 1 lists the most important results of neurological assessment per subject as well as other clinical and demographic data.

fMRI paradigm and procedure

Due to physical problems associated with SB and the demanding circumstances of MRI scanning, subjects were allowed to briefly relax and leave the scanner between sessions if they wished to do so, but none used this possibility.

We stimulated five *body areas* (see figure 1B) which were marked with a semi-permanent felt tip pen: the left and right half of the glans penis, the left and right inguinal area (L1 dermatome innervated by the IIN, area just superior to the inguinal ligament) and the radial surface of the left index finger (C8-T1 dermatome). We used an ethologically relevant mechanical stimulus in the context of normal penis sensation, namely moving touch, which was applied with a small

paintbrush for 2 s at a frequency of 1.5 Hz. The exact sequence and timing of the stimulus trials was programmed with E-prime v. 2.0 (Psychology Software Tools Inc., Sharpsburg, PA, USA) and were applied pseudo-randomly with jittered inter-stimulus intervals (minimal interval 12 s, jitter of 2.5 s). Jittering was applied to optimize data sampling and to minimize stimulus predictability. Stimulation cues were delivered auditory over a headphone to one of the experimenters (MLO) who was standing close to the subject and provided the paintbrush stimulations when so instructed. Subjects were instructed to keep their eyes closed so were unable to see when and where they were touched. The study protocol is summarized in **figure 2**.

The intact right inguinal area served as a control for the re-innervated penis because it is innervated by the IIN opposite to the operated side. The left index finger served as an additional control for central somatosensory processing and for the data preprocessing and analysis.

Because of marked brain abnormalities in this patient group (e.g. hydrocephalus [8]), as well as the limited sample size, we aimed to achieve optimal statistical power for a within-subjects statistical approach. Thirty stimulations were applied to all five skin areas distributed over three *sessions* (12, 12, 6 stimulations respectively), adding up to 150 stimulations per patient in total. Each session started and ended with a 30 s resting period which served as a baseline for the stimulation trials.

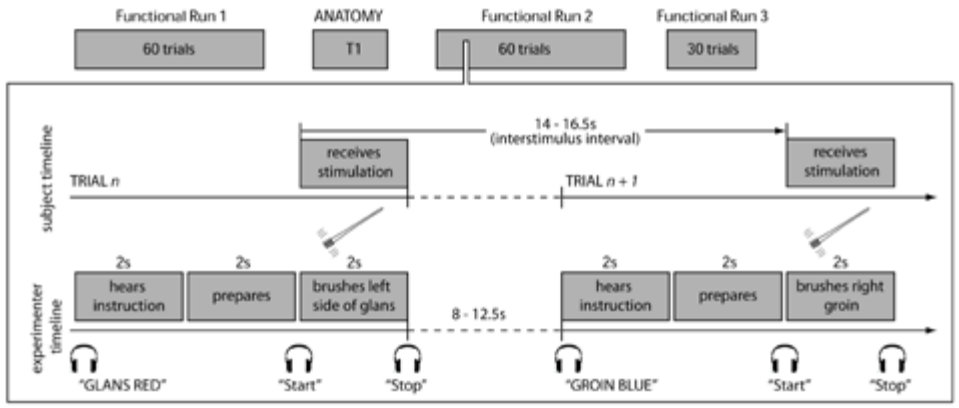

Figure 2: Set-up of the fMRI experiment. The experiment consisted of three functional runs comprising 60, 60 and 30 stimulation trials, respectively. A high resolution structural T1 MR image was acquired between runs 1 and 2 (top row). All paint brush stimulations were performed by M.L.E.O., whose timeline is illustrated in the bottom row (experimenter timeline). Stimulus timing and location were communicated to M.L.E.O. over headphones. Instructions 'red' and 'blue' corresponded to color marks placed on the skin sites that were stimulated, and were used instead of 'left' and 'right' to avoid miscommunication and/or confusion. As can be seen in the middle row (subject timeline), the subject only perceived the stimulation.

Image acquisition

Images were acquired on a Philips Intera 3T MR-scanner, equipped with SENSE 8-channel head coil. A series of echo planar imaging (EPI) volumes were acquired to measure the blood oxygen level dependent (BOLD) effect, which entailed a T2*-weighted gradient echo sequence with a repetition time (TR) of 2000 ms, echo time of 30 ms, water fat shift 7.067 pixels, EPI factor 29, SENSE 20.4, flip angle 70 degrees using whole-brain acquisition (matrix size 64 x 64 voxels) and interleaved slice acquisition order, with an inter-slice gap of 0 mm and plane thickness of 3.5 mm. EPIs were acquired at 3.5 x 3.5 mm in-plane resolution. Thirty six axial slices were acquired parallel to the anterior-posterior commissural plane. In total 1149 volumes were obtained per participant. A T1-weighted anatomical MRI (TR = 9 ms, TE = 3.5 ms, 170 x 1 mm slices, FOV 232 x 170 x 256 mm, water shift 2.269 pixels) was acquired after the EPI scans and served as anatomical reference for the brain activations.

Image pre-processing.

For image pre-processing and analysis we used Statistical Parametric Mapping software (SPM8; University College London, UK; http://www.fil.ion.ucl.ac.uk) and FSL 4.1.9 (www.fmrib.ox.ac.uk/fsl/). Because of pronounced morphological abnormalities in two patients, the brain scans were not normalized to standard space but kept in native (subject) space. Per subject, EPI volumes were slice time corrected (second slice as reference), realigned to the first volume acquired, and resliced to 2 x 2 x 2 mm isotropic voxels. A mean EPI image was created and the realignment parameters were inspected. Movements exceeding 2 mm in any direction would have caused the participant's exclusion from further analysis. All volumes were smoothed with an isotropic Gaussian kernel of 6 mm full-width at half-maximum. The T1 image was co-registered to the EPI images via the mean EPI image, allowing the individual's brain activity to be overlaid directly on their own brain anatomy.

Data modeling and Statistical analysis.

The pre-processed data were modeled and analyzed in two stages: first, a parametric event related analysis was performed to identify the foci of activation within the primary somatosensory cortex (SI) resulting from the paintbrush stimulation. Second, using time series extracted from these brain activations, we

investigated the functional connectivity of these SI regions to unveil the network associated with the novel sense of penile touch. We chose not to present a psycho-physiological interaction (PPI) analysis of the same time series because PPI lacks sensitivity in event related designs [9].

Stage 1: Identification of primary somatosensory cortex activity

Data were modeled with a General Linear Model (GLM) for each patient, containing three *sessions* and five *body areas* (L-glans, R-glans, L-inguinal, R-inguinal, L-finger), corresponding to five regressors. Data were analyzed in an event-related fashion where the 2 s stimulation epoch was convolved with the canonical hemodynamic response function (HRF). First derivatives of the five regressors' time courses were also added to the model, to compensate for slight temporal variations of the HRF; this allows for a better fit for the whole model, reduces unexplained noise, and increases resulting statistical significance. For each voxel a high-pass filter (cut-off 128 s) was applied to remove low-frequency noise from the fMRI time series; the same filter was applied to the model. Voxels' time series were prewhitened to improve estimation efficiency. Parameter weights were set to test the main effect of each of these *body areas*. The ensuing contrast images allowed us to identify the foci of activation in SI at $p < 0.001$ uncorrected for multiple comparisons, with the exception of Left Glans for subjects n3842 and n3877 ($p < 0.05$) and Right Groin for subject n3842 ($p < 0.02$). These more lenient thresholds are justified by the within-subject character of this study and by the fact that our main objective at this stage was to identify the SI activity resulting from these stimulations; it must also be noted that, as described later in more detail, the centers of these activations survived a conservative FWE corrected threshold of $p < 0.05$. Moreover, in most cases (see Supplementary Table 1) the activations survive a whole-brain FDR correction for multiple comparisons at p=0.05.

Identification was guided by the following sources. For localization of glans and inguinal SI we relied on two recent fMRI publications: Kell and colleagues [10] described a similar experimental setup with mechanical stimulation on penile shaft and groin while Georgiadis *et al*. [11] described a penis stimulation paradigm taking place in a sexually-relevant context, that is manual sexual stimulation of the erect penis including the glans. Both studies found the penis to be represented on the dorsal aspect of SI. Kell *et al.* moreover showed [10] that the groin SI representation was very similar to that of the penis. For localization of index finger SI we used Nelson *et al.* [12] as guidance. The finger is represented on the dorsolateral surface of SI in a location that is clearly distinct from that of penis or groin.

Because the present data were analyzed in subject space instead of standard space, the use of these resources is restricted to visual verification. The central sulcus (anterior border of the postcentral gyrus) was positively identified in all subjects. This observer-dependent approach is both necessary and superior to an automated approach, because of the pronounced hydrocephalus in two of the patients (n3842 and n3877).

After identification of the SI locations, spherical 56 mm^3 regions of interests (ROIs) were drawn around the center of the SI activation using MarsBar (http://marsbar.sourceforge.net/). Within these ROIs, the SI activations again reached $p<0.05$, FWE corrected. MarsBar was subsequently used to extract the time series per subject per *body area* per *session*.

Stage 2: network analysis using GC

The SI time series were used to perform a network analysis with Mutual Information via GC [13,14,15,16] to determine which brain areas are functionally connected with the SI ROIs.

The principle behind GC is that given two time series – a reference and a target – it is possible to calculate how much one time series helps to predict the other on a time span (lag) of order p [14,17]. Theoretically, GC could calculate separate directional (reference → target, target → reference) and non-directional (reference ↔ target) components. However, brain activation can rise during but also in preparation for neuronal activity [18]. Moreover, a post-surgery, complex, mutually intertwined series of both bottom-up and top-down processes is likely to have been generated in the patients' brains. Finally, it has been shown that directionality in GC can be biased [16], and sometimes even switch [19]. Therefore, at the expense of directionality, we used the sum of both directional and non-directional components as measure for whole brain connectivity with the SI ROIs. This sum corresponds to the total amount of linear information [14] exchanged between the reference and the target. This quantity, which is also known as Mutual Information [20,21], has been shown to be unaffected by the bias(es) mentioned above [14].

We followed a stringent approach to find the areas most consistently coupled to SI ROIs over *sessions* and subjects. Per subject per ROI, the first two *sessions* (which were of equal duration) were analyzed separately with GC. For each of these GC maps, the cut off was set at the 5% voxels most strongly correlated over time to SI time courses. The resulting maps were then binarized and multiplied with each other, so that only voxels belonging to the top 5 % in both *sessions* appeared in the composite GC map per SI ROI. Subsequently, the composite maps were visually inspected for consistency across subjects by two independent anatomists (RK & JRG). Brain areas that were recruited into the SI networks in all three patients during both sessions were considered most relevant.

Results

Identification of primary somatosensory cortex activity

Left and right sided glans stimulation resulted in clearly active brain foci in deep dorsal layers of the contralateral postcentral gyrus in subjects n3842 and n3877. Subject n3861 had bilateral activation to stimulation of the right half of the glans. Although subjects were only operated on the left side, they perceived stimulation on both sides of the glans **(Table 1)**.

Stimulation of both the left and the right inguinal area induced contralateral SI activity highly similar to that seen for the glans. In all three patients, stimulation of the left inguinal area (from which the IIN donor was used) gave more activation than stimulation of the intact right inguinal area.

Left index finger stimulation resulted in clear activation of its representation in SI on the right dorsolateral surface of the postcentral gyrus in all three subjects, see **figure 3**.

Network analysis: GC

For each subject, network analysis using GC revealed distinct functional sensory networks for the R-inguinal, L-glans, and L-finger. Characteristics of these functional networks are described below in as far as they were shared by two or three subjects, see also **figure 4**.

Glans stimulation network

In all three subjects, stimulation of the re-innervated glans induced functional connectivity in bilateral medial and paramedial superior cortical areas, centered

Table 1. Demographic and neurological data per subject on the day of the MRI scanning.

patient	n3842	n3861	n3877
age (year)	19	38	23
time post-TOMAX (year)	4.5	2.9	4.9
central abnormalities	hydrocephalus	none	hydrocephalus
general sensitivity, anamnestic	glans distinct, tactile + erotic sensations	glans distinct, tactile + erotic sensations	glans distinct, tactile + erotic sensations
glans sensitivity, neurological examination	soft: bilateral, sharp: bilateral,	soft: bilateral, sharp: ?	soft: bilateral, sharp: ?
groin sensitivity, neurological examination	soft: bilateral, sharp: bilateral	soft: ? 1. sharp: right only.	soft:? 2. sharp: bilateral

on the dorsal SI. This included parts of the superior parietal lobule, which lies posteriorly adjacent to SI. The pMCC and right posterior OIC also showed functional connectivity in all subjects. In two out of three subjects (n3842 and n3877) the glans network also included the right posterior thalamus (pulvinar or geniculate nuclei).

Groin stimulation network

The R-inguinal network was very similar to the L-glans network. Although the networks largely overlapped, this overlap was not complete. A detailed description of the differences is provided below.

Differences between glans and groin stimulation networks

For all three subjects the network activation produced by L-glans stimulation was larger than that for R-inguinal stimulation. Many of the extra activations were inconsistent over subjects. However, in all three subjects, penile stimulation induced the reqruitment of additional brain areas into the connectivity network comprising the right dorsal postcentral gyrus and right superior parietal lobule, pMCC, and right parietal operculum.

In two out of three subjects the right posterior insula (n3842, n3861) and right posterior thalamus (n3842, n3877) showed functional connectivity with penis SI during L-glans stimulation which was not seen during R-inguinal stimulation.

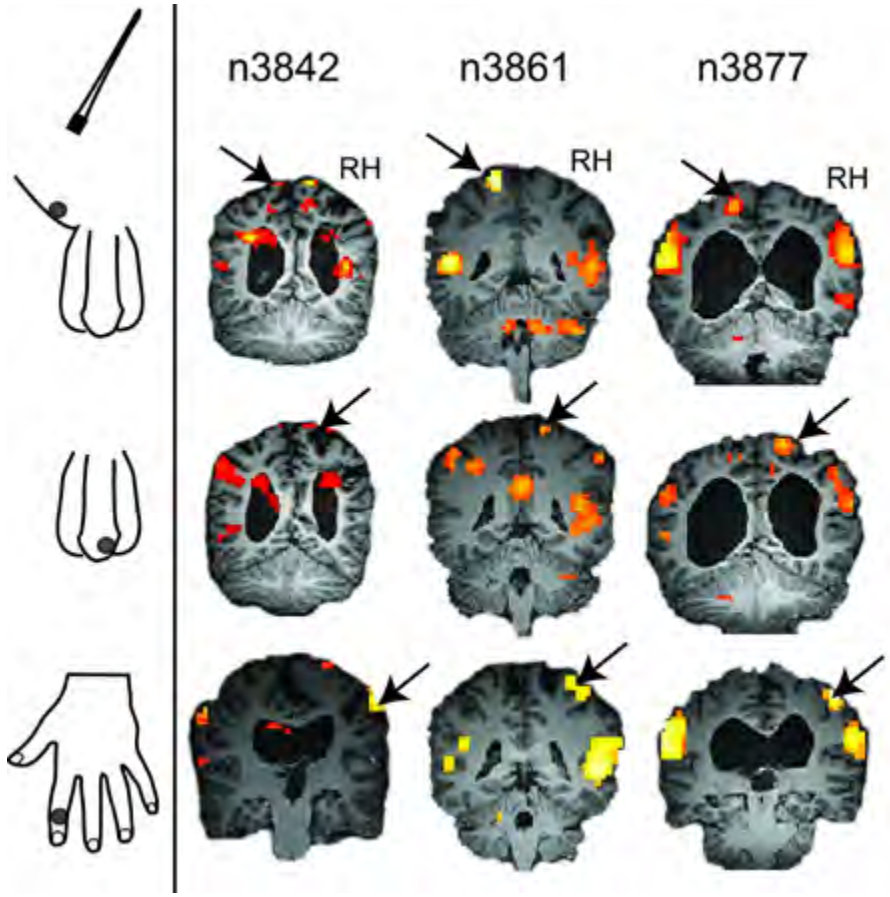

Figure 3: SI identification. Main effects of brushing the right groin (top row), the left side of the penile glans (middle row), and the left index finger (bottom row). The arrows indicate stimulation-induced activity falling within the known location of the primary somatosensory cortex (SI) of the respective stimulation sites. Note that groin and glans stimulation activate a similar SI location, which is in accordance with the literature [10]. All SI activity was $p<0.05$, corrected (for reduced SI search space). Analyses were performed in native space because of severely enlarged ventricles in two of the subjects (n3842 and n3877). RH, right hemisphere.

The reverse, i.e. extra network connectivity during R-inguinal stimulation relative to L-glans stimulation, present in all three subjects, was restricted to the left dorsal postcentral gyrus and left superior parietal lobule.

Finger stimulation network

The L-finger network was quite different from both L-glans and R-inguinal networks and revealed minor overlap. In all three subjects it was larger, more anterior, more lateral and more lateralized than the L-glans and R-inguinal networks. The focus of the lateralization was always in the right hemisphere i.e. more right than left hemispheric voxels were identified by GC.

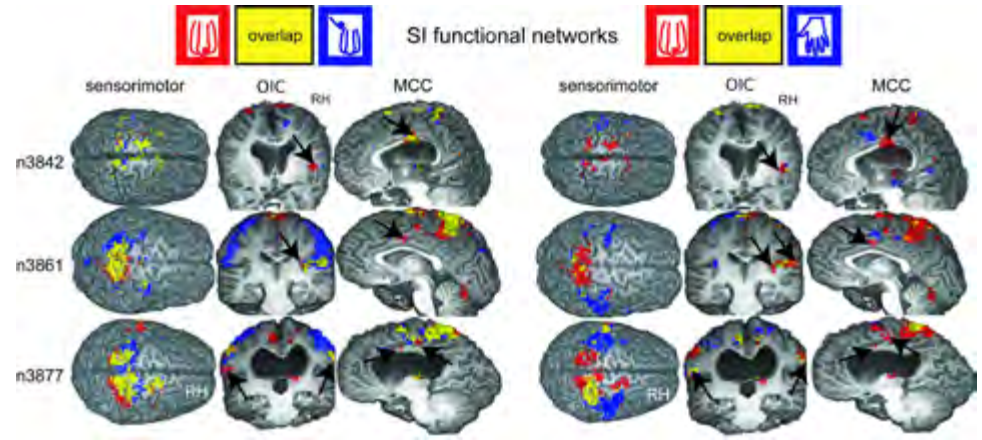

Figure 4: SI functional networks. Brain areas that correlated in time with the primary somatosensory cortex (SI) were determined by calculating the Granger causality total information for each voxel of the brain, representing SI functional networks. Depicted are voxels that over stimulation sessions were among the 5% most significantly correlated with SI regions of interest. The SI functional network activated by stimulation of the surgically re-innervated penile glans is depicted in red. The right panel shows this network together with the SI functional network associated with stimulation of the left index finger (blue), whereas the blue color in the left panel represents the SI functional network associated with stimulation of the right groin. Note how left-sided glans stimulation recruits an SI functional network that is more similar to that resulting from stimulating the right groin (yellow color, left panel) than to that resulting from left index finger stimulation (yellow color, right panel). Areas unique to the penis SI network (i.e., red color in both panels) over sessions and subjects are indicated with a black arrow. MCC, midcingulate cortex; OIC, operculoinsular cortex; RH, right hemisphere; SI, primary somatosensory cortex.

Discussion

In the present study we had a unique opportunity to study the cerebral functional correlates of newly acquired penile sensitivity in three male individuals with SB. This new function was obtained by transposing the disconnected penis to the IIN, a groin nerve (TOMAX-procedure, [6,7]). Our primary question was how the newly perceived penis would be mapped onto the brain after a life-long disconnection until surgery. Using non-sexual, non-painful sensory stimulation of penis, groin and finger, we found that SI activations due to penile and groin stimulation were similar, while stimulation of these two sites revealed segregated functional networks beyond SI.

The first crucial finding of our study was that indeed the SI cortical representation of the newly perceived penis remained virtually identical to that of the groin, even though subjects easily distinguished between the two regions. This unchanged site of activation was found on the expected location on the dorsal postcentral gyrus, contralateral to the site of stimulation in all three patients [9,10]. Paintbrush stimulation of the left index finger, which was used as

a positive control for the effectiveness of the stimulation paradigm, resulted in clear activation of the right hand area of SI, the dorsolateral postcentral gyrus [12].

Comparing the SI brain activations due to stimulation at the different sites revealed no clear and significant differences that could account for the subjective distinction of penis from groin. However, GC from SI revealed distinct functional networks for all three stimulation areas. As hypothesized, and consistent with the study's main effects, the networks that responded to glans and groin stimulation were very similar to each other with foci that particularly overlapped in bilateral medial and paramedial superior cortical areas of the two hemispheres, centered on the dorsal SI. This included in all subjects parts of the superior parietal lobule, which lies posteriorly adjacent to SI (consistent with the literature [10]). The symmetry is due to the fact that the right groin and the glans were connected to the right and left IIN respectively.

The networks also differed in some respects, most notably that the glans network was larger than the groin network. We were specifically interested in areas responding to glans but not to groin stimulation because this comparison might provide insight into the cerebral basis of a reorganized body scheme and potentially about erogeneity. It is important to stress that these network differences, although few in number, were robust and consistent across subjects and sessions.

One of the most conspicuous areas that was consistently coupled to glans SI and not to groin SI was the pMCC. The MCC is a major integrator of cognition, drive, and of motor and autonomic control [22]. Operating at this critical interface, MCC might assure that behavioral demands are met by appropriate levels of sympathetic arousal [23,24]. Sufficient sympathetic tone plays a crucial role in mammalian sexual activity [25] and the MCC has often been implicated in human sexual pleasure and arousal [11,26,27,28]. It also fails to activate in men with psychogenic erectile dysfunction watching pornography, relative to men who do have penile responses [26]. The volume of this part of the MCC is associated with the personality trait neuroticism [29] and may in this experiment be related to enhanced self-consciousness when the penis was touched relative to the control areas. These different lines of evidence suggest that pMCC recruitment into the glans SI network could be related to acquired meaningfulness and potential erogeneity of IIN tactile information after the TOMAX procedure.

The parietal operculum and insula are both related to emotional and higher

order aspects of bodily sensations and share the same cytoarchitecture [30]. Also, the areas are often coactivated and to reflect this functional similarity the term OIC is used here and elsewhere to indicate both indiscriminately [31,32,33,34]. In all three subjects and across both sessions, glans stimulation (relative to groin stimulation) recruited the right OIC into the glans SI network which could be related to the acquired meaningfulness (and possibly erogeneity) of IIN tactile information from a penile origin after the TOMAX procedure. The right parietal operculum is a plausible candidate area to encode additional meaning e.g. erogeneity because it is consistently activated during stimulation of the flaccid [10,35] or erect penis [11,36]. It is also activated during penile erection due to video stimulation [37,38]. The insula is an area well established as the physical substrate of the vital somatosensory body map [39], and the posterior insula is another plausible candidate area to encode erogeneity because it responds strongly to penile stimulation by the partner in an erotic context [11,36], to non-genital pleasant touch [40], and is correlated with penile circumference without stimulation [38,41]. The degree of insula activity reflects the emotionality and perceived intensity of a genital somatosensory stimulus in females [42]. Additional network activity in the posterior insula could thus reflect the pleasantness of touch, some link or transfer to penile erection, or both.

The conjoined MCC and OIC responses to neutrally intended penis stimulation may represent a more elaborate recruitment of the new body scheme (placing the penis in the midline) based on previous experience. Experiences with the new penile functions might thus be regarded to represent action-based reinforcement of body scheme in which particularly the secondary somatosensory cortex plays an important role [43,44,45]. Intriguingly, the monkey posterior insula is known to have reciprocal anatomical connections with an area that may be considered the homologue of human MCC [46], and such connectivity is confirmed by functional connectivity studies in humans [47]. An MCC-OIC network thus appears active in all three subjects in response to penile stimulation relayed to the nervous system through a groin nerve. Thus far, we consider this network as related to the altered meaning and potentially to acquired erogeneity of afferent IIN information after TOMAX surgery.

Some areas were recruited into the SI network for groin stimulation but not for glans stimulation. This was the case in all three subjects in the left dorsal postcentral gyrus and left superior parietal lobule. These areas are involved in localization of

touch and body scheme respectively. The fact that these are not emotional nor limbic areas confirms the notion that network activations specifically due to penis stimulation, i.e. OIC and pMCC, are more related to emotionality or salience.

Limitations are that we were only able to include three patients in this initial study and that brain abnormalities prevented a group level analysis. Post-TOMAX patients are rare and often MRI incompatible due to ventriculoperitoneal drains, osteosynthesis material or high emotionality. The brain activations we describe often had $p > 0.05$, but activation patterns were biologically plausible with little noise and the peak voxels did reach $p < 0.05$. We did not scan a healthy control cohort nor the pre-TOMAX situation in these three patients, instead we used the unoperated groin as a control condition in the same subjects. Another limitation was that we applied non-sexual tactile stimulation only.

A strength of the present study is the absence of penile somatosensation in unoperated men with SB making the present study unique at this moment. The network analysis using GC produced robust, repeatable, specific and biologically plausible functional networks related to SI function. The network that correlated with the penis SI was larger than that for groin SI, which is consistent with the notion that extra meaning became attached to the IIN somatosensory input after TOMAX.

From a broader perspective, we could speculate that the change in interpretation of genital information from a gnostic to a potentially erotic flavor, and an associated 'feeling of being more normal', in SB patients with a *de novo* innervated penis could be due to specific recruitment of pMCC and OIC. This might include an 'automatic' coupling to regions that mediate sympathetic arousal and enhanced interpretation of the sensory stimulus. Sensory information is used to maintain one's body scheme, which implies that spatial relationships of its constituents are adequately represented. In conclusion, changing the origin of the IIN receptive field from groin to penis recruits a higher order somatosensory pMCC-OIC network that presumably encodes enhanced meaning/salience or a remapped body scheme or both.

TOMAX patients may provide a possibility to study central somatosensory reorganization in relation to sexual development, which has so far been outside the reach of neuroscience.

Reference

1) Lassmann J, Garibay Gonzalez F, Melchionni JB, Pasquariello PS Jr, Snyder HM 3rd (2007) Sexual function in adult patients with spina bifida and its impact on quality of life. J Urol 178: 1611-1614.

2) Verhoef M, Barf HA, Vroege JA, Post MW, van Asbeck FW, Gooskens RH, Prevo AJ (2005) Sex education, relationships, and sexuality in young adults with spina bifida. Arch Phys Med Rehabil 86: 979-987.

3) Sandler AD, Worley G, Leroy EC, Stanley SD, Kalman S (1996) Sexual function and erection capability among young men with spina bifida. Dev Med Child Neurol 38: 823-829.

4) Dik P, van Gool JD, de Jong TP (1999) Urinary continence and erectile function after bladder neck sling suspension in male patients with spinal dysraphism. BJU Int 83: 971-975.

5) Palmer JS, Kaplan WE, Firlit CF (1999) Erectile dysfunction in spina bifida is treatable. Lancet 354: 125-126.

6) Overgoor ML, Kon M, Cohen-Kettenis PT, Strijbos SA, de Boer N, de Jong TP (2006) Neurological bypass for sensory innervation of the penis in patients with spina bifida. J Urol 176: 1086-1090.

7) Overgoor ML, de Jong TP, Cohen-Kettenis PT, Edens MA, Kon M (2012) Increased sexual health after restored genital sensation in male patients with spina bifida or a spinal cord injury: the TOMAX procedure. J Urol: doi: 10.1016/j.juro.2012.10.020.

8) Juranek J, Fletcher JM, Hasan KM, Breier JI, Cirino PT, Pazo-Alvarez P, Diaz JD, Ewing-Cobbs L, Dennis M, Papanicolaou AC (2008) Neocortical reorganization in spina bifida. Neuroimage 40: 1516-1522.

9) O'Reilly JX, Woolrich MW, Behrens TE, Smith SM, Johansen-Berg H (2012) Tools of the Trade: Psychophysiological Interactions and Functional Connectivity. Soc Cogn Affect Neurosci. 7:604-609.

10) Kell CA, von Kriegstein K, Rösler A, Kleinschmidt A, Laufs H (2005) The sensory cortical representation of the human penis: revisiting somatotopy in the male homunculus. J Neurosci 25(25): 5984-5987.

11) Georgiadis JR, Farrell MJ, Boessen R, Denton DA, Gavrilescu M, Kortekaas R, Renken RJ, Hoogduin JM, Egan GF (2010) Dynamic subcortical blood flow during male sexual activity with ecological validity: a perfusion fMRI study. Neuroimage 50: 208-216.

12) Nelson AJ, Staines WR, Graham SJ, McIlroy WE (2004) Activation in SI and SII: the influence of vibrotactile amplitude during passive and task-relevant stimulation. Brain Res Cogn Brain Res 19: 174-184.

13) Granger C (1969) Investigating causal relations by econometric models and cross-spectral methods.. Econometrica 37(3): 424-438.

14) Geweke J (1982) Measurement of linear dependence and feedback between multiple time series.. J Am Statist Assoc 77(378): 304-313.

15) Goebel R, Roebroeck A, Kim DS, Formisano E (2003) Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping. Magn Reson Imaging 21: 1251-1261.

16) Roebroeck A, Formisano E, Goebel R (2005) Mapping directed influence over the brain using Granger causality and fMRI. Neuroimage 25: 230-242.

17) Harrison L, Penny WD, Friston K (2003) Multivariate autoregressive modeling of fMRI time series. Neuroimage 19: 1477-1491.

18) Sirotin YB & Das A (2009) Anticipatory haemodynamic signals in sensory cortex not predicted by local neuronal activity. Nature 457: 475-479.

19) Schippers MB, Roebroeck A, Renken R, Nanetti L, Keysers C (2010) Mapping the information flow from one brain to another during gestural communication. Proc Natl Acad Sci U S A. 107(20):9388-9393.

20) Shannon CE (1948) A Mathematical Theory of Communication. Bell Sys Tech J 27: 379–

423 & 623–656.

21) Gel'fand I & Yaglom A (1959) Calculation of amount of information about a random function contained in another such function. Am Math Soc Transl Ser 2: 3-52.

22) Paus T (2001) Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci 2: 417-424.

23) Critchley HD, Mathias CJ, Josephs O, O'Doherty J, Zanini S, Dewar BK, Cipolotti L, Shallice T, Dolan RJ (2003) Human cingulate cortex and autonomic control: converging neuroimaging and clinical evidence. Brain 126: 2139-2152.

24) Critchley HD, Nagai Y, Gray MA, Mathias CJ (2011) Dissecting axes of autonomic control in humans: insights from neuroimaging. Auton Neurosci 161: 34-42.

25) Pfaff D, Ribeiro A, Matthews J, Kow LM (2008) Concepts and mechanisms of generalized central nervous system arousal. Ann N Y Acad Sci 1129: 11-25.

26) Cera N, Delli Pizzi S, Di Pierro ED, Gambi F, Tartaro A, Vicentini C, Paradiso Galatioto G, Romani GL, Ferretti A (2012) Macrostructural alterations of subcortical grey matter in psychogenic erectile dysfunction. PLoS ONE 7: p. e39118.

27) Georgiadis JR & Kringelbach ML (2012) The human sexual response cycle: brain imaging evidence linking sex to other pleasures. Prog Neurobiol 98: 49-81.

28) Georgiadis JR, Kringelbach ML, Pfaus JG (2012) Sex for fun: a synthesis of human and animal neurobiology. Nat Rev Urol 9: 486-498.

29) DeYoung CG, Hirsh JB, Shane MS, Papademetris X, Rajeevan N, Gray JR (2010) Testing predictions from personality neuroscience. brain structure and the big five. Psychol Sci 21: 820-828.

30) Mesulam MM & Mufson EJ (1982) Insula of the old world monkey. I. architectonics in the insulo-orbito-temporal component of the paralimbic brain. J Comp Neurol 212: 1-22.

31.) Iannetti GD, Zambreanu L, Wise RG, Buchanan TJ, Huggins JP, Smart TS, Vennart W, Tracey I (2005) Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. Proc Natl Acad Sci USA 102: 18195-18200.

32) Nir RR, Lev R, Moont R, Granovsky Y, Sprecher E, Yarnitsky D (2008) Neurophysiology of the cortical pain network: revisiting the role of SI in subjective pain perception via standardized low-resolution brain electromagnetic tomography (SLORETA). J Pain 9: 1058-1069.

33) Csifcsak G, Nitsche MA, Baumgärtner U, Paulus W, Treede RD, Antal A (2009) Electrophysiological correlates of reduced pain perception after theta-burst stimulation. Neuroreport 20: 1051-1055.

34) Longo MR, Iannetti GD, Mancini F, Driver J, Haggard P (2012) Linking pain and the body: neural correlates of visually induced analgesia. J Neurosci 32: 2601-2607.

35) Mäkelä JP, Illman M, Jousmäki V, Numminen J, Lehecka M, Salenius S, Forss N, Hari R (2003) Dorsal penile nerve stimulation elicits left-hemisphere dominant activation in the second somatosensory cortex. Hum Brain Mapp 18: 90-99.

36) Georgiadis J & Holstege G (2005) Human brain activation during sexual stimulation of the penis. J Comp Neurol 493: 33-38.

37) Redouté J, Stoléru S, Grégoire MC, Costes N, Cinotti L, Lavenne F, Le Bars D, Forest MG, Pujol JF (2000) Brain processing of visual sexual stimuli in human males. Hum Brain Mapp 11: 162-177.

38) Ferretti A, Caulo M, Del Gratta C, Di Matteo R, Merla A, Montorsi F, Pizzella V, Pompa P, Rigatti P, Rossini PM, Salonia A, Tartaro A, Romani GL (2005) Dynamics of male sexual arousal: distinct components of brain activation revealed by fMRI. Neuroimage 26: 1086-1096.

39) Karnath H & Baier B (2010) Right insula for our sense of limb ownership and self-awareness of actions. Brain Struct Funct 214: 411-417.

40) Björnsdotter M, Löken L, Olausson H, Vallbo A, Wessberg J (2009) Somatotopic organization of gentle touch processing in the posterior insular cortex. J Neurosci 29: 9314-9320.

41) Mouras H, Stoléru S, Moulier V, Pélégrini-Issac M, Rouxel R, Grandjean B, Glutron D, Bittoun J (2008) Activation of mirror-neuron system by erotic video clips predicts degree of induced erection: an fMRI study. Neuroimage 42: 1142-1150.

42) Pukall CF, Strigo IA, Binik YM, Amsel R, Khalifé S, Bushnell MC (2005) Neural correlates of painful genital touch in women with vulvar vestibulitis syndrome. Pain 115: 118-127.

43) Jäncke L, Kleinschmidt A, Mirzazade S, Shah NJ, Freund HJ (2001) The role of the inferior parietal cortex in linking the tactile perception and manual construction of object shapes. Cereb Cortex 11: 114-121.

44) Hinkley LB, Krubitzer LA, Nagarajan SS, Disbrow EA (2007) Sensorimotor integration in SII, PV, and parietal rostroventral areas of the human Sylvian fissure. J Neurophysiol 97: 1288-1297.

45) Beudel M, Zijlstra S, Mulder T, Zijdewind I, de Jong BM (2011) Secondary sensory area SII is crucially involved in the preparation of familiar movements compared to movements never made before. Hum Brain Mapp 32: 564-579.

46) Taylor KS, Seminowicz DA, Davis KD (2009) Two systems of resting state connectivity between the insula and cingulate cortex. Hum Brain Mapp 30: 2731-2745.

47) Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A (2011) Functional connectivity of the insula in the resting brain. Neuroimage 55: 8-23.

Chapter 7

Summary and Discussion

Summary and Discussion

Chapter 1

Patients with a low spinal lesion have many neurological deficits, but of the quality of life improvements desired by spinal lesion (SL) patients, regaining sexual function has highest priority. Most patients with a low spinal lesion are still actively interested in sex, with intact erectile function but no penile sensation: this can lead to considerable frustration. In a normal situation, sensory impulses from the glans penis are transmitted through both dorsal penile- (DNP) and pudendal nerves, to the 2nd–4th sacral roots. They continue through the spinal cord to the sensory cortex, unless interrupted by a spinal lesion, as in spina bifida (SB), or by spinal cord injury (SCI). Since there have been no studies dealing specifically with the role of penile sensation in SL patients, the aim of this thesis was to increase the sexual health in these patients by restoring their penile sensation.

Anatomical cadaver dissections were performed to design an operative TOMAX procedure (TO MAXimize sensation, sexuality and quality of life), in which the ilioinguinal nerve is cut distally in the groin and joined by microneuroraphy to the proximally divided DNP at the base of the penis on one side. The idea behind this nerve transfer is that the high spinal entry level (L1) of the ilioinguinal nerve might re-route sensory information from the glans via the DNP and ilioinguinal nerve to the sensory cortex, thereby restoring sensation and bypassing a spinal lesion below L1.

To test the hypothesis ***'Penile sensation in low SL patients can be restored (or created) and will contribute to their sexual health'*** five studies were performed to answer the following questions concerning the TOMAX procedure:

- Is the procedure technically feasible in SB patients and does it lead to penile sensation? **(Chapter 2)**
- Does it increase sexual health and satisfaction in SB and SCI patients? **(Chapter 3)**
- Can it be safely done bilaterally, and in which patients can it be performed? (**Chapter 4)**
- Can we describe the procedure in detail in order to teach other surgeons how to perform this surgery? **(Chapter 5)**
- Can we understand the possible changes in the brain provoked by the TOMAX procedure? **(Chapter 6)**

Chapter 2

This chapter describes a prospective pilot study, in which the TOMAX procedure was performed in three low SB patients (17, 18 and 21 years old) who had no penis sensation but normal sensation in the groin. Using simple neurological tests for touch and temperature, sensory changes in the penis and groin were measured. To gain more knowledge about sexuality in these patients, an independent sexologist conducted interviews and analysed questionnaires they filled in.

Postoperatively, all patients gained excellent sensation in the glans penis on the operated (unilateral) side. Groin sensation was diminished due to the division of the ilioinguinal nerve, but without any discomfort or pain. After 5-8 months post-operatively, the stimuli of the glans penis were experienced as if the groin was being touched, but after 12 months two patients had 'remapped' sensibility to their glans penis.

Postoperatively, all patients retained their ability to have an erection, while their ejaculation, if present, was unchanged. All patients were positive about the results of their operation: they felt sensations in an area where they had never had any sensation before; they felt less handicapped and their penis had become a more integrated part of their body. In two patients, masturbation had become more meaningful and in one patient the new, erogenous-like sensations stimulated him to be more sexually active, making the sexual relationship with his girlfriend more meaningful.

The differences between the patients might be explained by the fact that the capacity of the human brain to adapt to peripheral input depends on both the pattern and frequency of use: masturbation was performed more frequently by the two 'remapped' patients and one of them was also sexually active with a partner. These activities can be seen as sensory education programs. The ability to have erections depends on the preservation of the psychogenic and/or reflexive pathways of erectile function. Psychogenic erections are likely to be preserved in these patients because their spinal lesion was lower than Th10-L2. Reflexive erections, on the other hand, are elicited by direct penile stimulation through the DNP and pudendal nerves. Due to its role in reflexive erections, and taking into account that we wanted to retain the capacity of erection at all costs, we decided not to operate bilaterally but to leave one DNP intact.

Chapter 3

These promising preliminary results justified conducting a second study to investigate the outcome of the TOMAX procedure in 30 low-lesion SB and SCI patients, with no penile but normal groin sensation. Besides simple neurological tests for touch and temperature, more detailed quantitative Semmes-Weinstein monofilaments for fine touch were used. To protect reflex erections we left the right or left DNP intact, based on preoperative bilateral bulbocavernosus reflex (BCR) measurements. Psychological functioning and sexuality were measured by an independent sexologist using interviews and questionnaires, and patients were also asked about their urine continence management.

When exploring the groin in three SCI patients, the ilioinguinal nerve could not be used due to bilateral absence (anatomical variance) or damage caused by prior surgery. However, 27 patients were successfully operated (18 SB, median age 18.5 years (range 13–40 yrs) and 9 SCI patients, median age 30 years (21–42 yrs)). The nerve transposition resulted in unilateral glans penis sensation in 80% of the patients, which was experienced as *'groin'* by 54% and as '*glans'* by 46%. Donor groin sensibility was diminished in most patients, but was not missed and was without any discomfort or pain. Some patients felt cold sensations while introducing a catheter and became aware of urine passing through the urethra. These changes were hygienically and socially important for them.

Patients had more satisfaction with their erections during masturbation, which could be more easily maintained. They masturbated more frequently, had more pleasurable sensations and sometimes orgasms. Five patients masturbated for the first time ever, while three patients experienced their first orgasm. Patients were more confident in their sexual activities, aware of their partner touching the penis and able to appreciate the moment of intromission. This led to more frequent and more satisfying sexual activities, and a more open and meaningful sexual relationship. The new sensation significantly enhanced their quality of sexual functioning and satisfaction.

The sensory changes from *'groin'* to *'glans',* with the development of 'pleasurable sensations', can be attributed to brain plasticity. Interestingly, the patients with actual '*glans'* sensations were more likely to have erogenous benefits than those with sensations '*in the groin*'. Age, origin or level of SL were not factors in predicting sensory and functional recovery. The ability to have erections depends on preserving the psychogenic and/or reflex pathways of erectile function. In five

'psychogenic-only' patients, postoperative direct stimulation of the penis helped them to induce and maintain the erection more easily. Probably this is a *'sensory feedback-enhanced (psychogenic) erection*' rather than a 'real' reflex erection, since the neurological bypass did not reconstruct the reflex arc S2–S4.

Chapter 4

The TOMAX procedure restores genital sensation *unilaterally* because it connects *one* dorsal nerve of the penis to the ipsilateral ilioinguinal nerve. We wondered (and patients asked) if a *bilateral* procedure could be done safely with a chance of full glans sensation and even more erogenous sensations. This procedure, however, entails cutting both DNPs, probably risking patients' erection/ejaculation ability: besides transmitting penile sensory impulses to the brain, both DNPs play a crucial role in reflex erections (RE) and vibratory and other ejaculations through the sacral (S2-S4) reflex arc. Selection criteria for the performance of a safe bilateral TOMAX procedure should focus on the signs of remaining DNP function. To investigate this **,** we determined the integrity of the S2-S4 reflex arc in our patients by:

(1) bilateral needle EMG-BCR measurements (in this reflex, the right and/or left perineal bulbocavernosus muscle contracts on stimulating both DNPs) and,
(2) conducting interviews on their preserved ability to have RE (an erection elicited by direct penile stimulation).

We collected these data pre-operatively from the same 30 patients (18 SB and 12 SCI, median age 29.5 years (range 13-59 yrs), whose spinal lesions ranged from T12 (incomplete) to low sacral and who had already been selected for a unilateral TOMAX procedure (described in Chapter 3). This new study set out to determine how often signs of DNP function were still present in low SL patients and whether this knowledge could be used to decide on a unilateral or bilateral procedure. Eventually, this research should lead to bilateral TOMAX surgery.

We found that seven patients (23%) had RE, of which four (57%) had a positive bilateral BCR. On the other hand, there were nine (30%) patients with a positive BCR, of which four (44%) had RE.

This shows that even patients with a low spinal lesion (including sacral involvement) can have signs of remaining DNP function and/or an intact S2-S4 reflex arc, which means that a bilateral TOMAX procedure (involving cutting both

DNPs) might be risky in some cases.

The ability to have erections depends on preserving the psychogenic (PE) and/or reflex pathways (RE) of erectile function. PE is regulated by a centrally connected, sacral erection centre or, if the sacral region is damaged/disconnected, by a sympathetic spinal centre at T10–L2. The sacral region and DNP/pudendal nerves are mainly involved in RE. In theory, these reflexes imply that the level of spinal lesion influences erectile function in different ways: in high lesions (above T10-L2), PE will be lost but RE remains intact, whereas low lesions in the sacral area result in losing RE but retaining an intact PE. As the BCR reflects the integrity of the S2-S4 reflex arc, it should be intact in patients with RE. In the literature, it is generally stated that high-lesion patients have both an intact RE and BCR, while low-lesion patients have no remaining RE or BCR. However, we found no reliable association between BCR and RE in patients with a low lesion. These remaining signs of DNP function in low lesion patients might be explained by the fact that more nerve connections are intact than expected from the lesion level alone (incomplete lesions) or unknown nerve connections have re-routed the BCR and RE pathways via higher/other spinal levels.

This study revealed that self-reported RE and BCR measurements, when used independently, do not provide strong enough evidence to confirm or rule out remaining DNP function. We therefore propose that both parameters should be used in a pre-operative protocol that decides on performing either a unilateral - or bilateral TOMAX procedure (**Table 1)**.

Table 1. Pre-operative protocol to decide on a unilateral or bilateral TOMAX procedure

	RE +	RE-	Which side
BCR +/+	Unilateral	Unilateral	Right or left
BCR +/-	Unilateral	Unilateral	The 'BCR-'
BCR -/-	Unilateral		Right or left
BCR -/-		Bilateral	Right *and* left

This protocol shows that if a patient has an intact RE (RE+), a unilateral TOMAX procedure should be performed, in which the BCR determines which side to use. But if a patient has no RE (RE-), the BCR will determine whether a unilateral or bilateral procedure should be performed. As this protocol has been designed for future patients, its safety on preserving RE in a unilateral procedure and the

possible benefits of a bilateral procedure still have to be proven. But when this protocol is retrospectively applied to the 30 patients who had a unilateral TOMAX procedure, the results suggest that the use of BCR measurements is safe for ensuring RE are retained.

To address the potential additional benefit of bilateral surgery, we recently operated on three patients bilaterally, resulting in full glans sensation for two patients. Although based on only a small number of patients, we can report that a bilateral procedure is technically feasible and theoretically increases the chance of re-innervating the glans, with the possibility of full glans sensation and probably more erogenous sensation. We expect to be able to offer 60% of new patients a bilateral procedure.

Chapter 5

In the USA, the estimated birth prevalence of spina bifida in 2005 was 1.9 per 10,000 live births and, in 2010, there were 3.1 cases of SB per 10,000 children and adolescents, aged 0 to19 years. For spinal cord injury, the incidence is estimated at 40 cases per 1 million of the population in the USA and the prevalence is estimated at 223-755 cases per million worldwide. This means that ilioinguinal neurotization of the DNP can be used to restore erogenous penile sensation and improve the quality of life and sexual health in large numbers of patients with no penile but good groin sensation. These numbers justify making the TOMAX procedure easily available to peripheral nerve-surgeons worldwide.

For this reason **this chapter** describes the most up-to-date information on issues involving the TOMAX procedure from our recent experience with an expanded series of 43 nerve transfers in 40 patients. We place emphasis on a detailed description and provide a video of the surgical technique.

Patient selection

Absence of penile sensation, but with remaining groin sensation, was not only seen in low-lesion SB (n=21) and SCI (n=13) patients in our study of 40 patients. Other patients with a similar low-lesion neurological dysfunction due to a conus-medullaris- or cauda-equina syndrome (n=3), a spondylodiscitis (n=1), or following partial resection of the sacrum due to a chordoma (n=2) were included and operated. Half of these patients (3/6) finally developed tactile and/or erogenous sensation. This shows that all patients with no penile- but good sensation of the

groin might be candidates for TOMAX, no matter what the origin of their problem.

Although age is inversely related to sensory recovery, two older patients (aged 42 and 46 yrs) did develop erogenous-like glans sensations two years after having the TOMAX procedure performed. The age limit for good results still has to be determined.

Inguinal surgery

Non-usable and damaged/scarified ilioinguinal nerves were encountered in all patients with prior groin/lower abdominal surgery involving scars over the course of the ilioinguinal nerve: inguinal hernia repair (n=2), orchidopexy- (n=1) and extensive hip surgery (n=1). We now discourage patients with prior surgery involving scars over the course of the ilioinguinal nerve from having TOMAX surgery on that particular side.

Ilioinguinal anatomy

In three patients, the ilioinguinal nerve was absent bilaterally and in two it was absent unilaterally. Due to these anatomical variations, we now ensure that new patients are informed that the groin nerve may be unilaterally or bilaterally absent in 7-12% of cases, making contralateral exploration necessary in unilateral cases. In one case an alternative procedure was done in which we gained enough length of the iliohypogastric nerve by extended subcutaneous dissection for coaptation to the DNP. Unfortunately, one year later, the patient has developed no sensation . In another recent case (not published), we added a nerve graft to the iliohypogastric nerve, but no results are available yet.

DNP anatomy

The penile portion of the DNP consists of a medial bundle to the glans and a lateral bundle to the shaft and urethra bilaterally. At the dorsal base these bundles join together most of the time and can be used for the connection with the ilioinguinal nerve.

Bilateral surgery

As described in Chapter 4, a protocol was developed to safely select patients for a unilateral- or bilateral procedure, using self-reported RE combined with bilateral needle-EMG- bulbocavernosus reflex (BCR) measurements. If both RE and BCR

are absent, bilateral surgery can be performed. We recently operated on three patients on both sides, resulting in full glans sensation for two of them.

Surgical technique

A detailed description of the operating technique is given in this chapter including a step-by-step video *(http://links.lww.com/PRS/B52)*.

Patient information

Pre-operatively patients are told that they have about 80% chance of regaining unilateral/bilateral sensation, which will mature from groin- to glans sensation in about 46% of them, with the chance of erogenous sensations. The first signs of sensation normally appear after 4-6 months and can be somewhat painful although this will disappear over time. Patients are advised to do 'sensory (re-) educational-homework' to promote neural remapping of the brain. After 1-2 years, a definite outcome should have been attained, but it is important that the sensations should not be compared with a normal non-spinal-lesion situation (i.e. before the SCI). The sensations gained should be seen as a serious and positive step forwards. Diminished sensation in the groin is noticeable, but is without any problems, neuroma or pain.

In summary, this synthesis of the procedural and technical experience of 43 TOMAX nerve transfers over the last 12 years might help medical professionals involved in the care of low spinal lesion patients to adopt this concept and develop it further. Plastic surgeons skilled in peripheral nerve- and microsurgery should be aware of this procedure and be part of the team treating patients with SB or SCI. In addition, reliable and realistic information should be given to the patients to avoid disappointment. Recently, two successful penile re-innervations were performed in the USA, at Seattle Children's Hospital (Seattle, Washington) by Thomas Lendvay and Tony Avellino.

Chapter 6

Despite the different receptive properties of penile glans and inguinal skin, most men treated with TOMAX experience their new sensations from the glans as pleasant and, in the appropriate context, as erotic, leading to improved sexual health and function. The somatosensory plasticity that remaps groin sensation to penis sensation takes at least one year. This course of events is interesting,

because normal development of erotic genital feelings typically occurs during early adolescence, but these are difficult to study because of obvious ethical constraints. TOMAX patients could thus provide an adult human model of sexual development.

In this chapter we enrolled three MRI-compatible post-TOMAX patients and scanned them using functional MRI (fMRI), while penis, groin and finger were stimulated with a soft paint brush. We hypothesized that reorganization would not occur in the primary sensory cortex (SI), but that activation differences between groin and penis would become apparent beyond SI. Any differences in brain activation between the groin and penis could provide insight into the remapping process of the body scheme and could hint at areas that allow for development of erogeneity. We included three male SB patients (age 19, 23, 38 yrs; post-TOMAX 4.5, 4.9, 2.9 yrs). All subjects were right handed and had intact spinal cord function of at least innervation level L3 or higher. They all had TOMAX-acquired unilateral sensation on the left side of the glans penis, as well as intact sensibility in the contralateral (unoperated) right inguinal region.

We stimulated five body areas: the left and right half of the glans penis, the left and right inguinal area, and the radial surface of the left index finger. We used moving touch as a mechanical stimulus, which was applied with a small paintbrush for 2 s at a frequency of 1.5 Hz. The intact right inguinal area served as a control for the re-innervated glans penis because it is innervated by the ilioinguinal nerve opposite to the operated side. The left index finger served as an additional control for central somatosensory processing and for the data pre-processing and analysis. Thirty stimulations were applied to all five skin areas, they were distributed over three sessions, adding up to 150 stimulations per patient in total. Images were acquired on a Philips Intera 3T MR-scanner, equipped with SENSE 8-channel head coil. A T1-weighted anatomical MRI was acquired after the echo planar imaging (EPI) scans and served as anatomical reference for the brain activations.

The data were analysed in two stages: first, the foci of activation within the primary somatosensory cortex (SI) resulting from the paintbrush stimulation were identified and spherical 56 mm^3 regions of interests (ROIs) were drawn around the centre of the SI. Second, we used Granger Causality (GC) analysis to identify brain areas that were functionally connected with the identified SI-ROIs.

The first crucial finding was that, indeed, the SI cortical representation of the

newly perceived penis remained virtually identical to that of the groin, even though subjects easily distinguished between the two regions. This unchanged site of activation was found at the expected location, on the dorsal postcentral gyrus, contralateral to the site of stimulation in all three patients. The functional networks that responded to glans and groin stimulation were very *similar* to each other, with foci that particularly overlapped in the bilateral medial and paramedial superior cortical areas of the two hemispheres, centered on the dorsal SI. The symmetry is due to the fact that the right groin and the glans were connected to the right and left ilioinguinal nerve respectively.

The networks also *differed* in some respects. It was found that the glans network was larger than the groin network and that the middle cingulate cortex (pMCC) and the right parietal operculum and insula (OIC) were consistently coupled to glans SI and not to groin SI. Interestingly, pMCC is an integrator of cognition, drive, and of motor and autonomic control, and has often been implicated in human sexual pleasure and arousal. OIC is related to emotional and higher order aspects of bodily sensations and penile stimulation. This suggests that pMCC and OIC recruitment into the glans SI network could be related to acquired meaningfulness and potential erogeneity of ilioinguinal nerva tactile information from a penile origin after the TOMAX procedure.

Some areas were recruited into the SI network for groin stimulation but not for glans stimulation. This was the case in all three subjects in the left dorsal postcentral gyrus and left superior parietal lobule. These areas are involved in localization of touch and body scheme, respectively. The fact that these are neither emotional nor limbic areas confirms the notion that network activations specifically due to penis stimulation, i.e. OIC and pMCC, are more related to emotionality or salience.

From a broader perspective, we could speculate that the change in interpretation of genital information from a gnostic to a potentially erotic flavour, and an associated 'feeling of being more normal', in SB patients with a de novo innervated penis could be due to the specific recruitment of the pMCC and OIC. This might include an 'automatic' coupling to regions that mediate sympathetic arousal and enhanced interpretation of the sensory stimulus. Sensory information is used to maintain one's body scheme, which implies that the spatial relationships of its constituents are adequately represented. In conclusion, changing the origin of the ilioinguinal nerve receptive field from groin to penis recruits a higher-

order somatosensory pMCC-OIC network, which presumably encodes enhanced meaning/salience, or a remapped body scheme, or both.

Discussion on erogenous development

Besides remapped or changed interpretation of the sensory information, the reason why erogenous sensations develop may be explained by more factors. The glans contains predominantly free nerve endings (FNE) and unique genital end bulbs.[1,2] These are the end organs of the DNP axons and might be important in the cultivation of erogenous sensations. The sole role of these genital corpuscles in the development of erogenous sensations is probably limited, because large numbers of FNE are also present in the cornea and stimulation of the cornea[1] does not lead to erogenous sensations. It is more likely that erogenous sensation might be the quality of the pudendal nerve due to its correct cortical representation. Proof can be found in female-to-male transformations studies. If the reconstructed neo-phallus was re-innervated by the pudendal nerve, erogenous sensations were noticed, but using the ilioinguinal nerve only tactile sensibility developed.[3,4] Erogenous sensations could also be elicited by massaging the distal end of a cut pudendal nerve after trauma.[3] Genital corpuscles could not play a role in these patients.

Because the pudendal nerve is not involved in the TOMAX procedure, the development of erogenous sensations might be due to a combination of the above factors. There is evidence that sensory corpuscles are still present in SCI patients in 'under-lesional' glabrous skin.[5] However, we are the first to have studied genital corpuscles in SB and SCI patients, which are anatomically present as we have shown in biopsies taken from the glans of TOMAX operated patients.[6] Sensory impulses from these genital corpuscles are re-routed by the ilioinguinal nerve to an area in the sensory cortex close to the primary penile representation. We (Chapter 6) and others[7] have shown by fMRI study that the lower abdominal wall (i.e. groin) overlaps with that of the primary penile cortical representation.

The resultant of these factors, combined with a functional remodelling of the brain cortex (recruitment of a higher order somatosensory network) influenced by sensory (re-)education, might explain the development of erogenous sensations. This process is likely to be enhanced by the ability of the sensory cortex to interpret other peripheral stimuli as erogenous in nature.[8] In our patients the 'other peripheral stimuli' are actually coming from the genitals, making the erogenous

interpretation probably easier. Socially, the penis is a more accepted erogenous zone compared to other compensatory erogenous zones in SL patients. Restored penile sensation might therefore lead to more self-assurance. For example, in one patient, the groin area was an important erogenous zone. These sensations were now transferred to the glans, which was a more practical and socially acceptable location. Additionally, the tactile sensitivity gained can help in a physical and psychological way in sexual activities and is therefore beneficial to the excitement.

Discussion on other nerve transfers

Several other peripheral nerve re-routing strategies are available for SL patients. Like the TOMAX procedure, they involve a functional nerve from above the injury site being re-routed and connected to a nerve (root) affected by paralysis. These interventions use a vascularized ulnar or intercostal nerve graft often supported by additional sural-interposition grafts. Most are intended to restore leg muscle function [transposition to spinal canal,[9] lumbar nerve roots, femoral or obturator nerves[10]] or bladder- and bowel control [transposition to sacral roots[11] or muscular branches of pudendal nerve[10]]. Very few studies, however, have addressed restoration of some sensory function,[10] and none have been specifically designed to enhance penile sensation and sexual function. Only Zhang et al.[10] describes a technique especially to enhance some lateral gluteal, medial thigh and vulva sensation in high SCI patients, using the ulnar or intercostal nerves to re-innervate the ilioinguinal nerve and/or lateral femoral cutaneous nerves. These studies were, however, poorly designed and without any adequate follow-up. Although fascinating and promising, these interventions are particularly indicated for high SL patients and involve complex surgical techniques with significant (i.e. ulnar nerve) donor morbidity. Whereas the TOMAX procedure is designed for a different goal: the introduction of (erogenous) sensation to the penis in low lesion patients. It does not need nerve grafting and has a short re-innervation distance. Interestingly, combining Zhang et al.'s procedure with the TOMAX procedure might lead to glans sensations in patients with an SL above L1.

Theoretically, by using the 4th intercostal nerve to the nipple, erogenous sensations are more likely to develop.

Reference

1) Halata Z, Munger BL. The neuroanatomical basis for the protopathic sensibility of the 1) human glans penis. Brain Res. 1986;371:205-230.

2) Yang CC, Bradley WE. Somatic innervation of the human bulbocavernosus muscle. Clin Neurophysiol. 1999;110:412-418.

3) Gilbert DA, Horton CE, Terzis JK, Devine CJ,Jr, Winslow BH, Devine PC. New concepts in phallic reconstruction. Ann Plast Surg. 1987;18:128-136.

4) Gilbert DA, Jordan GH, Devine CJ,Jr, Winslow BH, Schlossberg SM. Phallic construction in prepubertal and adolescent boys. J Urol. 1993;149:1521-1526.

5) Marquez J, Perez-Perez M, Naves FJ, Vega JA. Effect of spinal cord and peripheral nerve injury on human cutaneous sensory corpuscles. an immunohistochemical study. J Peripher Nerv Syst. 1997;2:49-59.

6) R. de Wijn, M.L.E. Overgoor, M.Kon. Penile re-sensibilisation in low spinal lesion patients by the TOMAX procedure: histological background. Manuscript in preparation.

7. Kell CA, von Kriegstein K, Rosler A, Kleinschmidt A, Laufs H. The sensory cortical representation of the human penis: Revisiting somatotopy in the male homunculus. J Neurosci. 2005;25:5984-5987.

8) Gilbert DA, Williams MW, Horton CE et al. Phallic reinnervation via the pudendal nerve. J Urol. 1988;140:295-299.

9) Oppenheim JS, Spitzer DE, Winfree CJ. Spinal cord bypass surgery using peripheral nerve transfers: Review of translational studies and a case report on its use following complete spinal cord injury in a human. experimental article. Neurosurg Focus. 2009;26:E6.

10) Zhang S, Wang Y, Johnston L. Restoration of function in complete spinal cord injury using peripheral nerve rerouting: A summary of procedures. Surg Technol Int. 2008;17:287-291.

11) Livshits A, Catz A, Folman Y et al. Reinnervation of the neurogenic bladder in the late period of the spinal cord trauma. Spinal Cord. 2004;42:211-217.

Chapter 8

Conclusions and Future perspectives

Conclusions

We have shown that restoring penile sensation using the TOMAX procedure can enhance sexual health, sexual functioning and satisfaction in most male patients with a low spinal lesion. It also resulted in some improvement in managing urine incontinence, which helped increase personal hygiene and independence. Although low spinal patients have no sensation of the penis, signs of remaining DNP function can still be present, risking reflex erectile function in bilateral surgery. Using a newly designed protocol to select patients for a unilateral or bilateral procedure, the first bilateral cases have been operated on with promising results: bilateral surgery may enhance sexual function and satisfaction even further.

It was found that somatosensory plasticity takes at least one year to remap groin sensation to penis. The change of the origin of the ilioinguinal receptive field from groin to penis recruits a higher order somatosensory network, which presumably encodes enhanced meaning, or a remapped body scheme, or both.

Our experience of performing 43 TOMAX nerve transfers has led to guidelines on the surgical technique and possible pitfalls, and on indication, patient selection and providing realistic expectations. These tools are of importance for all medical and surgical professionals involved in the quality of life issues of low spinal lesion patients.

The TOMAX procedure can be used to restore penile sensation in large numbers of patients worldwide who have no penile but good groin sensation. TOMAX should become a standard procedure in such patients.

Future perspectives

As our experience with the TOMAX procedure continues to expand, in the future, we may be able to offer the procedure to young SB patients before puberty or restore clitoral sensation in women with a low SL. Patients with higher SL might benefit from the use of alternative (intercostal) nerve transfer to the DNP in combination with vascularized ilioinguinal- or non-vascularized sural nerve-grafts.

As the Ilioinguinal nerve can be anatomically absent, preoperative high-resolution echo or MRI might help to determine its presence or not. On the other hand, the value of the iliohypogastric nerve, with or without a nerve-graft, as alternative to an absent ilioinguinal nerve, needs to be studied more.

Patients with intact BCR might be offered an end-to-side nerve coaptation

technique, if the ilioinguinal nerve is long enough. Future studies may be designed comparing pre- and post-op BCR-measurements in unilaterally operated TOMAX patients to gain more knowledge on BCR (unilateral or bilateral) distribution.

Long-term follow up (5-10 years) will give a final insight in the meaning/ incorporation of the (re-) gained sensations in patients' daily life. Besides this, long-term follow up will show how often bilateral glans sensations will be developed following a unilateral TOMAX-procedure since we have noticed this in two patients.

Comparing pre- and postoperative fMRI in larger groups of TOMAX-patients might further expose the somatosensory network involved in remapping the brain from groin to glans to erogenous-like feelings.

General surgeons should now about the TOMAX-procedure, so they can use nerve sparing (endoscopic) techniques in inguinal hernia surgery in SL patients or plan a combined-TOMAX-procedure-and-hernia-repair in one session.

Sensory (re-) education programs might be developed by sexologists. For example, if the intact (donor) groin area and the still non- sensitive glans penis are already pre-operatively erotically stimulated while looking at the stimulated areas, the brain might prepare itself for what to come. Post-operatively, standardised glans penis stimulation protocols with visual feedback might help to recruit even more and higher order somatosensory networks in the brain with increased chance of developing erogenous sensations.

Chapter 9

Nederlandse
Samenvatting,
conclusies en toekomst

Hoofdstuk 1

Patiënten met een lage ruggenmergbeschadiging (spinaal letsel – SL) hebben veel neurologische uitvalsverschijnselen waarbij verminderde seksuele functie vaak als een probleem wordt ervaren. De meeste mannelijke patiënten met een beschadiging op laag spinaal niveau zijn net als iedereen, actief geïnteresseerd in seks, kunnen vaak een erectie krijgen, maar hebben geen gevoel in de penis: dit kan tot grote frustratie leiden. In een normale situatie worden de gevoels-impulsen van de eikel doorgegeven via de peniszenuw (nervus dorsalis penis - DNP) naar de 2e-4e heiligbeen (sacrale) wortel in het ruggenmerg. De impulsen worden vervolgens via het ruggenmerg naar de hersenschors (somatosensorische cortex) geleid waar gevoel wordt geregistreerd. Wanneer er sprake is van een beschadiging van het ruggenmerg, zoals spina bifida (open rug - SB) of een dwarslaesie (DL), gebeurt dit niet. Tot nu toe blijkt er geen wetenschappelijk onderzoek uitgevoerd te zijn dat zich specifiek richt op de rol van penile-sensatie bij SL-patiënten. Wij wilden dan ook met dit proefschrift de seksuele gezondheid bij deze patiënten proberen te verbeteren door het gevoel in hun penis te herstellen.

Na een aantal "operaties" op kadavers in het anatomische laboratorium werd een operatieve TOMAX-procedure ontwikkeld (*TO MAXimize* gevoel, seksualiteit en kwaliteit van leven). Bij deze ingreep wordt aan één zijde, de lieszenuw (nervus ilioinguinalis) vlak bij de basis van de penis doorgesneden en gehecht met behulp van de operatiemicroscoop aan de eveneens aan de basis van de penis doorgesneden penis zenuw. Het idee achter deze zenuw-omzetting (bypass) is dat het hoge ruggenmerg niveau waaruit de lieszenuw ontspringt, namelijk boven het niveau van de eerste lumbale wervel (L1), het mogelijk maakt de sensorische-gevoels informatie van de eikel via de penis zenuw en de lieszenuw om te leiden naar de hersenen. Hierdoor zou het gevoel in de penis hersteld kunnen worden omdat de spinale beschadiging onder L1 wordt omzeild.

Er werden vijf onderzoeken uitgevoerd om de hypothese '***peniele sensatie bij SL-patiënten kan worden hersteld (of gecreëerd) en zal bijdragen aan hun seksuele gezondheid***' te testen en een antwoord te kunnen geven op de volgende vragen ten aanzien van de TOMAX-procedure:

- Is de procedure technisch haalbaar bij patiënten met SB en leidt het tot gevoel in de penis? **(Hoofdstuk 2).**
- Verbetert de ingreep de seksuele gezondheid en tevredenheid bij patiënten met SB en DL? **(Hoofdstuk 3).**

- Kan de ingreep veilig aan beide zijden (bilateraal) worden uitgevoerd en welke patiënten komen in aanmerking voor deze ingreep? (**Hoofdstuk 4).**
- Kunnen wij de ingreep duidelijk stap voor stap beschrijven en andere chirurgen leren hoe zij deze ingreep moeten uitvoeren? **(Hoofdstuk 5).**
- Begrijpen wij de veranderingen in de hersenen die mogelijk door de TOMAX-procedure worden veroorzaakt? (**Hoofdstuk 6).**
-

Hoofdstuk 2

In dit hoofdstuk wordt een prospectieve pilot beschreven waarin de TOMAX-procedure werd uitgevoerd bij drie patiënten (17, 18 en 21 jaar oud) met een lage SB die geen gevoel in de penis hadden maar wel een normale huidgevoeligheid in de lies. Sensorische veranderingen in de penis en de lies werden met behulp van eenvoudige gevoels-testen voor tast en temperatuur gemeten. Om meer informatie te verkrijgen over de beleving van seksualiteit bij deze patiënten werden door een onafhankelijk seksuoloog interviews afgenomen en vragenlijsten geanalyseerd die door de patiënten waren ingevuld.

Na de operatie hadden alle patiënten een erg goed gevoel in de eikel aan de geopereerde (unilaterale) zijde. De huidgevoeligheid in de lies was iets afgenomen vanwege het gebruik van de lieszenuw, maar patiënten ervoeren geen ongemak of pijn. Vijf tot acht maanden na de operatie ervoeren de patiënten stimuli van de eikel alsof de lies werd aangeraakt, maar na 12 maanden was bij twee patiënten de sensibiliteit echter omgezet ('remapped') naar de eikel zelf.

Alle patiënten konden na de ingreep onveranderd een erectie krijgen en de ejaculatie, indien aanwezig, bleef ongewijzigd. Alle patiënten waren positief over de resultaten van hun operatie: zij ervoeren huidgevoeligheid in een gebied waarin zij niet eerder gevoel hadden gehad; zij voelden zich minder gehandicapt en hun penis was een meer geïntegreerd onderdeel van hun lichaam geworden. Twee patiënten vonden masturbatie intenser en bij één patiënt waren de nieuwe erogene gevoelens een stimulans om meer seksueel actief te zijn waardoor de seksuele relatie met zijn vriendin verbeterde en een diepere betekenis kreeg.

Hoofdstuk 3

Naar aanleiding van deze veelbelovende eerste resultaten werd een tweede onderzoek uitgevoerd waarin de uitkomsten werden onderzocht van de TOMAX-procedure bij 30 patiënten met SB en DL met ruggenmergletsel op laag niveau,

die geen gevoel in de penis hadden maar wel een normaal gevoel in de lies. Naast eenvoudige testen voor tast en temperatuur werden er ook de uitgebreidere kwantitatieve Semmes-Weinstein-monofilamenten voor fijne tastzin gebruikt. Psychologisch functioneren en seksualiteit werden door een onafhankelijk seksuoloog aan de hand van interviews en vragenlijsten gemeten. Eventuele problematiek met urinecontinentie kwam daarbij ook aan bod.

Tijdens de ingreep bleek dat bij drie DL-patiënten de lieszenuw niet kon worden gebruikt vanwege een beiderzijdse afwezigheid (anatomische variant) of beschadiging door eerdere operaties. Zeventwintig patiënten werden wel succesvol geopereerd (18 SB-patiënten, 13-40 jaar en 9 DL-patiënten, 21-42 jaar). Bij 80% van de patiënten resulteerde de zenuwomzetting in een enkelzijdige gevoeligheid van de eikel. Dit gevoel werd bij 54% ervaren als '*lies*' en bij 46% als '*eikel*'. Sensibiliteit van de donorlies was bij het merendeel van de patiënten afgenomen, maar dit werd niet als een gemis ervaren en veroorzaakte geen ongemak of pijn bij de patiënt. Een aantal patiënten voelden koude bij het inbrengen van een katheter en voelden de urine door de urinebuis stromen. Deze veranderingen hadden een positieve impact op hygiënisch en sociaal gebied.

Patiënten waren meer tevreden over hun erectie tijdens masturbatie, omdat de erectie langer kon worden vastgehouden. Zij masturbeerden frequenter, ervoeren meer plezierige gevoelens en kregen soms een orgasme. Vijf patiënten masturbeerden voor de eerste keer in hun leven, en drie patiënten hadden voor het eerst een orgasme. Patiënten voelden zich zekerder bij hun seksuele activiteiten, voelden hoe hun partner hun penis aanraakte en waren in staat te genieten van het moment van het inbrengen van de penis. Dit leidde tot een meer frequente en meer bevredigende seksuele activiteit en een meer open en intieme seksuele relatie. Het nieuwe gevoel bracht een significante verbetering in de kwaliteit en tevredenheid van het seksueel functioneren.

Hoofdstuk 4

De TOMAX-procedure herstelt *unilateraal* (aan één zijde) het genitale gevoel omdat bij deze ingreep *één* peniszenuw wordt verbonden aan de lieszenuw aan dezelfde zijde. Om het gevoel in de volledige eikel te herstellen en het erogene gevoel te verdiepen zou deze ingreep bilateraal (aan beide kanten) moeten worden uitgevoerd. Wij wilden weten, en onze patiënten ook, of dit veilig zou kunnen omdat bij de bilaterale ingreep beide penis-zenuwen moeten worden

doorgesneden en daarbij de kans aanwezig is dat het vermogen van de patiënt tot erectie/zaadlozing verdwijnt. De beide penis-zenuwen geven namelijk niet alleen gevoels-impulsen uit de penis aan de hersenen door, maar spelen ook een belangrijke rol bij reflexmatige erecties (RE) en zaadlozingen via de sacrale reflexboog (niveau S2-S4). Selectiecriteria voor de uitvoering van een veilige bilaterale TOMAX-procedure moeten gericht zijn op eventuele tekenen van een resterende peniszenuw-functie. Om dit te onderzoeken stelden wij de integriteit van de reflexboog S2-S4 bij onze patiënten vast door:

(1) bilateraal uitgevoerd zenuwgeleidingsonderzoek: bulbocavernosus reflex meting (BCR)
(2) specifieke vragen over het aanwezige vermogen tot reflex erectie (RE) (een erectie opgewekt door directe stimulatie van de penis).

Deze gegevens werden preoperatief verzameld bij dezelfde 30 patiënten die eerder waren geselecteerd voor een enkelzijdige TOMAX-procedure zoals beschreven in hoofdstuk 3 (18 met SB en 12 met DL, leeftijd 13-59 jaar), met spinale beschadigingen variërend van het niveau T12 (incompleet letsel ter hoogte van de 12^{e} borst wervel) tot beschadigingen waar het heiligbeen (sacrum) bij betrokken is). Met dit nieuwe onderzoek wilden wij vaststellen hoe vaak tekenen van resterende peniszenuw-functie toch nog aanwezig is bij patiënten met een lage ruggenmerg beschadiging en of deze kennis kon worden ingezet bij de keuze voor een enkelzijdige of dubbelzijdige ingreep. Dit inzicht moest uiteindelijk leiden tot het daadwerkelijk uitvoeren van een of meerdere dubbelzijdige TOMAX-operaties.

Het bleek dat zeven patiënten (23%) RE hadden, waarvan vier (57%) met een positieve bilaterale BCR. Er waren echter ook negen patiënten (30%) met een positieve BCR van wie vier (44%) RE hadden. Hieruit blijkt dat er zelfs bij patiënten met een lage ruggenmergbeschadiging (waaronder beschadiging in het sacrum (heiligbeen)) sprake kan zijn van tekenen van een aanwezige peniszenuw-functie en/of een intacte sacrale reflexboog op ruggenmergsegmenten S2-S4. Dit betekent dat een bilaterale TOMAX-procedure (waarbij beide peniszenuwen worden doorgesneden) in sommige gevallen riskant kan zijn.

Uit dit onderzoek bleek ook dat de zelf-gerapporteerde RE en de BCR-metingen, wanneer deze onafhankelijk van elkaar worden gebruikt, niet voldoende bewijs leveren om een nog aanwezige peniszenuw-functie te kunnen bevestigen of uit

te sluiten. Wij stellen dan ook voor dat beide parameters worden opgenomen in een preoperatief protocol dat leidt tot de keuze voor een unilaterale of bilaterale TOMAX-procedure. Indien de patiënt geen RE heeft *en* de BCR links en rechts afwezig is, kan de ingreep veilig beiderzijds worden uitgevoerd; indien de patiënt wel nog RE heeft en/of een intacte BCR moet voor een unilaterale ingreep worden gekozen.

Om de mogelijke voordelen van een bilaterale ingreep te onderzoeken hebben wij recentelijk bij drie patiënten een bilaterale ingreep uitgevoerd. Bij twee patiënten leidde dit tot gevoel in de gehele eikel. Het blijkt dus dat een bilaterale procedure technisch haalbaar is en in theorie een grotere kans op gevoelsherstel van de eikel geeft. Daarnaast bied het de mogelijkheid het gevoel in de gehele eikel te herstellen met waarschijnlijk een sterker erogeen gevoel. De verwachting is dat wij in de toekomst 60% van de nieuwe patiënten een bilaterale ingreep kunnen aanbieden.

Hoofdstuk 5

In Nederland worden elk jaar ongeveer 110 kinderen met SB geboren en in de periode 2004-2008 hadden, 1.7-2.7 per 10.000 mensen SB. In de VS zijn de aantallen vergelijkbaar. Het aantal DL-patiënten wordt geschat op 40 gevallen per 1 miljoen van de bevolking in de VS. Wereldwijd ligt dit hoger: 223-755 gevallen per miljoen. In Nederland komen er ongeveer 300 nieuwe dwarslaesie patiënten per jaar bij door een ongeval, infectie, tumor of problemen met de bloedvoorziening van het ruggenmerg.

Bovenstaande betekent dat de TOMAX-procedure kan worden gebruikt om de kwaliteit van leven en de seksuele gezondheid te verbeteren bij een zeer groot aantal patiënten. Om dit voor elkaar te krijgen moet de ingreep overal ter wereld toegankelijk gemaakt worden voor (plastisch-) chirurgen die perifere-zenuwchirurgie verrichten. Dit hoofdstuk beschrijft dan ook de meest actuele informatie op basis van een uitgebreide serie van 43 zenuwomleggingen bij 40 patiënten. Het gaat hier vooral over een gedetailleerde beschrijving- en demonstratievideo van de chirurgische techniek.

Patiënten selectie

Afwezigheid van penis gevoel, met wel aanwezige normale huidgevoeligheid in de liesstreek, kwam in ons onderzoek met 40 patiënten niet alleen voor bij patiënten

met SB (n=21) en SCI (n=13) op laag spinaal niveau, maar ook bij patiënten met gelijksoortige neurologische problemen: conusmedullaris/caudasyndroom (n=3), een spondylodiscitis (ontsteking van een tussenwervelschijf) (n=1), of na een gedeeltelijke verwijdering van het sacrum vanwege een chordoom-tumor (n=2). Bij de helft van deze patiënten (3/6) ontstond uiteindelijk een aanraak en/of erogene gevoeligheid. Dit suggereert dat eigenlijk alle patiënten zonder gevoel in de penis, maar met een normaal gevoel in de lies, in aanmerking kunnen komen voor TOMAX, ongeacht de oorzaak van hun klacht.

Ondanks het feit dat leeftijd omgekeerd evenredig gerelateerd is aan sensorisch herstel hadden twee oudere patiënten (42 en 46 jaar oud) twee jaar na de TOMAX-operatie een gevoel in de eikel dat zij beleefden als erogeen. De leeftijdsgrens voor een goed resultaat moet echter nog worden vastgesteld.

Lies-operatie

Een onbruikbaar beschadigde- of onderbroken lieszenuw werd aangetroffen bij alle patiënten die een eerdere operatie in de liesstreek hadden ondergaan met als gevolg littekenweefsel in het verloop van de lieszenuw: hersteloperatie liesbreuk (n=2), orchidopexie (n=1) en een heup operatie (n=1). Als gevolg van deze bevindingen krijgen toekomstige patiënten die eerder zijn geopereerd in de lies, nu het advies geen TOMAX-procedure aan de desbetreffende zijde te ondergaan.

Anatomie van de lies zenuw

De lieszenuw was bij drie patiënten afwezig aan beide kanten en bij twee patiënten aan één kant. Aangezien er altijd sprake kan zijn van een dergelijke anatomische variant moet aan toekomstige patiënten vooraf worden verteld dat in 7-12% van de gevallen de lieszenuw enkel- of dubbelzijdig afwezig kan zijn. Dit betekent dat er in enkelzijdig geplande operaties er een kans bestaat dat bij afwezigheid, de lieszenuw aan de andere zijde opgezocht moet worden.

Dubbelzijdige TOMAX-procedure

In hoofdstuk 4 is een protocol beschreven waarmee patiënten veilig kunnen worden geselecteerd voor een enkel- of dubbelzijdige ingreep. Wij hebben onlangs drie patiënten aan beide zijden geopereerd. Bij twee van deze patiënten leidde dit tot gevoel in de gehele eikel.

Operatietechniek

In dit hoofdstuk wordt de chirurgische techniek uitgebreid beschreven. De ingreep wordt ook stapsgewijs op een video gedemonstreerd *(http://links.lww.com/PRS/B52)*.

Informatie voor de patiënt

Vóór de ingreep wordt patiënten verteld dat zij ongeveer 80% kans hebben dat het gevoel terugkeert. Bij ongeveer 46% van hen wordt het gevoel '*als of de lies wordt aangeraakt*' in de loop van de tijd omgezet naar het daadwerkelijke gevoel '*als of de eikel zelf wordt aangeraakt*' (penisgevoel) en is de kans aanwezig dat het gevoel als erogeen wordt ervaren. De eerste tekenen van gevoeligheid verschijnen meestal 4-6 maanden na de operatieve ingreep en kunnen ietwat pijnlijk zijn. De pijnsensaties zullen echter na enige tijd verdwijnen. Om de hersenen te stimuleren de gevoelens om te zetten van-lies-naar-eikel-naar-erogeen gevoel (plasticiteit van de hersenen), wordt patiënten geadviseerd 'gevoels-training' te doen. De verwachting is dat na 1 tot 2 jaar het definitieve resultaat wordt bereikt. Het nieuwe gevoel lijkt niet helemaal vergelijkbaar met een normale situatie waarin geen sprake is van een ruggenmergbeschadiging (d.w.z. vóór de dwarslaesie). Om eventuele teleurstelling te voorkomen kan men beter spreken over een belangrijke en positieve stap voorwaarts. In de liesstreek is een verminderde huidgevoeligheid merkbaar, maar dit leidt niet tot klachten of (zenuw-) pijn.

Hoofdstuk 6

Ondanks de verschillende sensibele eigenschappen van de huid van de eikel en de huid van de lies ervaren de meeste mannen die met TOMAX werden behandeld de nieuwe gevoeligheid in de glans als prettig en, binnen de juiste context, als erotisch, met als gevolg een verbeterde seksuele gezondheid en functie. De hersen-plasticiteit die het '*liesgevoel*' omzet naar een '*penisgevoel*' duurt minstens één jaar. Dit is een interessant proces. De normale ontwikkeling van erotische genitale gevoelens vindt namelijk tijdens de vroege adolescentiefase plaats en is dus vanwege duidelijke ethische bezwaren zeer moeilijk te onderzoeken. TOMAX-patiënten zouden derhalve een volwassen model van de seksuele ontwikkeling bij de mens kunnen zijn.

In deze studie zijn bij drie TOMAX-geopereerde patiënten, functionele

MRI-scans (fMRI) gemaakt van de hersenen terwijl penis, lies en vinger werden gestimuleerd met een zacht kwastje. Onze hypothese was dat reorganisatie van de hersenen niet zou plaatsvinden in de primaire sensorische cortex (S1) (deel van de hersenschors dat verantwoordelijk is voor het gevoel van tast van het lichaam), maar dat activatieverschillen tussen lies en penis zichtbaar zouden worden in een regio *voorbij* de primaire sensorische cortex, in 'dieper' gelegen delen van hersen. Enig verschil in hersenactivatie tussen de lies en de penis zou het 'herschikkingsproces' (remapping) van het lichaamsschema inzichtelijk kunnen maken en gebieden kunnen aanwijzen waar ontwikkeling van erotische gevoelens/erogeniteit mogelijk zou zijn.

Wij includeerden drie mannelijke SB-patiënten (leeftijd 19, 23, 38 jaar; post-TOMAX 4,5, 4,9, 2,9 jaar). Zij hadden alle drie na TOMAX, enkelzijdig gevoel aan de linkerzijde van de eikel gekregen en het gevoel in de andere (niet-geopereerde) rechter liesstreek was intact. Deze intacte rechter liesstreek diende als controlegebied voor de opnieuw geïnnerveerde eikel omdat dit gebied wordt geïnnerveerd door de lieszenuw, die aan de tegenovergestelde kant van de geopereerde zijde ligt.

De eerste cruciale bevinding was dat, zoals verwacht, de corticale S1-representatie van het nieuw ervaren gevoel in de penis vrijwel identiek bleef aan die van de lies, ook al konden de proefpersonen de twee gebieden eenvoudig van elkaar onderscheiden.

De beide corticale S1-representatie-gebieden (eikel en lies), hadden verbindings-netwerken met 'dieper gelegen' hersen gebieden die vrij identiek waren, maar kenden in een aantal opzichten ook verschillen. Het bleek dat het netwerk van de eikel groter was dan dat van de lies en dat speciale hersen gebieden [de middelste cingulaire cortex (pMCC) en de rechter pariëtale operculum en insula (OIC)] consequent werden gekoppeld aan de S1 van de eikel en niet aan de S1 van de lies. Opmerkelijk genoeg speelt één deze speciale hersen gebieden (pMCC) een rol bij cognitie, motivatie, motoriek en autonome controle en blijkt vaak betrokken bij seksueel genot en opwinding bij de mens. Het andere gebied (OIC) speelt een rol bij emoties en hogere orde aspecten van lichaamsbeleving en stimulatie van de penis. Dit suggereert dat inschakeling van speciale hersen gebieden in het S1-netwerk van de eikel in verband zou kunnen staan met een diepere betekenis en mogelijke erogeniteit van de tactiele informatie van de lieszenuw vanuit de penis na de TOMAX-procedure.

Kortom, wanneer de oorsprong van het sensitieve veld van de lieszenuw, dus het gebied waarin de sensoren liggen die verbonden zijn met deze zenuw, wordt gewijzigd (van lies naar penis), wordt een netwerk van een hogere orde ingeschakeld. Dit zorgt dan waarschijnlijk voor een diepere emotionele betekenis en/of voor een opnieuw gerangschikt lichaamsschema.

Conclusies

Wij hebben aangetoond dat herstel van gevoel in de penis met de TOMAX-procedure het seksueel functioneren en de seksuele gezondheid en tevredenheid bij de meeste mannelijke patiënten met een letsel op laag ruggenmergs-niveau kan verbeteren. De ingreep had daarnaast een positief effect op de controle over urine-incontinentie, waardoor de persoonlijke hygiëne en onafhankelijkheid van de patiënt werden verbeterd.

Een patiënt met een lage ruggenmerg beschadiging heeft geen gevoel in de penis maar mogelijk wel tekenen die duiden op een residuele DNP-functie. Hierdoor kan de reflexmatige erectiele functie mogelijk gevaar lopen bij een operatie aan beide kanten. Met behulp van een nieuw ontwikkeld patiënten selectie protocol voor een enkelzijdige- of dubbelzijdige ingreep, zijn de eerste dubbelzijdige gevallen geopereerd met veelbelovende resultaten: met een dubbelzijdige operatie is mogelijk de seksuele functie nog verder te verbeteren.

De ervaring die wij hebben opgedaan met 43 TOMAX-operaties heeft geleid tot richtlijnen met betrekking tot de chirurgische techniek, mogelijke valkuilen, indicatie, patiënten selectie en het scheppen van realistische verwachtingen. Deze handvaten zijn van belang voor alle medische en chirurgische professionals die betrokken zijn bij de verbetering van de kwaliteit van leven van patiënten met lage ruggenmergletsels.

Wij ontdekten dat de hersenen tenminste één jaar nodig hebben om het 'liesgevoel' om te zetten (remappen) naar de penis. Wanneer de oorsprong van het receptieve veld van de lieszenuw wordt gewijzigd (van lies naar penis), worden er speciale hersen gebieden van een hogere orde ingeschakeld. Deze zorgen dan waarschijnlijk voor een diepere emotionele betekenis en/of voor een opnieuw gerangschikt lichaamsschema.

De TOMAX-procedure is geschikt om het gevoel in de penis te herstellen bij een groot aantal patiënten wereldwijd, die geen gevoel in de penis hebben maar wel een normaal gevoel in de lies. De TOMAX-procedure zou bij dergelijke patiënten een standaard ingreep moeten worden.

Toekomst

Onze ervaring met de TOMAX-procedure groeit en in de toekomst is het mogelijk om deze operatie aan jonge SB-patiënten aan te bieden voor zij de pubertijd bereiken. Daarnaast is het misschien mogelijk om met deze ingreep het gevoel in de clitoris bij vrouwen met een lage ruggenmergbeschadiging te herstellen. Verder moet onderzocht worden of patiënten met een beschadiging in een hoger gelegen ruggenmergsegment baat zullen hebben bij het gebruik van een alternatieve (intercostale) zenuwomzetting naar de penis-zenuw in combinatie met een gevascullariseerd zenuwtransplantaat uit de lies of niet-gevascullariseerd zenuwtransplantaten uit de kuit.

Er kan sprake zijn van een anatomisch afwezige lieszenuw. Daarom zou het waardevol kunnen zijn om preoperatief de aan- of afwezigheid van deze zenuw te kunnen vaststellen met behulp van echografie of MRI. De waarde van een alternatieve iliohypogastrische-lieszenuw, met of zonder zenuwtransplantaat, moet als alternatief voor een afwezige ilioinguinale-lieszenuw nog verder worden onderzocht.

Patiënten met een mogelijke residuale functie van de penis zenuw kunnen mogelijk worden geholpen door de zenuwen met een *end-to-side*-techniek aan elkaar te verbinden, mits de lieszenuw lang genoeg is.

Lange termijn follow-up (5-10 jaar) kan ons definitief inzicht verschaffen welke betekenis het verkregen of herwonnen gevoel heeft voor het dagelijks leven van de patiënt. Daarnaast kan een lange termijn follow-up aantonen hoe vaak bilaterale sensaties van de eikel voorkomen na een enkelzijdige TOMAX-operatie. Wij hebben dit namelijk bij twee patiënten waargenomen.

Wanneer pre- en postoperatieve fMRI-scans bij grotere groepen TOMAX-patiënten worden vergeleken, kan het speciale hersen netwerk dat wordt ingeschakeld bij de reorganisatie (remappen) van het 'liesgevoel,' naar het 'gevoel in eikel,' naar meer erogene gevoelens, nog verder worden in kaart gebracht.

Algemeen-chirurgen moeten worden geïnformeerd over de TOMAX-operatie zodat zij tijdens een liesbreukoperatie bij SL-patiënten lieszenuw sparende (endoscopische) technieken kunnen inzetten of een combinatie operatie van een TOMAX-operatie en een liesbreukoperatie in één sessie kunnen inplannen.

Seksuologen kunnen sensorische (her)educatieprogramma's opstellen. Zo kunnen door de intacte (donor)liesstreek en de niet-gevoelige eikel preoperatief erotisch te stimuleren, de hersenen zich mogelijk al voorbereiden op wat komen

gaat. Postoperatief is het misschien mogelijk om met gestandaardiseerde protocollen voor stimulatie van de penis met visuele feedback, nog meer hogere orde hersenen netwerken in te schakelen, wat de kans op het ontwikkelen van erogene gevoelens zou kunnen vergroten.

Appendices

Abbreviations

Yeah!

Bibliography

Curriculum Vitae

DNP	dorsal nerve of the penis
EMG	electromyography
fMRI	functional MRI
GAS	Groninger Arousability Scale
GC	granger causality
HADS	Hospital Depression and Anxiety Scale
NPV	negative predictive value
OIC	parietal operculum and insula
PE	psychogenic erection
pMCC	middle cingulate cortex
PPV	positive predictive value
RE	reflex erection
ROI	regions of interest
SB	spina bifida
SCI	spinal cord injury
SCL-90-R®	Symptom Checklist-90-Revised
SI	primary sensosensory cortex
SL	spinal Lesion
SW	semmes weinstein monofilaments
VAS	visual analogue scale

Appendices

Abbreviations

Yeah!

Bibliography

Curriculum Vitae

Moshe Kon
Ralph Franken
Frank Niessen
Jackie Senior
Jan de Witte
Paul Werker
Robert de Wijn
Mireille Edens
Jeroen van Uchelen
Ingrid Janssen
Winkie Sandberg
Tom de Jong
Ronald Bleys
M. Post
Luca Nanetti
M. Malessy
Peggy Cohen-Kettenis
Niels de Boer
Marieke van Wijk
Annet van Rijssen
Ruud Kortekaas
alle TOMAX-patiënten!!
Janniko Georgiades
Saskia Strijbos
Marijke
Bouke de Jong
Peter Houpt
Michiel Tellier
Tjeerd de Jong
AIOS Plastische Chirurgie Zwolle
Liselot
Jan Braakhekke
Tijn
Joosje
C. Kalkman

Appendices

1. Overgoor ML, de Jong TP, Kon M. Restoring tactile and erogenous penile sensation in low-spinal-lesion patients: procedural and technical aspects following 43 TOMAX nerve transfer procedures. Plast Reconstr Surg. 2014 Aug;134(2):294e-301e.

2. Overgoor ML, Braakhekke JP, Kon M, De Jong TP. Restoring penis sensation in patients with low spinal cord lesions: The role of the remaining function of the dorsal nerve in a unilateral or bilateral TOMAX procedure. Neurourol Urodyn. 2014 Jan 30. doi: 10.1002/nau.22566. [Epub ahead of print]

3. Overgoor ML, de Jong TP, Cohen-Kettenis PT, Edens MA, Kon M. Increased sexual health after restored genital sensation in male patients with spina bifida or a spinal cord injury: the TOMAX procedure. J Urol. 2013 Feb;189(2):626-32.

4. Melenhorst WB, Maas M, Houpt P, Overgoor ML. A unique case of partial, radial-sided lunatomalacia. J Hand Surg Eur Vol. 2010 Sep;35(7):586-8.

5. Melenhorst WB, Overgoor ML, Gonera EG, Tellier MA, Houpt P. Nerve decompression surgery as treatment for peripheral diabetic neuropathy: literature overview and awareness among medical professionals. Ann Plast Surg. 2009 Aug;63(2):217-21.

6. Overgoor ML, Kon M, Cohen-Kettenis PT, Strijbos SA, de Boer N, de Jong TP. Neurological bypass for sensory innervation of the penis in patients with spina bifida. J Urol. 2006 Sep;176(3):1086-90; discussion 1090.

7. Overgoor ML, Carroll SM, Papanicolau G, Carroll CM, Ustüner TE, Stremel RW, Anderson GL, Franken RJ, Kon M, Barker JH. Can angiogenesis induced by chronic electrical stimulation enhance latissimus dorsi muscle flap survival for application in cardiomyoplasty? Plast Reconstr Surg. 2003 Jan;111(1):178-88.

8. Wan C, Maldonado C, Papanicolaou G, Anderson GL, Overgoor M, Kon M, Barker JH. Reducing the vascular delay period in latissimus dorsi muscle flaps for use in cardiomyoplasty. Plast Reconstr Surg. 2002 Apr 15;109(5):1630-7.

9. Houwing R, Overgoor M, Kon M, Jansen G, van Asbeck BS, Haalboom JR. Pressure-induced skin lesions in pigs: reperfusion injury and the effects of vitamin E. J Wound Care. 2000 Jan;9(1):36-40.

10. Franken RJ, Werker PM, Peter FW, Overgoor ML, Wang WZ, Anderson GL, Schuschke DA, Banis JC Jr, Kon M, Barker JH. Microcirculatory changes following different temperature washouts in a free flap model. Microsurgery. 1999;19(5):214-22.

11. Carroll CM, Carroll SM, Overgoor ML, Tobin G, Barker JH. Acute ischemic preconditioning of skeletal muscle prior to flap elevation augments muscle-flap survival. Plast Reconstr Surg. 1997 Jul;100(1):58-65.

12. Werker PM, Kon M, Green CJ, Fryer PR, Franken RJ, Overgoor ML. Cold (0 degree C) ischaemic tolerance of latissimus dorsi free flaps in rats: a macroscopic and morphological study. Microsurgery. 1994;15(3):187-92.

13. Werker PM, Green CJ, Kon M, Overgoor ML, Franken RJ. The benefit of a single-passage perfusion with a hypertonic citrate solution on the cold ischemia tolerance of epigastric free flaps in Dark-Agouty rats. Ann Plast Surg. 1993 Mar;30(3):233-7; discussion 237-8.

14. Franken RJ, Werker PM, Overgoor ML, Kon M. Non-revascularized epigastric free flap: no all-or-none survival pattern. Microsurgery. 1993;14(9):579-83.

15. Werker PM, Kon M, Green CJ, Franken RJ, Overgoor ML. Neither desferrioxamine nor lipoic acid enhances the cold ischaemic tolerance of epigastric free flaps in rats. Microsurgery. 1993;14(9):574-8.

16. Werker PM, Kon M, Green C, Franken RJ, Overgoor ML. Survival characteristics of the epigastric free flap in DA-rats. Microsurgery. 1992;13(2):67-71.

Appendices

Abbreviations
Yeah!
Bibliography
Curriculum Vitae

Max Overgoor was born on November 14th, 1964 in the Steeg, The Netherlands. After graduation from the Thomas á Kempis College in Arnhem he studied Medicine at the University of Utrecht. In 1991 he started his military service at the department of Plastic Surgery (dr. W. Rijnders) of the Military Hospital in Utrecht. Afterwards he worked one year (1994-1995) as research fellow under supervision of dr. J.H. Barker at the Plastic Surgery Research department in Louisville, USA. The main focus of his research was on latissimusdorsi muscle flap survival for the use in cardiomyoplasty. In 1996 he started three years of General Surgery training in the Diakonessen Hospital in Utrecht (dr. P. Leguit and dr. G.J. Clevers) followed by his three years Plastic Surgery residency at the department of Plastic-, Reconstructive-, and Hand Surgery at the University Medical Centre in Utrecht (prof. dr. M. Kon). During this residency, lively discussions with Tom de Jong, paediatric urologist, and Moshe Kon, plastic surgeon, stimulated him to develop the TOMAX procedure. He operated the first two patients at the UMCU in 2001 which was the start of this thesis. After board certification at the end of 2001 he was welcomed at the Plastic-, Reconstructive and Hand Surgery group at the Isala Clinics in Zwolle. Besides his busy clinical practise including training plastic surgery residents and his engaged family life with Marijke, Liselot, Joosje and Tijn, he managed to further develop the TOMAX-procedure which resulted in the research presented in this thesis.

The first **TOMAX**-procedure
from right to left : **TO**m, **M**oshe, m**AX**