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# Reducing the Morbidity of Transurethral Resection of the Prostate Based on Patient Selection, Fluid Absorption, and Blood Loss



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***Cover pictures***

Upper row, from left:

1. Karolinska Scales of Personality: The five scales describing anxiety in men with bladder outlet obstruction having a small or a large prostate (Paper I).

2. Incidence of neurological symptoms during and after transurethral resection of the prostate for different ranges of absorption of mannitol 3% and glycine 1.5% (Paper II).

3. Cardiac output during experiments in which high-dose intravenous infusions of irrigating fluids containing glycine 1.5% or mannitol 5% were given to anesthetized pigs (Paper IV).

4. Intracranial pressure during the experiments in the pigs.

5. Total blood loss depending on resectate weight during transurethral resection of the prostate in finasteride-treated patients and controls (Paper V).

Lower row, from left: Morphological examination of hearts after infusions of irrigating fluid in pigs (Paper IV):

1. Mannitol 5%: The interstitium is dilated and, in the central area, there is focal necrosis with hemorrhage.

2. Mannitol 5%: Proximal part of the left side of the interventricular septum of the same heart as in 1. Purkinje fibers are embedded in a loose, cell-rich interstitium.

3. Glycine 1.5%: The pale area in the center represents leakage of myoglobin. Numerous small areas of necrosis were also noted.

4. Mannitol 3%: The subendocardial area showing thick, fragmented, wavy or contracted reticulum fibers. The capillary lumina are narrowed (arrows).

5. Glycine 1.5%: The capillaries of the subendocardial muscle layer are dilated (arrows); a subendocardial lymph vessel is extremely dilated and forms a bubble.

**"**As to diseases, make a habit of two things – to help, or at least, to do no harm"

Hippocrates

460–377 BC

*To Bibbi, Josefine, Jonathan, and Jasmine*

# ABSTRACT

**Reducing the Morbidity of Transurethral Resection of the Prostate**

**Based on Patient Selection, Fluid Absorption, and Blood Loss**

A higher long-term mortality due to myocardial infarction after TURP, compared to open surgery, irrigating fluid absorption, and blood loss, prompted me to investigate whether prostate size correlates with cardiovascular risk factors, whether two common fluids differ in terms of harmful effects, and whether premedication with finasteride may reduce the blood loss during TURP.

**Paper I;** Fifty-two patients were studied before the treatment of their bladder outlet obstruction. Men with a large prostate had higher arterial pressures, higher serum glucose, were less assertive, and were more likely to undergo open surgery, than men with a small gland. **Paper II;** Fifty-two patients who had absorbed more than 500 ml of fluid were examined. The risk of neurological symptoms after TURP was 4.8 times higher for glycine 1.5% than for mannitol 3%. An increase of 1000 ml in the volume of fluid absorbed increased the risk of circulatory and neurological symptoms by a factor of 3.4 and 4.4, respectively. **Paper III;** Twelve volunteers were investigated. Intravenous infusions of glycine 1.5% caused more symptoms than mannitol 3%. Only glycine hydrated the cells. The excretion of urine and sodium was greater after mannitol. Both fluids decreased the blood and interstitial volumes in the end of the experiments. **Paper IV;** Twenty-five pigs were studied. Cardiac output, the aortic blood flow rate and arterial pressures fell to below baseline after large infusions of glycine 1.5% and mannitol 5%. The intracranial pressure was lower and the oxygen consumption in the brain decreased during the infusions of mannitol. Glycine caused the most myocardial damage. **Paper V;** Fifty-five patients who had taken finasteride or placebo before TURP were investigated. Finasteride reduced the mean surgical blood loss by 223 ml, when the resectate weight was equal to or larger than 18.6 g (the median).

Men with bladder outlet obstruction due to a large compared to a small prostate have more cardiovascular risk factors. Mannitol is less harmful than glycine and pretreatment with finasteride reduces the blood loss during TURP.

**Key words:** absorption; blood loss, surgical; cardiovascular disease; electrocardiography; ethanol; finasteride; glycine; hemodynamics; intracranial pressure; mannitol; myocardium; personality; prostatectomy; prostatic hyperplasia; risk factors; transurethral resection of prostate; ultrasonography; urodynamics.                    ISBN 91-628-4897-6

# PAPERS INCLUDED

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. Sandfeldt L, Hahn RG. Relationships between personality, prostate size and risk factors for cardiovascular disease in men with bladder outlet obstruction. Submitted.

II. Hahn RG, Sandfeldt L, Nyman CR. Double-blind randomized study of symptoms associated with absorption of glycine 1.5% or mannitol 3% during transurethral resection of the prostate. J Urol 1998;160:397-401.

III. Sandfeldt L, Hahn RG. Comparison of urological irrigating fluids containing glycine and mannitol in volunteers. Prostate 1999;41:89-98.

IV. Sandfeldt L, Riddez L, Rajs J, Ewaldsson CA, Piros D, Hahn RG. High-dose intravenous infusion of irrigating fluids containing glycine and mannitol in the pig. J Surg Res 2001;95:114-25.

V. Sandfeldt L, Bailey DM, Hahn RG. Blood loss during transurethral resection of the prostate after 3 months of treatment with finasteride. Urology, in press.

# CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AMI | acute myocardial infarction |
| ANOVA | analysis of variance |
| AUR | acute urinary retention |
| B-Hb | blood hemoglobin concentration |
| BMI | body mass index |
| BOO | bladder outlet obstruction |
| BPE | benign prostatic enlargement |
| BPH | benign prostatic hyperplasia |
| Ch | Charrière |
| CO | cardiac output |
| CT | computerized tomography |
| DHT | dihydrotestosterone |
| ECG | electrocardiogram |
| F | French |
| HDL | high-density lipoprotein |
| HF | high frequency |
| HRV | heart rate variability |
| ICP | intracranial pressure |
| IPSS | International Prostate Symptom Score |
| kPa | kilopascal |
| KSP | Karolinska Scales of Personality |
| LDL | low-density lipoprotein |
| LF | low frequency |
| LUTS | lower urinary tract symptoms |
| MHz | megahertz |
| mosm | milliosmole |
| mSv | millisievert |
| MVD | microvessel density |
| NSAID | non-steroid anti-inflammatory drug |
| $P_{det}$ | detrusor pressure |
| $P_{det}$ at $Q_{max}$ | detrusor pressure at maximum urinary flow |

| | |
|---|---|
| $Q_{max}$ | maximum urinary flow |
| S-CK | serum creatine phosphokinase activity |
| S-Cl | serum chloride concentration |
| S-K | serum potassium concentration |
| S-Na | serum sodium concentration |
| S-osm | serum osmolality |
| S-PSA | serum prostate-specific antigen concentration |
| S-TNT | serum troponin T concentration |
| SD | standard deviation |
| SEM | standard error of the mean |
| TCRE | transcervical resection of the endometrium |
| TRUS | transrectal ultrasonography |
| TUIP | transurethral incision of the prostate |
| TUMT | transurethral microwave thermotherapy |
| TURP | transurethral resection of the prostate |
| TUR syndrome | transurethral resection syndrome |
| UTI | urinary tract infection |
| VEGF | vascular endothelial growth factor |
| VLF | very low frequency |

# INTRODUCTION

## General background

Benign prostatic hyperplasia (BPH), which implies excessive growth of the glandular, fibrous, and muscular tissues of the prostate, is a widespread disease in the Western countries and the prevalence increases with older age. The related enlargement of the gland, which starts in the thirties, may cause lower urinary tract symptoms (LUTS), impairing the quality of life and giving rise to such complications as urinary retention, reduced renal function, and even death. The first-generation treatment consisted in removal of the prostate adenoma via open surgery, with a relatively high rate of mortality and morbidity. Transurethral resection of the prostate (TURP), which came into use in the 1930s, is generally considered to be less traumatic for the patient. However, to allow cutting with electricity, an electrolyte-free irrigating fluid is necessary to dilute the mucosal spaces and remove pieces of resected tissue and blood from the operating field. The two most dangerous complications in TURP are large blood loss and fluid absorption, directly via injured veins surrounding the prostate or indirectly via perforations in the prostatic capsule or bladder wall. The risk of developing a transurethral resection (TUR) syndrome, consisting of symptoms from the cardiovascular and central nervous systems, increases with the volume absorbed, and several fatal cases have been reported in the literature. Interestingly, Roos et al. reported in 1989 a higher long-term mortality due to acute myocardial infarction (AMI) after TURP compared to open surgery after an adjustment was made for comorbidity.[1] Hahn et al. showed that this long-term risk seemed to be higher after absorption of more than 500 ml of glycine and still higher after blood losses less than 275 ml, indicating that constitutional patient factors could be responsible.[2]

The reason why I made the studies presented in this thesis was my hope that the short and long- term complications of TURP could be better understood and possibly reduced. I wanted to determine whether men with bladder outlet obstruction differ in the prevalence of risk factors for cardiovascular disease according to the size of the prostate (I); whether some of the most widely used irrigating fluids differ in their tendency to cause symptoms and tissue damage when entering the body (II-IV); and whether it is possible to reduce the blood loss during TURP by three months of medication with finasteride (Proscar®) before surgery (V).

# Benign prostatic hyperplasia

## Etiology

Benign prostatic hyperplasia is a glandular, fibrous, and muscular proliferation of tissues building up nodules in the periurethral region of the prostate, which may compress the urethra and cause bladder outlet obstruction.[3] About half of the total urethral pressure in men with BPH is regulated via the stimulation by norepinephrine of the alpha-adrenergic receptors of the smooth muscle in the prostate, bladder base, and proximal urethra.[4] The prevalence of BPH depends on how it is defined, but is extraordinarily common in older men.[5] The weight of a normal gland is 20 grams during life. The annual growth of a gland with BPH is 0.4 g[6] or 1.6%.[7] Four percent of men more than 70 years old have severe benign prostatic enlargement (BPE) with glands weighing more than 100 grams.

Metabolic, dietary, and genetic factors affect the development of BPH. A testosterone metabolite, 5α-dihydrotestosterone (DHT), is essential for prostate growth.[8] One of the growth suppressor genes, p53, is important in the balance between cell proliferation and cell death, and promotes apoptosis. The larger prostates in young men with an inherited form of BPH are characterized by a higher stromal/epithelial ratio than for similar-sized prostates in older men with sporadic BPH.[9] Asian vegetable food contains products that are metabolized in the intestine to phytoestrogens[10] which are reported to inhibit 5α-reductase and angiogenesis. Furthermore, Hammarsten et al. have proposed a causal relationship between hyperinsulinemia and BPH.[11] The extrinsic factors mentioned above mediate their biological effects via intrinsic peptide growth factors produced by the gland, such as epidermal growth factor, keratinocyte growth factor, and fibroblast growth factor. Fibroblast growth factor 7, which is produced by stromal fibroblasts, is particularly important, and exerts a mitogenic effect on epithelial cells via a receptor protein.[12] Estradiol and DHT may have synergistic effects in the production of fibroblast growth factor 2,[13] which is produced by epithelial and stromal cells and has an effect only on the stromal cells.[14] Neuroendocrine cells in the prostate may produce vascular endothelial growth factor (VEGF), which promotes angiogenesis, and serotonin, which stimulates smooth muscle and fibroblast mitogenesis.

## Symptoms

The transition zone index, the ratio of the transition zone volume and the prostate volume, correlates with LUTS, maximum urinary flow, and detrusor pressure.[15] Lower urinary tract symptoms become more frequent with increasing age and are divided into filling and emptying symptoms. The former describes problems pertaining to storing the urine in the bladder and the latter, problems pertaining to voiding, often summarized as bladder outlet obstruction (BOO), which often causes detrusor instability, incomplete bladder emptying, urinary infection (UTI), and, in more advanced cases, acute urinary retention (AUR). There is only a statistically significant correlation between the urodynamic parameters of obstruction and two of the voiding symptoms, namely, hesitancy and weak stream. In fact, urgency, frequency, and nocturia increase almost equally. Lower urinary tract symptoms are equally common in Asia, Europe and North America, according to the International Prostate Symptom Score (IPSS).[16] Many men have prostatic enlargement and bladder outlet obstruction without being bothered by their weak urinary stream.

## Complications

The risk of developing acute urinary retention increases with age, urinary symptom score, prostate volume, and diminished maximum urinary flow. For men with mild or no urinary symptoms, the incidence of acute urinary retention was approximately 2.6 in 1000 men aged 40-49 years and 9.3 in 1000 men aged 50-69 years, increasing to 34.7 in 1000 men aged 70-79 years with moderate to severe symptoms. Men with a maximum urinary flow <12 ml/s were 5 times more likely to develop AUR and men with a prostate volume >30 ml were 3 times more likely.[17]

In a retrospective study of 3885 men after TURP, hematuria was the main indication for the operation in 12% of them.[18]

Late complications include stone formation, infection, and upper urinary tract damage. The death rate due to BPH has declined all over the world. In the USA, the age-adjusted mortality rate fell from 7.5 per 100,000 in 1950-54 to 0.3 per 100,000 in 1985-89.

## Economics of management

The mean age of the population in the Western world is increasing, and the birth rate is declining, which means that there are fewer and fewer people under the age of 65 years to

financially support each patient suffering from BPH. Avoiding unnecessary investigations in the evaluation of BPH and offering the most adequate treatment might save money. Furthermore, modern methods of monitoring patients during surgery, such as measurements of fluid absorption and blood loss during operations,[19] reduce the cost associated with the management of complications. Trying to save money by avoiding such patient monitoring might be counterproductive because the symptoms of fluid absorption are far more common 30-60 min after the end of surgery, than during it.[20] The costs for the treatment of a single patient in the intensive care unit due to massive fluid absorption is enough to cover the costs of ethanol monitoring for a whole year.[21]

Open surgery was once the only therapy for BPH.[22] Today the physician and the patient may choose between several methods for the treatment of BPH. The prostate volume, IPSS, and uroflowmetry may be used to classify the patients with LUTS and BPH into categories depending on the severity of the disease. The cost per point change per year for patients belonging to the same category, from the beginning of different modes of treatment to evaluation of the effect, can be compared, using the formula given below. Seven (7) is a weight factor because the quality of life score contains only one question.

$$\frac{\text{Cost}}{(\text{Change in IPSS} + \text{change in QOL} \times 7) \times \text{years}}$$

The most costly strategy of management in all age groups was mixed medical and surgical therapy.[23]

## Evaluation

*Aim*

The aim of the evaluation is to examine whether obstructive BPH alone or combined with other diseases causes the LUTS and to suggest adequate therapy.

*Medical history*

A history of pelvic surgery, trauma, and the outcome of previous treatment for LUTS are standard information. Diabetes with polyuria, cardiac and vascular diseases, diuretics and drugs interfering with lower urinary tract function may influence voiding patterns. A known family history of urological disease, such as prostate cancer, may lead to directed investigations. Some treatment often interferes with sexual function. Previous or current smoking and the general condition and health status of the patient are important information.

*Symptom questionnaires*

*The International Prostatic Symptom Score* is the most widely used prostate symptom questionnaire[24] and is designed for self-administration. It consists of seven questions and the patient is allowed to choose one out of six answers, scored from 0 to 5, per question. The total score may range from 0 to 35 points depending on the severity of the symptoms:

> 0 – 7     =mildly symptomatic
>
> 8 – 19     =moderately symptomatic
>
> 20 – 35     =severely symptomatic

*The Quality of Life Question* is a single global question in the IPSS concerning how much the patient is bothered by the symptoms.

*Voided volumes* at night that are equal to or greater than those during the day indicate nocturnal polyuria.

### Blood and urinary chemistry

A urinary sample is checked with reference to red and white blood cells and the nitrite test.

Among the blood tests, serum creatinine is used routinely to evaluate patients suffering from BPH. Renal insufficiency is a risk factor for complications[18] and death[25] after surgical treatment for BPH. Symptoms of absorption are almost 5 times more severe in patients with impaired renal function and the risk of death is increased six-fold.[26]

Prostate-specific antigen (PSA) is organ-specific. Cancer, BPH, inflammation, and advanced age may elevate the plasma concentration of this prostatic enzyme. A high PSA/prostate volume ratio or a low free PSA/total PSA ratio may increase the specificity in distinguishing men with prostate cancer from men with BPH only.

### Urological investigation

#### Anatomy

Digital rectal examination of the prostate and endoscopy underestimate volumes of glands weighing more than 40 grams.[27] Digital palpation may reveal occult carcinoma of the prostate. Transrectal ultrasonography (TRUS) is the appropriate method for measuring prostate volume,[28] and it can also disclose a median lobe and bladder stones. Intravenous pyelography or renal ultrasonography is not indicated without hematuria or elevated serum creatinine.

#### Uroflowmetry

This is a screening method for bladder outlet obstruction, but may not distinguish obstruction from impaired detrusor contractility. When the maximum flow was less than 10 ml/s and more than 15 ml/s, 88% and 24% respectively of patients admitted to hospital for BPH were obstructed.[29]

#### Residual urine

A residual urine volume is a sign of myogenic or neurogenic detrusor impairment, or both. It should be assessed twice due to intraindividual variations, unless it is less than 50 ml. Evaluating residual urine by means of transabdominal ultrasonography makes it noninvasive.

#### Pressure-flow measurements

Pressure-flow measurements are used to diagnose and grade the BOO. The most important parameters are the detrusor pressure ($P_{det}$) at maximum urinary flow ($Q_{max}$) and $Q_{max}$. The International Continence Society recommends plotting the data in the form of a pressure-flow

curve. Pressure flow studies should be reserved for patients who are under 50 or have flow rates higher than 12-15 ml/s, for patients with neurological disorders, and for men with a high symptom score after surgical treatment. From 20% to 30% of nonselected BPH patients are unobstructed and half of them have impaired detrusor contractility. Cerebrovascular accidents, Parkinson's disease, and dementia result in detrusor hyperreflexia due to a lack of central inhibition. Diabetic or uremic peripheral neuropathy causes bladder hyposentivity or detrusor hypocontractility, or both.

*Urethrocystoscopy*

Urethrocystoscopy is not a routine method in the evaluation of LUTS without hematuria. Not all obstructed patients have bladder trabeculation. About 50% of unobstructed, but overactive, bladders are obviously trabeculated.[30]

## Adrenergic alpha-antagonists

Terazosin[31] and doxazosin[32] were originally developed for the treatment of hypertension. They are selective, long-acting $alpha_1$-adrenergic receptor blockers with effects on LUTS and urinary flow but may also cause dizziness due to the blocking effect on the $alpha_1$-adrenergic receptors in the vessels of the central nervous system. Tamsulosin[33] is a selective $alpha_{1A}$-adrenergic receptor blocker developed only for the treatment of BPH and has not so pronounced side effects on the cardiovascular system as terazosin and doxazosin. The mechanism of action of the alpha-adrenergic receptor blockers is to prevent norepinephrine from stimulating the receptors and thereby causing a relaxation of smooth muscle in the prostate, bladder base, and proximal urethra. Approximately half of the total urethral pressure in men with BPH is regulated via this mechanism.[4] Treatment with these drugs reduces symptoms by 30%-40% and improves the maximum flow by 16%-25%.[34]

## 5-alpha-reductase inhibitors

Finasteride inhibits the intracellular enzyme 5-alpha-reductase, which converts testosterone to the more potent androgen and important prostate growth factor dihydrotestosterone. Four years of treatment with finasteride decreased the mean quasi-AUASI score by 3.3 points, increased the maximum urinary flow by 1.9 ml/s and decreased the prostate volume by 18%, compared to a 14% increase with placebo. Medication with finasteride decreased libido (6.4% vs 3.4%) and caused erectile dysfunction (8.1% vs 3.7%) compared to placebo, but the prevalence of these disturbances returned to baseline after the first year. Ten percent of placebo-treated men compared to 5% of finasteride-treated men developed acute urinary

retention or required BPH-related surgery.[35] The positive effect of finasteride is more pronounced in men with larger prostates.[36] Patients with BPH-related chronic, intermittent hematuria, treated with finasteride, showed less recurrence of hematuria than men in the control group.[37]

## Transurethral incision of the prostate

This method implies that a surgeon makes an incision with a scalpel, free beam, or contact laser from inside the bladder neck down to the verumontanum, deep enough to penetrate the prostate capsule.[38] The operation is convenient when the volume of the gland is less than 30 ml and there is no median lobe. The risk of retrograde ejaculation and bladder neck stenosis is lower, the effect on symptoms and the quality of life score is similar but the improvement in urinary flow is less compared to TURP.[39] The risk of a large blood loss and irrigating fluid absorption is smaller than in TURP.[40]

## Transurethral resection of the prostate

Transurethral resection of the prostate is the surgical treatment of choice for glands with a size of 50 to 100 ml. The Nesbit technique comprises three stages.[38] First, the surgeon resects the fibers at the bladder neck and those of the immediately adjacent prostatic adenoma circumferentially around the bladder neck. Thereafter, the adenoma is resected in quadrants to the fibers of the surgical capsule and, finally, the tissue surrounding the verumontanum. Bleeding vessels are coagulated, pieces of prostate tissue are removed and a catheter is placed in the bladder for irrigation until the fluid return is sufficiently clear. Data collected in the United States indicate that, between 1962 and 1989, the mortality within 3 months of the operation decreased from 2.5%[25] to 0.2%, but the mean probability of surgical complications after TURP was still about 15% and was higher in patients with renal insufficiency and urinary retention.[18] The transfusion rate is still about 1%,[41] the probability of secondary intervention for bleeding is 2.2% and the risk of fluid absorption in excess of 1000 ml is 7%.[20] Other complications include postoperative UTI (15.5%) and epididymitis (1.1%). The risk is 1.0% for total urinary incontinence, 3.1% for urethral stricture, and 68% for retrograde ejaculation.[42] Evidence of a higher long-term risk of fatal AMI after TURP than after open surgery[1] has led to the hypothesis that men with bladder outlet obstruction due to a very large gland have another disease than those with the same symptoms due to a smaller gland.[43]

## Open surgery

Open surgery is the first-generation treatment of BPH.[22] The prostatic adenomas may be enucleated by the transvesical and retropubic techniques, respectively.[38] Today, open surgery is preferred when the prostate volume exceeds 100 ml.[44] In one study, the early complication rate was 19.6%, the medically justified blood transfusion rate was 2.1%, and reoperation for clot retention was required in 2.9% of the patients.[45] The postoperative risk for epididymitis is 3.6%, for UTI 2.6%, and for total incontinence 0.5%. The mortality rates within 3 months of the operation range from 3.8%[38] to 0%.[45] The risk of urethral stricture is 2.6% and 1.8% for bladder neck contracture for both techniques together, and 81% for retrograde ejaculation after the suprapubic technique.

## Other methods of treatment

### *Watchful waiting*

Watchful waiting is an accepted procedure in bladder outlet obstruction when surgery is not clinically indicated. In the majority of cases, symptoms do not worsen and urodynamic studies show little change.[46]

### *Phytotherapy*

Saw Palmetto *(Serenoa repens)* is the most common herbal medicine used for LUTS due to BPH[47] but, as yet, studies of sufficient quality on the long-term effects of this therapy are lacking.

### *Stents*

Biodegradable stents are required after laser treatment of the prostate and disintegrate after 3 weeks to 4 months. Temporary stents are used after laser treatment, after high-energy transurethral microwave thermotherapy (TUMT) and as an alternative to surgery. Permanent stents are ideal for patients who cannot manage to undergo surgery.

### *High-Intensity Focused Ultrasound (HIFU)*

A beam of ultrasound generates temperatures of 80-100°C, leading to coagulation necrosis of the cells within the focus of the beam. The energy is delivered transrectally under general, spinal, or regional anesthesia. There are few postoperative complications.

### *Minimally Invasive Treatment*

*Transurethral microwave thermotherapy (TUMT)*

Marion Devonec in Lyon developed the thermotherapy concept, which is based on irradiative heating of the prostate gland to temperatures in excess of 43.5°C using a urethral microwave applicator causing destruction of the sensory neurons in the posterior urethra and necrosis and apoptosis of the adenomatous tissue. Low or high-energy versions may be chosen according to degree of bladder outlet obstruction.

*Transurethral needle ablation*

Radiofrequency energy creates temperatures up to 60-100°C, which causes zones of coagulation necroses in the adenomatous tissue while the prostatic urothelium remains intact.

*Laser*

Laser at different wavelengths through a variety of treatment fibers causes coagulation, vaporization and cutting. Examples of two methods are visual laser ablation of the prostate (VLAP) and interstitial laser coagulation (ILC).

### *New electrosurgical methods*

Electrosurgical TURP and transurethral electrovaporization (TVP) use higher amounts of energy to execute cutting, coagulation, and vaporization, using newly developed loops and electrodes.[48]

## Irrigating fluids in endoscopic surgery

## General

An irrigating fluid is used during urological, gynecological, and orthopedic endoscopic surgery to dilate anatomic spaces and remove blood and pieces of resected tissue from the operating field. The ideal fluid must be nonelectrolytic in order to prevent dispersion of the high-frequency current during electrocautery. It must be nontoxic both in local tissue action and when administered intravenously. It must be transparent so as not to interfere with visual acuity during surgery. It must be relatively cheap to allow its use in large quantities. Nesbit also suggested that the fluid should be isotonic so as to prevent kidney damage due to intravascular hemolysis.[49] In the past, an accurate, fast, and noninvasive method of detecting and quantifying fluid absorption was lacking. Lennart Jorfeldt's idea to tag the fluid with ethanol made it possible to detect even small volumes of fluid absorption by measuring the

concentration of ethanol in the expired breath with an alcolmeter. The further research and development by Robert Hahn and Jan Hultén has led to the ethanol method, which is in common clinical use, especially in Sweden and the United Kingdom.[50-52]

## Distilled water

Distilled water is the simplest irrigating fluid and has been used since TURP came into use in the 1930s. It is still in use in Europe, in the USA, and especially in the developing countries due to its low price. It is hypo-osmotic (osmolality 0 mosm/kg without ethanol) and causes hemolysis, which is an advantage for the surgeon during TURP because the visibility may remain good despite the bleeding. The osmotic hemolysis proved to be a disadvantage, however, since excessive water absorption resulted in large amounts of free hemoglobin (Hb) in plasma, which caused vacuolation, necrosis, and desquamation of epithelium in Henle's loop and the distal convoluted tubules, causing renal failure.[53] After the operation, the patient might present with anemia, which is not commensurate with the surgical blood loss, marked oliguria or anuria, loss of appetite, progressive nitrogen retention, and jaundice. Fatal cases have been reported.[54] Water molecules are rapidly distributed in the total body water, resulting in less hypervolemia and less hyponatremia than with glycine and mannitol solutions. Distilled water with ethanol added may be used for irrigation during TURP if the ethanol method is used.[55]

## Glycine

Glycine, $NH_2CH_2COOH$, is a nonessential and the simplest of the amino acids. The normal concentration in plasma is 150-350 μmol/L corresponding to 13-17 mg/L. It is the most common fluid used in Sweden and in the USA[56] and constitutes about 70% of the sales value. In the UK, the use of glycine is even more frequent. Glycine solutions are available on the market in several concentrations. Glycine 1.5% with ethanol 1% was introduced in Sweden in 1989. Nesbit reported the use of glycine in a 2.1% solution in 45 and in a 1.1% solution in 30 transurethral resections of the prostate without demonstrable hemolysis.[49] Glycine 1% with ethanol does not cause hemolysis in vivo.[57] However, glycine acts as an inhibitory transmitter on the central nervous system.[58] Furthermore, one of the products of its metabolism is ammonia, which may cause encephalopathy.[59] Glycine 1.5% is hypotonic and may cause brain edema.[60] Hahn et al. reported a higher long-term risk of AMI after glycine absorption during TURP, suggesting that glycine might produce permanent myocardial damage.[2]

## Mannitol

Mannitol, $H-C_6H_{12}-OH$, is a hexahydrate sugar alcohol, which is not metabolized but excreted by the glomerulus without tubular reabsorption or tubular excretion.[61] Therefore, it acts as an osmotic diuretic. Mannitol has been used as an irrigating fluid since the 1950s and has a 15% market share. The fluid was given intravenously to protect the kidneys when distilled water was used as irrigation fluid during TURP.[62] Mannitol 3% with ethanol 1% was introduced in Sweden in 1991. This solution results in a larger urinary excretion of water and electrolytes, such as sodium (Na) and chloride (Cl), than glycine solutions. Arterial hypotension due to osmotic diuresis has been reported after absorption of mannitol 3%[63] and, in particular, after mannitol 5%.[64] In mice, the 5% solution was associated with better survival than with both glycine 1.5% and sorbitol with mannitol.[65]

## Other fluids

Sorbitol, $H-C_6H_{12}-OH$, is an isomer of hexols, 6-carbon alcohols. It induces marked diuresis after absorption. In contrast to mannitol, it is metabolized in the liver to fructose by sorbitol dehydrogenase and then to glycogen.[66] The fluid has a 15% marked share. Creevy used glucose 4% in 158 transurethral resections of the prostate without any instance of hemolysis, but he pointed out that the solution makes the surgeon's gloves and instruments sticky. Postoperative blood sugar measurements in diabetics are important in case of absorption.[53] Sorbitol 2% with mannitol 1%, which was introduced in Sweden in 1991, is a modification of the irrigating fluid Cytal®. Mannitol 0.54 % with sorbitol 2.75% (Purisole®) has been used in the USA and Germany for more than 20 years.

# Absorption

## Intravascular absorption

Absorption directly into the circulation via injured veins is the far most common mechanism by which the fluid is taken up by the patient.[20] A rapid fall in the elevated breath ethanol level after irrigation with a fluid containing ethanol is the criterion that indicates absorption via the intravascular route (Figure 1).[52] This is also seen during intravenous infusions of irrigating fluid.[57]

## Extravascular absorption

In this form of absorption, the irrigating fluid is deposited in a pool around the urinary bladder or leaks into the peritoneal cavity after instrumental perforation of the prostatic capsule, urinary bladder, or during endometrial resection of the uterus. During monitoring by the ethanol method, the breath ethanol concentration curve increases to a plateau after the operation (Figure 1).[52] The same pattern of ethanol changes is also seen during intraperitoneal infusions of irrigating fluid.[67] The plateau is used to estimate the volume of the absorbed fluid.[68] As compared to the intravascular route, this type of absorption is associated with a higher risk of bradycardia and arterial hypotension while the incidence of nausea is lower.[69]
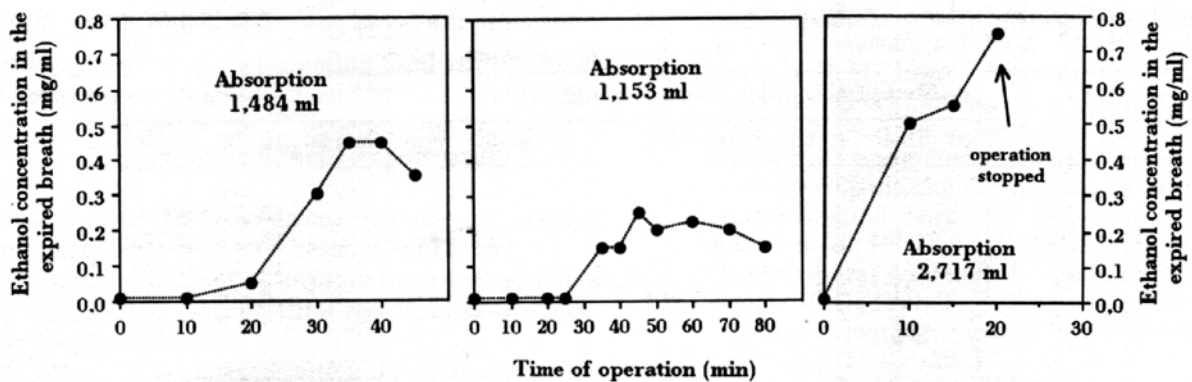


Figure 1: **Blood-ethanol concentration as indicated by exhaled breath during 3 transurethral prostatic resections** The last operation was stopped because of a risk of severe TUR syndrome. The patient still had a mild form of the syndrome with bradycardia, headache, and long-lasting nausea. With the kind permission of the authors.[52]

## Absorbed volume and risk of symptoms

Absorption of at least 150 ml occurs during nearly half of the TURPs performed.[52] The absorption of one liter of irrigating fluid is a useful limit dividing patients with a small or large risk of having symptoms of the TUR syndrome.[60] Five to 8 percent of patients absorb more than this amount during TURP.[70] If the volume of fluid absorbed increases from 1 to 2 liters, intraoperative and postoperative circulatory and neurological symptoms become more frequent[20] and deaths have been reported.[71] The incidence of symptoms doubles and the severity score triples when the absorption increases from 1 to 2 liters to more than 3 liters.[72] There are more symptoms after than during the operation. Bradycardia, acute arterial hypotension and nausea are the most common. Marked chills due to a cooling effect by the

fluid and diarrhea due to accumulation in the intestine are both typical postoperative problems.[69] Severe cases may exhibit a depressed sensorium and epileptic seizures.[73] A checklist for symptoms and definitions of severity scores are useful for both research and in clinical practice.[20]

## Traditional monitoring of irrigating fluid absorption

Before Jorfeldt invented the ethanol method,[50] the fluids were tagged with other substances and the levels of the tracers were measured in the blood, for example, salicylic acid,[74] glucose,[53] and radioactive tracers,[75] but these methods were time-consuming, invasive, and expensive. Weighing the patient before and after surgery[76] did not give the surgeon any immediate information during the resection about ongoing absorption. Measuring changes in the serum sodium concentration (S-Na) during TURP is a specific method for determining the degree of fluid absorption,[77] but it is time-consuming and invasive. Calculating the volumetric fluid balance presents many sources of error, for example, spillage on the floor, variations in bucket size, content of fluid in bags,[78] urine excretion, and blood loss.

## Blood loss

Blood loss contributes significantly to the morbidity of TURP.[26] Men who undergo TURP usually have cardiovascular disease, which makes them vulnerable to hypovolemia, low blood pressure, and decreased oxygen transport. As early as the end of the 1930s, Pilcher worked out a method of determining blood loss following TURP and other surgical procedures by using a photometer accurate to within 3% to 5%.[79] In the 1940s, Nesbit and Conger calculated the concentration of blood in irrigating fluids by comparing the color of tubes colored to correspond to known concentrations of hemoglobin.[79] LeVeen and Rubricius introduced a blood loss monitoring device which registered changes in conductivity associated with different concentrations of blood and electrolytes.[80] In the 1960s, Desmond and Gordon started routine measuring of blood loss with a photometer with which it was possible to measure within 2 min how much hemoglobin had been lost.[81] In the 1980s, Ekengren and Hahn started to use the portable and battery-run HemoCue TUR-Hemoglobin photometer with disposable vials already containing the reagent. In their study of 700 patients, the blood loss ranged from 10 to 3825 (median 300) ml and the weight of the resectate was 2-138 (18) g.[82]

# Long-term mortality after TURP

There has been a debate as to whether TURP is associated with an increased long-term risk of acute myocardial infarction. A summary of some of the studies dealing with this question follows.

Roos et al. published the first of these studies in 1989.[1] The outcomes of TURP were compared with those of open surgery in an attempt to evaluate alternative treatments for BPH. In total, 39,077 men after TURP and 14,990 after open surgery were identified in Denmark, England, and Canada. The patients were followed retrospectively for 8 years by using data from large administrative databases. The relative risk of a second operation and of death was higher after TURP than after open surgery in all three countries. The patients who had a TURP were less healthy before surgery. After an adjustment was made for comorbidity, they still had an increased risk of dying of AMI (relative risk 2.5, p=0.0001). The authors recommended prospective studies, as they could not explain this increased mortality.

The study was commented upon in an Editorial in the Lancet, in which much more basic information about the medical state of the patients was considered necessary, since patients might have cardiovascular disease without showing symptoms. The journal also stressed the potential importance of intraoperative cardiac function, measurements of electrolyte disturbances, type of irrigating fluid, and the duration of anesthesia to the results.[83] Therefore, in another retrospective study, the charts of 268 men after TURP and 248 men after open surgery were used to follow the patients for 5 and 8 years respectively for mortality and reoperation. The patients who had a TURP showed more comorbidity, such as angina, than those managed by open surgery, who were more frequently cigarette smokers and were more likely to have complications of prostatic hyperplasia. The relative risk of reoperation after TURP, compared to open surgery, was 3.46 and the adjusted relative risk of death was 1.69. The authors believe that the less complete removal of tissue during TURP may explain the increased risk of re-operation. Glycine 1.5% was used as an irrigating fluid, but no information was collected on postoperative electrolyte problems. The increased mortality might be due to myocardial damage after glycine absorption or factors of comorbidity not taken into account. Here, too, prospective studies were recommended.[84]

In another retrospective study, 3885 patients were reviewed retrospectively after TURP. The most common intraoperative complications were bleeding requiring transfusions in 2.5% of the patients, the TUR syndrome in 2%, myocardial arrhythmia in 1.1% and extravasation in 0.9%. The TUR syndrome was treated by diuretics and observation in 66% of the patients.

There were 700 complications (18%) in the immediate postoperative period. The most common complications were failure to void (6.5%), bleeding requiring transfusion (3.9%), clot retention (3.3%), and genitourinary infections (2.3%). Increased morbidity was found in patients with a resection time of more than 90 minutes, a gland weight of more than 45 g, an AUR and patient age of more than 80 years. The mortality rate had fallen from 2.5% to 0.2% during 27 years. Causes of death were 5 cases of sepsis, 1 patient with AMI, and 3 with other conditions.[18]

A reevaluation was made of the previously reported excess mortality from AMI after TURP.[1] In Denmark, 38,067 patients were followed for a maximum of 10.5 years via data from large databases. After adjustments for age and preoperative health status, the relative risk of death for a patient after TURP was 1.19. Surprisingly, the most common cause of death among these patients was chronic bronchitis, which is to be compared with AMI in the Canadian patients. The results point in different directions with regard to possible biological mechanisms behind the cause of death.[85]

The hospitalizations records and data from administrative data files were linked in a study in which 2617 patients were followed for two years after surgery for BPH. Open surgery was performed in 168 and TURP in 2449 of them. The risk of having a repeat operation was 2.72% after TURP and 1.84% after open surgery. This risk was not statistically significant. After correction for comorbidity, there was no statistically significant difference in the risk of death between the two groups.[86]

The records of 126 patients who were managed by open surgery for BPH and 126 patients by TURP were reviewed retrospectively to determine the 5-year mortality. During the 5 years, 22 of 126 patients after TURP and 17 of 126 patients after open surgery had died. The relative risk of death decreased to 1.03 for TURP after adjustment for old age and the severity of comorbid illness.[87]

Twenty-five patients were followed during 6 years after TURP for BOO together with 50 age-matched controls with so-called prostatism, who were not operated on. In the group operated on, 4 patients (16%) died as compared to 5 patients (10%) in the control group. There were 2 (8%) fatal cases with AMI in the operated group, compared to 3 (6%) in the control group. The other causes of death were cancer (n=3) and a ruptured aneurysm (n=1). The patients in the TURP group reported higher consumption of tobacco and alcohol than those in the control group.[88]

Hospital and death records were analyzed for 13,815 men undergoing prostate surgery during 1963-85. Standardized mortality ratios were calculated, taking the population of the

study area as the standard. Mortality after elective and immediate admissions was examined separately. TURP had a lower 30-day case fatality rate than open surgery, a similar 90-day rate but a higher one-year rate. The men in the TURP group were somewhat younger but had more circulatory disease than those managed by open surgery. Long-term mortality after TURP was close to that expected from background population rates, with a standard mortality ratio of 100, whereas long-term mortality after open surgery was lower than expected from population rates with a standardized mortality ratio of 79.[89]

In a retrospective study in Japan, 717 patients after TURP and 48 after open surgery were followed for at least 12 years. The reoperation rate was 5.6% and 2.1%, respectively. Survival rates did not differ between the two groups and exceeded those of the same age group in the Japanese male population. Age at operation, presence of azotemia, and abnormal electrocardiograms (ECG) were all risk factors for death after surgery, but indices of extensive surgery such as weight of the removed specimen, operating time, hyponatremia and blood transfusion requirements were not.[44]

Computer data were analyzed from 81,958 men who were managed by TURP (55,030) or open surgery (26,928) of the prostate in Scotland between 1968 and 1989. The cumulative risk of reoperation at 8 years was 13% after TURP and 3.2% after open surgery. The age-corrected relative risk of death after TURP, compared to open surgery when patients with cancer had been excluded, was 1.06.[90]

In a retrospective study in Australia, data on 19,598 men operated on for prostatic hyperplasia during 1980-95 were linked to hospital morbidity data, mortality records, and prostate cancer registrations. The relative risk of death, adjusted for age, calendar year, admission type, and comorbidity after TURP, compared to open surgery, was 1.07. The incidence rate of prostate cancer was 44% higher after TURP than after open surgery. The authors concluded that there is a small and clinically unimportant excess mortality risk from TURP, which could be due to a protective effect of open surgery on the long-term risk of prostate cancer and a lower rate of repeat operations.[91]

Another study compared the operative course of TURP with the morbidity of acute myocardial infarction among 846 patients. The relative risk was 1.6 of having a first-time AMI after TURP, 6.1 for a reinfarction, and 2.2 for a first-time or a reinfarction combined if more than 500 ml of glycine had been absorbed during the operation. Patients who absorbed more than 500 ml and bled less than 275 ml had 4.4 times the risk of having an acute myocardial infarction.[2]

In another study, 888 patients who underwent an elective TURP between 1988 and 1994 and 478 patients managed by TUMT between 1991 and 1994 were followed up until December, 1995. Cases of AMI were identified in the AMI Incidence Register in Stockholm and the National Cause-of-Death Register. The observed number of AMI cases was compared with the corresponding expected number based on regional age-specific incidence rates in Stockholm County obtained from the National Myocardial Infarction Register and on the number of person-years at risk among members of the cohorts. A corresponding analysis of mortality compared the observed with the expected number of deaths. The incidence of AMI was higher than expected; the standardized morbidity ratio was 1.23 for TURP and 1.31 for TUMT. The standardized mortality ratio was 1.19 for TURP and 1.11 for TUMT.[92]

In summary: Three studies[1,84,85] have shown an increased relative risk (1.19-1.45) of death 8-10.5 years after TURP compared to open surgery for BPH. Subsequent studies have not shown any increased risk at all[86,88,89] or only a slightly elevated relative risk of 1.03-1.07.[44,87,90,91] Holman et al. suggested that the difference could be due to a protective effect of open surgery on the long-term risk of prostate cancer and a lower rate of repeat operation. Koshiba found that indices of extensive surgery such as hyponatremia and blood transfusion requirements were not risk factors for death after surgery. However, these observations indicate that the patients were monitored regarding these potentially dangerous events during the operation, thus making it possible to start treatment before a serious situation occurred. A consistent observation is that the patients who underwent a TURP had more comorbidity than those managed by open surgery. The two Swedish studies[2,92] show that absorption of glycine during TURP may increase the long-term risk of AMI, but also that men with lower urinary tract symptoms due to BPH without undergoing TURP have risk factors for cardiovascular disease. According to Hahn's observations, it is possible that glycine absorption potentiates the cardiovascular risk factors among men with LUTS and BPH. However, there is still a possibility that comorbidity, such as smoking,[93] can explain this difference, despite that fact that a correction for smoking was used in the first of these analyses.

The prostate receives innervation from the sympathetic and parasympathetic nervous systems. Adrenergic nerves release norepinephrine, which stimulates $alpha_1$-adrenoceptors in the prostatic smooth muscle and the bladder neck.[94] Muscle tone may constitute about half of the total urethral pressure in patients suffering from BPH.[95] This mechanism might cause bladder outlet obstruction even if the prostate adenomas are of small or medium size, as they are in appropriate patients for TURP. If the muscle tone were caused by an imbalance in the autonomic nervous system, i.e., an increased sympathetic tone, this would perhaps be a part of

the explanation behind the increased mortality due to heart disease among men after TURP, since sympathetic stimulation increases the risk of ventricular fibrillation.[96] Open surgery, on the other hand, is recommended when the weight of the prostate exceeds 100 grams,[44] and the bulging adenomas might cause obstruction in the absence of increased smooth muscle tone. Koshiba concluded, in opposition to some other authors, that both TURP and open surgery are safe for the treatment of obstruction due to BPH and do not shorten the long-term survival of the patients.

# AIMS OF THE THESIS

The reason why I made the studies presented in this thesis was my hope that the short and long-term complications of TURP could be better understood and reduced.

1. Patient selection is one possible explanation of the previously described increased long-term mortality after TURP, as compared to open surgery. To test this hypothesis, I wanted to compare risk factors for cardiovascular disease in patients with moderately enlarged (treated by TURP) and much enlarged glands (treated by open surgery) in those suffering from bladder outlet obstruction.

2. I wanted to examine, in the clinic, whether the choice of an alternative irrigating fluid, mannitol solution, instead of the more conventional glycine solution, reduces the incidence of symptoms of fluid absorption.

3. To examine whether more discreet differences in adverse effects between mannitol and glycine solution can be discerned by laboratory methods when moderate amounts of these solutions are infused intravenously in volunteers.

4. To examine what differences in pathophysiological effects and cardiac morphology that occur when large amounts of mannitol and glycine solution are infused. The danger associated with these experiments required them to be performed in animals (pigs).

5. To test whether 3 months of oral pretreatment with finasteride (Proscar) can reduce the blood loss, and possibly also the fluid absorption, during TURP.

# ETHICAL CONSIDERATIONS

The Karolinska Scales of Personality (KSP) questionnaires in Paper I contain delicate information but they are kept locked in and the identities of the patients are coded in the data file.

Transrectal ultrasonography is an invasive examination, but its use in Papers I and V was of invaluable help in selecting the most appropriate management of the patients' symptoms.

We offered the patients in Paper II the choice of being operated on with the aid of a fluid without ethanol, but this might be questionable because the use of the ethanol method may prevent large fluid absorption.

Absorption of moderate volumes of glycine 1.5% during TURP and transcervical resection of the endometrium (TCRE) is associated with depression or inversion of the T wave on the ECG 24 h after surgery,[97] a doubling of the long-term risk of acute myocardial infarction,[2] and the occurrence of nausea and cerebral edema.[60] Our assumption that infusion of 1.25 L of fluid in Paper III would not cause any severe TUR syndromes was reasonable because the volunteers were much healthier and younger than ordinary patients scheduled for TURP and men are not as vulnerable to a hypotonic fluid load[98] as women.

Due to the total radiation dose of 4.4 mSv from the computerized tomography (CT) investigations of the brain, exclusion criteria were smoking or living in a house with radon gas levels above the nationally acceptable limit, which is 400 Bq/m$^3$ of air. Swedes receive a main effective dose of 2 mSv/year and 3 mSv from radon gas.

The pigs in Paper IV were taken care of by professional animal keepers, received premedication before the experiments and the depth of anesthesia was checked repeatedly. The animals were killed at the end of the trials.

The period of tablet intake before TURP in Paper V did not delay surgery in any case because the waiting time for surgery was longer than three months at our department during the period in question. Common finasteride-related adverse events are of a sexual nature and transient, illustrated by two patients in the finasteride group who reported decreased libido, impotence, or a semen abnormality. No serious drug-related adverse events were observed.

# METHODS

This thesis is based on five papers. Paper I studies risk factors for cardiovascular disease in 52 patients with bladder outlet obstruction due to a small or large prostate. Paper II compares symptoms in 52 patients who absorbed more than $500 - 700$ ml of one of two fluids during TURP. Paper III evaluates pathophysiological effects of two irrigating fluids in 12 volunteers who received them intravenously on separate occasions separated by at least ten days. Paper IV studies the pathophysiology of the TUR syndrome in 25 anesthetized pigs, including 2 controls. Paper V compares the surgical blood loss during TURP in 60 patients who had taken either finasteride or placebo for 3 months before surgery. The appropriate local Ethics Committee approved all protocols.

## Paper I

The purpose of this study was to determine whether men with bladder outlet obstruction differ with respect to the prevalence of risk factors for cardiovascular disease depending on the size of the prostate.

Fifty-two men, 52-85 (mean 68) years old, with voiding symptoms were enrolled from 1995 to 2000 at the Departments of Urology at the Söder Hospital and the Huddinge University Hospital. The prostate volume was measured by transrectal ultrasonography in order to obtain two groups of patients of similar size, one with only a moderately enlarged gland and one with a markedly enlarged one. The occurrence of bladder outlet obstruction was verified and measured by functional testing (urodynamics) with a pressure and flow investigation. The personality characteristics were measured using the Karolinska Scales of Personality questionnaire. The function of the autonomic nervous system was studied in terms of heart rate variability (HRV) analyzed on a 24-hour electrocardiographic recording. The amount of catecholamines excreted in the urine from 8.00 a.m. to 4.00 p.m. was quantified. The patient's height and weight were recorded. The blood pressure was measured after 15 min of rest in the sitting position, after which blood samples were taken to analyze the serum concentrations of glucose, cortisol, lipids, vascular endothelial growth factor, and albumin-corrected fructosamine. After this initial evaluation, the investigator selected treatment for the voiding symptoms according to his clinical judgment.

## Paper II

The purpose of this study was to evaluate which irrigating fluid, glycine 1.5% or mannitol 3%, is associated with the most favorable adverse effects profile when absorbed by the patient during TURP.

All the patients who underwent TURP at the Söder Hospital in Stockholm between April, 1995, and December, 1996, were asked to participate. The anesthetic staff contacted the researchers when the breath ethanol concentration exceeded 15 mg × 230 L$^{-1}$ air, which corresponds to 500 to 700 ml of fluid absorption, depending on the absorption time.[51] Of the total 394 enrolled patients, 52 men, 53-90 (median 74) years of age, fulfilled the criterion. They underwent a symptom recording procedure to determine the incidence and severity of 13 symptoms associated with the TUR syndrome at the end of the operation and also two or three times at hourly intervals during convalescence.[69,99] The patient was interviewed the morning after the operation, and night reports of the nurses were checked for evidence of symptoms associated with fluid absorption. A reaction was considered febrile if the body temperature was 38°C or higher before noon one day postoperatively.

## Paper III

The purpose of this study was to investigate the fluid distribution and symptoms in 12 volunteers who received glycine 1.5% and mannitol 3% intravenously at least ten days apart.

Twelve healthy male volunteers aged 22-35 (median 28) years, with a body weight of 73-98 (median 83) kg were recruited for the investigation. The subjects had a light breakfast at home but all fasted during the experiments. An electrocardiographic recording was started before the experiments and continued until the next morning. Computerized tomography of the brain was performed before and 4 hours after the start of the infusion, which was given at a constant rate of 0.5 ml/kg/min over 30 min. Symptoms and signs of adverse effects were noted during and after the infusions and the volunteers were asked to report any feeling of uneasiness on the morning after the experiment. Cognitive function was examined before and 1 and 3 hours after the start of the infusion. Blood pressure and heart rate were measured at regular intervals for 3 hours from the start of the infusion. Blood samples were drawn from a venous cannula at 0, 30, 60, and 180 min in each experiment. The urinary excretion and the urine concentration of sodium and potassium were measured just before and at 1 and 3 hours after the start of the infusion. The expired breath ethanol concentration was measured every 5 min during the infusions. The distribution of infused fluid between the body fluid

compartments and the expansion of blood volume were calculated. The changes in the volumes of the fluid compartments in the whole body and in one leg were assessed by bioelectrical impedance analysis, which took place before and 1 and 3 hours after the start of the infusions.

## Paper IV

The purpose of this study was to examine the gradual development of the TUR syndrome in 23 pigs that received large volumes of glycine 1.5% or mannitol 5% and to examine whether mannitol 3%, i.e. of the same osmolality as glycine 1.5%, raises the intracranial pressure (ICP).

Twenty-five pigs of both sexes ages between 8 and 10 weeks and with a mean body weight of 22 (19-29) kg were studied. The infusions were given during 90 min and the animals were observed during 120 min. Seventeen of them were included in an invasive study using multiple determinations of blood flow rates, arterial and ICP, electrolyte status, blood gases, and urinary excretion. These animals received glycine 1.5% or mannitol 5%. Six of the remaining pigs were given mannitol 3%, but only the ICP, electrolyte status, and urinary excretion were studied. Two pigs served as controls and received no fluid. They underwent monitoring of the ICP and pulse oximetry. After the experiments were completed, the animals were killed with an overdose of thiopental and ethanol. The heart was removed from 15 animals, rinsed with saline, and fixed in buffered formaldehyde 4% (Solveco Chemicals, Täby, Sweden).

After surgical preparation under general anesthesia, the pigs were allowed to reach hemodynamic steady state for 30 min before starting the infusions. Blood samples for the analysis of blood gases and acid-base balance were collected from a catheter placed in the left external jugular vein with the tip as close as possible to the base of the skull. Through the same incision, another catheter was directed to the heart for the purpose of infusing ketamine and irrigating fluid. Via a paramedian right neck incision, a flow-directed catheter was inserted through the right external jugular vein and advanced through the right ventricle to the pulmonary artery to measure mixed venous blood gases, pulmonary arterial pressure, and cardiac output (CO). The right carotid artery was dissected and its blood flow rate was measured continuously by a perivascular ultrasonic flow probe applied to the vessel and connected to a Transonic T101 analyzer (Transonic System, Inc., New York, NY). Via an incision in the left groin, a catheter was introduced into the femoral artery to monitor the pressure and sample blood for measurements of the blood hemoglobin concentration (B-Hb),

blood gases, and the serum concentration of sodium (S-Na), potassium (S-K), and troponin T (S-TNT), and the activity of creatine phosphokinase (S-CK). Via an incision in the skin and a drilled hole in the parietal bone, about 1 cm lateral to the midline, a 15-cm standard Medtronic PS Medical ventricular catheter (Medtronic, Inc., Minneapolis, MN) was inserted 5 cm for ICP monitoring. A laparotomy was then performed and a Foley catheter was inserted through a cystostomy into the urinary bladder to measure the urinary excretion of fluid and electrolytes. A perivascular ultrasonic flow probe was applied to the abdominal aorta and connected to the Transonic system. The abdominal midline incision was then closed.

## Paper V

The purpose of this study was to inquire whether pretreatment with finasteride (Proscar®), compared to placebo, reduces the blood loss, operating time, amount of irrigating fluid absorbed, resources used, and other exploratory indices of extensive surgery during TURP.

Sixty men scheduled for TURP or referred due to LUTS were included from August, 1998, until May, 1999, in this double-blind, randomized, placebo-controlled, single-centre, parallel group pilot study. The key inclusion criteria were a prostate volume between 30 ml and 90 ml as determined by TRUS and a PSA density <0.14 μg/L/g. Men were excluded who had undergone invasive procedures for the treatment of BPH, previous treatment with finasteride, showed evidence of malignancy, had coagulation disorders or were on treatment with anticoagulants during the past 3 months. Intake of non-steroid anti-inflammatory drugs and aspirin was discontinued 2 weeks prior to surgery. Based on the 880 patient files evaluated, 300 letters with patient information, questions about past and present history, a time micturition list and the International Prostate Symptom Score (IPSS) questionnaire were sent out. One hundred and seventy-eight patients were invited to the first visit. After being screened and providing their written informed consent, the 60 patients finally included were randomly allocated to receive either finasteride 5 mg (Proscar®, Merck & Co., Whitehouse Station, USA) or placebo daily during 12 weeks prior to TURP. I performed all of the examinations and operations myself to reduce variations in the results due to surgical technique.

The research nurse assessed the resources consumed by the patient during visits 2, 3 and 4 as well as once every two weeks between the visits, via discussions and phone conversations with the patients. The research nurse asked questions related to the previous two weeks and noted the answers in the patient's research file.

Safety is summarized by adverse experience counts. The experience analyses are based on: (1) the nonserious adverse experiences occurring from the start of therapy to withdrawal of the study drug or until discharge from hospital after TURP (whichever is later); (2) the serious adverse experiences occurring from the start of therapy up to 14 days after study drug withdrawal or until discharge from hospital after TURP, whichever is later; (3) clinically significant postoperative bleeding occurring up to the follow-up visit.

## Monitoring of fluid absorption

Since the irrigating fluid contained 1% ethanol, the ethanol concentration in the patients' (Papers I, II, V) and volunteers' (Paper III) exhaled breath was used to indicate and quantify the amount of fluid absorbed[100] or infused. This concentration was measured just before and every 10 minutes during the operation, using a portable Alcolmeter S-D2 (Lion Laboratories, Barry, UK). In case of absorption and during the intravenous infusions, these measurements were performed every 5 min. The alcolmeter was calibrated by administering an alcohol-in-gas standard test gas. The total absorption or infusion was calculated using a computer program,[51] while the nursing staff estimated the absorption for clinical purposes by means of a nomogram.[100] The urologist was informed of ongoing fluid absorption. When the ethanol method indicated that more than 1000 ml had been absorbed most surgeons then usually shortened the operation. Surgery was stopped when more than 2000 ml had been absorbed.

| | Blood Loss | | | Fluid absorption |
|---|---|---|---|---|
| Paper | TURP | | Open surgery | TURP: I, II, V Infusion: III |
| | TUR-Hemoglobin method | Low Hemoglobin System | Visual estimation | Ethanol method |
| I | Nurse | | Nurse | Nurse (n), Invest (cp) |
| II III IV | Nurse | | | Nurse (n), Invest (cp) Invest (cp) |
| V | Nurse | Invest | | Nurse (n), Invest (cp) |

Table 1: **Blood loss measurements were performed by the nursing staff using the TUR Hemoglobin method and by visual estimation and by the investigator using the Low Hemoglobin method** Fluid uptake was estimated by the nursing staff using a nomogram (n) and calculated by the investigator using a computer program (cp).

## Irrigating fluids in the studies

| Paper | | | | | Fluid | Osmolality, mosm/kg[101] | Effective osmolality (tonicity) |
|---|---|---|---|---|---|---|---|
| I | II | III | | V | Mannitol 3% + ethanol 1% | 400 | Hypo-osmolar |
| I | II | III | | | Glycine 1.5% + ethanol 1% | 430 | Hypo-osmolar |
| | | | IV | | Glycine 1.5% | 190 | Hypo-osmolar |
| | | | IV | | Mannitol 3% | 170 | Hypo-osmolar |
| | | | IV | | Mannitol 5% | 290 | Iso-osmolar |

Table 2: **The irrigating fluids used in Papers I-V** Although the addition of ethanol increases the osmolality of the fluids, the ability of the fluid to enter the cells (effective osmolality, tonicity) does not decrease to the same extent because ethanol is quickly distributed across the cell membrane. The normal osmolality of blood plasma is 290. The pH of the irrigating fluids is about 6, in normal arterial blood 7.4, and in venous blood and interstitial fluids 7.35.

In Paper II, the fluid bags were blinded by the pharmacy. The randomization was based on one weekly change, that is, the type of fluid in the blinded bags was either changed or not changed every week for 74 weeks, summer vacation excluded. No one working with the patient had any knowledge of the fluid used. In Paper III, each volunteer received, after resting 20 min to reach hemodynamic steady state, in random order and separated by at least 10 days, an intravenous infusion of one of the fluids and, on the second occasion, the other one. Two infusion pumps (Flo-Gard 6201, Baxter Healthcare, Deerfield, IL) were used. In Paper IV, the 23 pigs were randomly allocated to receive a constant-rate intravenous infusion of 100 ml $kg^{-1}$ $h^{-1}$ of glycine 1.5% (n=9), mannitol 5% (n=8), or mannitol 3% (n=6) with the aid of two infusion pumps. Another two pigs served as controls and received no irrigating fluid. In Paper V, the fluid bags were heated to $38^{o}$C before use and maintained at a level of 50 to 75 cm over the prostate.

## Fluid distribution

*Mathematical model*

In Papers III and IV, the distribution of infused irrigating fluid between the body fluid compartments was calculated with the following assumptions and formulas:

[1] The extracellular fluid volume makes up 20% of the body weight and corresponds to the distribution volume of Na,

[2] The *change* in water content of the intracellular fluid compartment ($\Delta ICF$) after infusion of a volume of irrigating fluid (IFV) is calculated as the difference between the [3] *change in Na space and* [5] *the expected change in water content of the ECF,*

[3] Change in Na space (= *true* ECF volume): Estimated amount of Na in the ECF ($Na_{ECF}$) divided by the S-Na at any time (S-$Na_n$):

$$\frac{Na_{ECF}}{S\text{-}Na_n},$$

[4] $Na_{ECF} = ECF_0 \times S\text{-}Na_0 - U\text{-}Na_{loss}$

(S-$Na_0$ is the S-Na before the experiment and U-$Na_{loss}$ is the quantity of Na ions lost in the urine)

[5] The *expected ECF volume:*

$ECF_n = 0.2 \times$ body weight $+$ IFV $- \Sigma$ urine volume

($\Sigma$ urine volume= cumulative volume of urine excreted during the experiment)

[6] $\Delta ICF = ECF_n - (Na_{ECF}/S\text{-}Na_n)$.

In Paper III, the baseline blood volume was estimated according to a regression equation based on the height and body weight of the subject.[102] In Paper IV, the baseline blood volume of the pigs was taken to be 7% of the body weight. The blood volume expansion was calculated as the product of the baseline blood volume and the hemodilution, with a correction for blood sampling (Papers III, IV).[103]

*Bioimpedance*

In Paper III, the changes in volume of the fluid compartments in the whole body and in one leg were assessed by Xitron 4000 bioelectrical impedance analysis (Xitron Technologies, Inc., San Diego, CA). Two electrodes were placed on the right wrist, iliac crest, and ankle joint. The bioelectrical analysis involves sending small currents in a series of 50 frequencies between 5 and 500 kHz through these electrodes.[104,105] The fluid volumes were calculated from the recorded impedance by the computer software delivered with the apparatus, using the baseline body weight on all occasions, while the percentage change in impedance was reported for the leg measurements. The intracellular volume (ICV) was obtained as the difference between the total body water and the extracellular volume. The subject was supine for at least 15 min before all examinations, which took place before and at 1 hour and 3 hours after the start of the infusion. Each reported value represents the mean of three measurements. The coefficients of variation were 0.3% for the extracellular fluid volume and 2.0% for total body water.

## Evaluation of symptoms associated with absorption

In Paper II, the incidence and severity of 13 symptoms associated with the TUR syndrome were recorded until noon one day postoperatively. In Paper III, symptoms and signs of adverse effects were noted during and after the infusions. The volunteers were also asked to report any feeling of uneasiness on the morning after the experiment. Symptoms were evaluated according to a scoring system: headache, vertigo, tiredness, and dyspnea (mild=score of 1, more severe=score of 2, fainting=score of 2 and prolonged complaints of prickling or heat sensations=score of 1).

## Monitoring of blood loss

The blood loss during transurethral surgery (Papers I, II, V) was monitored by using a portable HemoCue photometer (HemoCue AB, Ängelholm, Sweden) and disposable microcuvettes containing reagents in dry form.[82] The chemical reaction in the cuvette is a modified azidomethemoglobin reaction. Absorbance was measured at 570 and 880 nm. The used fluid was collected in 10-liter buckets with heparin added to prevent coagulation. When a bucket was full, the fluid was stirred with a paddle for 10 to 15 seconds and a sample of it was taken from the periphery of the bucket. In Papers I and II, the nursing staff used the TUR-Hemoglobin method. A formula is employed to calculate the blood loss:

$$\frac{\text{Photometric value} \times \text{Volume}}{5.2 \times \text{B-Hb}} = \text{Blood loss (L)}$$

where the *photometric value* is shown within 15 s with a TUR-Hemoglobin cuvette. The *volume* is the amount of fluid in the bucket (L). *B-Hb* is the patient's blood hemoglobin level (g L$^{-1}$) before surgery. *5.2* is a factor used; since the TUR-Hemoglobin cuvette is thicker than the B-Hemoglobin cuvette, the value obtained in a photometer calibrated for B-Hb should be divided by 5.2 to obtain the concentration of hemoglobin in the irrigating fluid. In Paper V, the investigator used the HemoCue Low Hemoglobin system. The samples were put in a freezer at -20°C and the hemoglobin concentration of the collected samples was analyzed in duplicate once a month (coefficient of variation 3.7%, n=158). The mean of the two photometric values was multiplied by the fluid volume in each bucket to yield the Hb content. The blood loss during TURP was obtained as the sum of the amount of hemoglobin in all buckets used, divided by the preoperative B-Hb:[106]

$$\frac{\text{Photometric value} \times \text{Volume}}{\text{B-Hb}} = \text{Blood loss (L)}$$

In Paper I, during open surgery, the blood from the operating field and the squeezed compresses was collected in suction bottles. The remaining blood content of each compress was estimated to be 25 ml. These volumes were added to yield the sum of the blood loss during each transvesical adenoma enucleation.

## Urological investigations

### *Transrectal ultrasonography*

In Paper I, one of two methods of TRUS was used to determine whether the patient had a prostate size smaller than 45 ml or larger than 54 ml. ***Step-section planimetry:*** The ultrasound probe was mounted in a ratcheted stepping device. At each 5-mm stepped, an image of the prostate was calculated by tracing its circumference. The prostate volume was calculated by multiplying the sum of these areas by the 5-mm stepping interval. ***Prolate spheroid volume:*** The following formula

$$\text{Volume} = \frac{\pi}{6} \times (\text{transverse diameter})^2 \times (\text{anteroposterior diameter})$$

was employed. Both of these diameters were measured in the axial plane.[28] For the first of these methods, a Bruel & Kjaer ultrasound system model 1846 was used and a 4.0 MHz axial transducer (model 1850, Bruel & Kjaer, Copenhagen, Denmark). For the second method, a Bruel & Kjaer Cheetah Type 2003 with a 6.5-Mhz probe Type 8561 was used. In Paper V, the second method was used at the screening visit and 3 months after TURP. Transrectal ultrasonography was also performed just prior to TURP but, since finasteride shrinks the prostate, the surgeon only recorded the dimensions of the gland without calculating its volume in order to prevent unblinding. The surgeon was also blinded to the result of the first TRUS until the study file was closed.

### *Urodynamics*

In Paper I, after initial uroflowmetry, the patient lay down in a lithotomy position and the bladder was emptied. A PolyUro System (Synetics®) transurethral double-lumen catheter as well as a rectal one were adapted to a pressure transducer. Cystometry was performed by infusing 50 ml min$^{-1}$ of 0.9% saline until the patient desired to void. The pressure transducer was adapted to a suprapubic catheter. The transurethral catheter was removed and the patient stood up and voided. The maximum urinary flow, $Q_{max}$, and the detrusor pressure at maximum urinary flow, $P_{det}$ at $Q_{max}$, were plotted on a pressure-flow nomogram.[107] With this nomogram, patients could be classified as obstructed, equivocal, or unobstructed. If the point was located in the "Equivocal" area, a line was drawn between this point and the minimum voiding detrusor pressure, which is the minimum detrusor pressure needed to keep the urethra open and is normally attained as the urethra closes at the end of micturition. A slope of more than 2 cm $H_2O$ per ml/s implied obstruction. This nomogram has been validated in clinical studies.[108,109]

## Personality and mental testing

The Karolinska Scales of Personality (KSP, Paper I) is a self-assessment questionnaire consisting of 135 items, which are statements concerning habits, opinions, reactions, and feelings in different situations, forming 15 scales.[110] The patient chooses one of four answers, ranging from "Does not apply at all" to "Applies completely". The result is scaled in terms of the expected response for the Swedish population as a whole, where the mean is 50 and standard deviation (SD) is 10.

| | |
|---|---|
| 7 | I find it hard to object if I'm neglected at a restaurant. |
| 19 | When someone is pushing himself forward in the line, I usually tell him off. |
| 27 | I find it difficult going back to a store to ask if I can exchange an item I have bought. |
| 35 | I think that an argument can clear the air sometimes. |
| 51 | I feel embarrassed having to complain when I get too little change back. |
| 59 | When someone is teasing me, I never find a good answer until later. |
| 67 | I have difficulties turning someone down when asked for a favor, even though I don't feel like doing it. |
| 79 | I sometimes wish that I could speak up when I dislike something. |
| 83 | I feel very ill at ease when witnessing a fight in the street. |
| 135 | If someone is scolding me, I become sad rather than angry. |

Table 3: **The 10 items of the scale "Lack of Assertiveness"** Questions number 19 and 35 have reversed scoring.

In Paper III, cognitive function was examined using a questionnaire (mini-mental status) just before and 1 and 3 hours after the start of the infusion.[111,112] This test, which is considered to be reliable even when repeated, covers orientation, attention, recall, calculation, and language and takes about 5 min to complete. The maximum score is 30. To avoid excessively high scores due to a recall effect, 7 of the 11 questions were modified in both the second and the third mini-mental status test during the same experiment, but the same questionnaires were used in the two experiments.

## Cardiovascular investigations

### *Hemodynamics*

In Paper I, before treatment in the initial evaluation, the blood pressure was measured with a stethoscope and a blood pressure cuff. In Papers I, II and V, the systolic arterial pressure was measured with a blood pressure cuff, and the heart rate was recorded every 5 minutes during and every 15 minutes after the operation. In Paper III, the blood pressure and heart rate were measured at regular intervals during 3 hours from the start of the infusion with an automatic digital monitor (Hewlett Packard M 1008 A or M 1020 A, Hewlett-Packard, Böblingen, Germany). In Paper IV, measurements were effectuated just before and 5, 10, 15, 20, 30, 40,

50, 60, 70, 80, 90, 100, 110, and 120 min after the start of the infusion. The measurements included CO, blood pressures in the femoral and pulmonary arteries, blood flow rates in the internal carotid artery and abdominal aorta, and the ICP.

### *Oxygen delivery and consumption*

In Paper IV, CO and the arterial oxygen content ($CaO_2$) were used to calculate oxygen delivery ($DO_2$) and oxygen consumption ($VO_2$), as follows:[113]

$$CaO_2 = 1.34 \times \text{B-Hb}_n \times SaO_2 + 0.223 \times PaO_2$$

$$DO_2 = \frac{\text{cardiac output} \times CaO_2}{\text{body weight}}$$

$$VO_2 = \frac{\text{cardiac output} \times \left(CaO_2 - CvO_2\right)}{\text{body weight}}$$

where $CaO_2$ is expressed in ml $L^{-1}$, B-Hb in g $L^{-1}$ of whole blood, $SaO_2$ in percent, arterial oxygen tension ($PaO_2$) in kilopascals (kPa), $DO_2$ in ml $min^{-1}$ $kg^{-1}$, CO in L $min^{-1}$, body weight in kg, $VO_2$ in ml $min^{-1}$ $kg^{-1}$, and $CvO_2$ in ml $L^{-1}$. To calculate $DO_2$ and $VO_2$ for the brain, the input data consisted in the carotic blood flow rate and the blood gas analyses ($SaO_2$ and $PaO_2$) obtained from the samples taken from arterial blood and from the cephalic part of the external jugular vein.

### *Electrocardiographic recordings*

In Papers I and III, a 24-hour electrocardiographic recording was made using a cassette-based two-channel recorder (Reynolds Sherpa, Reynolds Medical, Hertford, England). Electrode positions similar to $V_1$ and $V_5$ were used. The analysis was carried out as described elsewhere.[114] The signal was digitalized and stored using a commercially available PC-based system (Aspect Holter System, Daltek, Borlänge, Sweden). In Paper I, the heart rate variability was used to study the prevalence of increased sympathetic or reduced vagal activity, which indicates an increased risk of lethal arrhythmias.[115] This method is based on the fact that the oscillation in the interval between consecutive heart beats and the oscillations between consecutive instantaneous heart rates are quantitative markers of autonomic activity. The power spectrum of the frequency domain was divided into four different frequency

bands:[116] total power, 0.0033 to 0.40 Hz (ms$^2$); very low frequency (VLF) power, 0.0033 to 0.04 Hz (ms$^2$); low frequency (LF) power, 0.04 to 0.15 Hz (ms$^2$); and high frequency (HF) power, 0.15 to 0.40 Hz (ms$^2$). These parameters were reported for the whole 24-hour period, for day (07.30-21.30) and night (0.00-05.00). In Paper III the data were analyzed with respect to rhythm, incidence of supraventricular and ventricular arrhythmias, and aberrant QRS complexes. The complete set of recordings was scanned manually for T-wave abnormalities. Using the Holter system, maximum T-wave amplitude was measured beat-to-beat in all recordings. In Paper IV, electrocardiographic monitoring with respect to arrhythmias was performed in all animals, and a printout for detailed analysis was obtained every 10 min in eight of them (three receiving glycine 1.5%, and five receiving mannitol 5%). The QT-interval was corrected for variations in heart rate (QT$_c$) by dividing the length of the interval between the onset of the QRS complex and the end of the T wave by the square root of the average interval between three consecutive heart beats (RR interval):

$$QT_c = \frac{QT}{\sqrt{RR}}$$

## Blood and urine chemistry

In Paper I the serum concentration of lipoprotein (a) was analyzed by turbidimetry on a Hitachi 917 (Hitachi Co., Naka, Japan) using DAKO reagents. Serum glucose, S-triglycerides, S-cholesterol, and S-high-density lipoprotein (HDL) cholesterol was analyzed by enzymatic photometry on a Hitachi 917 using Roche reagents. S-low-density lipoprotein (LDL) cholesterol was calculated. S-cortisol was analyzed by fluoroimmunoassay using the AutoDELFIA™ Cortisol kit (Wallac Oy, Turku, Finland). Albumin-corrected S-fructosamine was analyzed by the nitroblue tetrazolium method using the Roche reagent Unimate FRA (Roche Diagnostics, Mannheim, Germany). Vascular endothelial growth factor, VEGF$_{165}$, was measured with the Quantikine VEGF Immunoassay (R&D Systems Europe Ltd, Oxon, UK). In vivo, VEGF can induce angiogenesis and is expected to play important roles during normal and pathological angiogenesis. The serum concentrations of VEGF in men with small and large glands were compared. Insulin was also measured by immunoassay. All the urine excreted between 8.00 a.m. and 4.00 p.m. during an ordinary day was collected to determine the amounts of epinephrine, norepinephrine, and dopamine.[117] In Paper III, B-Hb was determined using a Technicon H2 (Bayer, Tarrytown, NY) and the serum and urine

concentrations of sodium and potassium using an Ektachem 950IRC System (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). S-osm was determined by means of an Osmometer 3C2 (Advanced Instruments, Inc., Norwood, MA). Plasma ammonia was measured by an enzymatic method on a Hitachi 917 just before the glycine-ethanol infusion began and again at 60 min. In Paper IV, B-Hb was determined using Multi-Species software on a Technicon H1 (Bayer Diagnostica) on the same occasions as the hemodynamic measurements. Blood and urine samples were also taken and the urine volume was measured before and 10, 20, 30, 40, 50, 60, 70, 80, 100, and 120 min after starting of the infusion, and the serum and urine concentrations of sodium and potassium were measured on a Hitachi 917. To detect possible damage to the myocardium, S-CK was measured on the Hitachi 917 and the S-TNT by immunoassay on an ES Enzymun system (Boehringer Mannheim GmbH, Mannheim, Germany) before and 60 min after the start of the infusion. Samples for measurements of blood gases were obtained on the same occasions as the electrolyte concentrations, using an AVL 995-Hb (AVL List GmbH Medizintechnic, Graz, Austria) in the operating room. In Paper V hematological analyses were performed on a Bayer H3 Hematology System (Bayer-Technicon). Prothrombin time was determined only at visit 3 and the following at visits 1, 3, and 4: Hb, hematocrit, red blood cells, platelet count and white blood cells (total and differential). Routine serum chemistry, including sodium, potassium, chloride, urea, creatinine, total bilirubin, SGOT, SGPT, alkaline phosphatase, glucose, and calcium, was carried out at visits 1, 3, and 4 on Hitachi 917 Automatic Analyzers utilizing reagents from Roche Diagnostics S.A. (Basel, Switzerland). Prostate-specific antigen in serum was quantitated at visits 1 and 4 by Enhanced Lanthanide FluoroImmunoAssay using the AutoDelphia 1235 Automatic Immunoassay System (Wallac Oy). Urinalysis, including pH, protein, glucose, ketone, blood, leukocytes and nitrite, was performed at visits 1, 3 and 4 using Multisticks 7 (Bayer).

## Radiographic investigations

In Paper III, computerized tomography examinations of the brain were carried out using GE HiSpeed Advantage equipment (GE Medical Systems, Milwaukee, WI), with continuous transaxial sections parallel to the skull base. Each examination comprised 16-18 sections. Three senior radiologists independently of each other evaluated the films. In assessing the presence of edema on a 3-point scale (0=none, 1=minor, 2=pronounced edema), as proposed by Istre et al.,[60] attention was paid to the width of the sulci, ventricles, and basal cisterns and also to the discrimination between gray and white matter. In Paper IV, X ray verified the

position of the intracranial catheter in the two controls after injecting iohexol contrast through the cannula used for measuring the ICP.

## Histopathology

### *Heart*

In Paper IV, the hearts of the pigs were inspected with regard to pathological alterations and weighed. Light microscopy was used to investigate the subendocardial, atrial, and ventricular myocardium. Besides routine hematoxylin-eosin staining, Gordon and Sweet's silver impregnation method was used to visualize collagen and reticulum fibers of the myocardial histoskeleton, i.e. the basal membranes of the capillaries and the matrix. An immunohistochemical method for detecting leakage of myoglobin from myocytes was used to demonstrate early stages of myocardial hypoxia.[118,119] Rabbit anti-human myoglobin, based on a purified immunoglobulin fraction of rabbit antiserum, was tested and found useful for this purpose (Dako AB, Glostrup, Denmark). Observations were scored as 0 (normal), 1 (mild change), and 2 (severe change). The score was reduced by 50% if the alteration was found only in the subendocardium or deeper in the myocardium. All examinations of the hearts were performed by one investigator (J.R.) without prior knowledge of any details concerning the treatment of the particular animal.

### *Microvessel density*

In Paper V, one pathologist (D.M.B.) counted the number of small blood vessels below the suburothelial connective tissue of the prostate specimens. Four-μm-thick sections were cut from three paraffin-embedded blocks obtained from each TURP specimen. In addition to routine hematoxylin and eosin staining, an immunoperoxidase technique was used including antibodies to factor VIII/CD34 (Dako AB, Glostrup, Denmark), which are endothelial cell antigens marking blood vessels of varying maturity. The number of vascular cross-sectional profiles was counted on a unit grid ($0.81$ mm$^2$) using a high-power objective at 400x magnification (Olympus, Tokyo, Japan). Ten fields were counted at random across each block, giving a total of 30 fields per patient, and the mean microvessel density per unit grid was calculated.[120]

### *Prostate cancer*

When there was a suspicion of prostate malignancy, fine-needle puncture cytology or middle core biopsy cuts were performed before treatment. The prostate specimens obtained during

surgery were weighed on an electronic scale and underwent light microscopic morphological investigation (Papers I, II, V).

## Initial treatment for lower urinary tract symptoms

In Paper I, after the initial evaluation, the investigator selected treatment for the voiding symptoms according to his clinical judgment. The patients were treated with transurethral resection (TURP, n=18) or incision (TUIP, n=1) of the prostate, and transvesical adenoma enucleation (n=12). Other treatment options were watchful waiting (n=3), herbal drugs (Cernitol®, n=1), adrenergic alpha-antagonists (n=14), finasteride (Proscar®, n=1), and TUMT (n=1). One patient scheduled for TUIP was rescheduled for a TRUS guided biopsy cut, due to a serum S-PSA of 7.9. A highly differentiated adenocarcinoma was found in two of six biopsies and radiation therapy was planned. In Papers II and V, only TURP was performed. In Paper V, the same surgeon performed all resections, beginning with the median lobe (if present) then the floor and right and left lobes, the roof and, finally, the tissue at the level of the verumontanum. The cutting current was set to 130 W. Bleeding vessels were coagulated continuously by diathermy set at 50 W (Erbotom ICC 350, Erbe Elektromedizin, Germany). All but three patients had a suprapubic catheter, which was kept open during the resection. The resection time was measured from the first cut to the completion of diathermy. A 24-Ch Mauer-Mayer resectoscope (Karl Storz, Tuttlingen, Germany) was used (Papers I, II, V).

## Anesthesia

Spinal anesthesia was used in Papers I, II, and V except for one patient in Papers I and V who underwent open surgery and TURP, respectively. Data are missing for one patient who underwent TURP (Paper I). In Paper IV, the study was performed under general anesthesia. The pigs were premedicated with diazepam, ketamine, and atropine. Anesthesia was induced with thiopental and additional doses of ketamine and diazepam as outlined in detail in the paper. A Servo Ventilator 900C (Siemens-Elema, Solna, Sweden) was used to achieve normocapnea, the ventilatory rate being 20-24 breaths $min^{-1}$. Adequate surgical anesthesia was maintained by 12-16 ml $h^{-1}$ of ketamine administered with a syringe pump (IVAC Model 770, MPP Scandinavia AB, Täby, Sweden) and intermittent doses of 2 ml of diazepam. The depth of the anesthesia was checked repeatedly by pinching the skin between the hooves.

## Treatment follow-up

The follow-up of the treatment in Papers I and V was evaluated by using a time micturition list and the IPSS.[24] In Paper I, the patients filled out these protocols 13 months (median) after TURP, 9 months after open surgery, and 3 months after the start of medication with an adrenergic alpha-antagonist and, in Paper V, at inclusion, just prior to TURP, and 3 months later.

## Statistics

Normally distributed results are expressed as the mean and standard deviation (SD) (Papers I, III) or the mean and the standard error of the mean (SEM) (Paper IV). Data with a skewed distribution were presented as medians (Papers I, II, III) and range (Paper II) or the 10th and 90th percentiles (Paper III). The data were square root-transformed before statistical analysis (Paper I).

Differences between groups were evaluated by one-way analysis of variance (ANOVA) (Papers I, V). When data showed a skewed distribution, the Mann-Whitney U test was used (Paper V). Differences between fluids (Paper III) were evaluated by using the paired t-test when the data showed a normal distribution, or else by means of the Wilcoxon matched-pair test.

Repeated-measures ANOVA was employed to study differences between groups during the period of time specified for each analysis, i.e. 5-120 min, during the experiment, 5-90 min, during the infusion, and 100-120 min, after the infusion (Paper IV) and to study changes from before to after treatment (Papers I, III) and the comparison with the baseline was made using Dunnett's post hoc test (Paper III).[121]

Correlations between parameters were studied by stepwise multiple regression and significant parameters were presented followed by their univariate correlation coefficient (Paper I) and by linear regression analysis (Papers IV, V).

Differences in outcome variables were compared by contingency table analysis (single symptoms) or the Mann-Whitney U test (sum of many symptoms). A professional statistician performed the logistic regression analysis in Paper II; here, the most powerful predicting factors with respect to patient symptoms were determined.[122] Estimates of the odds ratio were obtained by exponentiation of the regression coefficient together with its confidence limits. The odds ratio represents how much more likely it is for the symptom to be present among those with and without the factor.

# RESULTS

## Paper I

The average patient with a large prostate (>54 ml, n=30) had a higher mean arterial pressure (105 *versus* 95 mmHg, respectively; p<0.01) and higher serum glucose (5.3 mmol/L *versus* 4.8 mmol/L; p<0.01) than those with a small gland (<45 ml, n=22). They also tended to have higher serum insulin (55 *versus* 46 pmol/L) and cortisol (423 *versus* 362 nmol/L). Differences between the groups were very small with respect to serum levels of fructosamine, lipids, and the excretion of catecholamines.

The two groups differed significantly in the scale "lack of assertiveness" in the Karolinska Scales of Personality inventory (Table 3). Patients with a large prostate had a score similar to the mean of the control population, while those with a small gland showed more assertiveness in all of the 10 items creating this scale (p<0.03). The greatest differences were found regarding the questions "I find it hard to object if I am neglected at a restaurant", "I feel very ill at ease when witnessing a fight in the street", and "I sometimes wish that I could speak up when I dislike something".

The results of the heart rate variability indicated a higher sympathetic tone in men with a large prostate, where all frequency bands tended to have a lower power, both in the daytime and for the entire 24-h period (all differences, 0.05<p<0.10). Furthermore, the heart rate at night tended to be higher (median 66.4 *versus* 59.0 beats per min, p=0.07) and the ratio of the low-frequency and high-frequency (LF/HF) power was also higher for men with a large gland (2.80 versus 1.97, p=0.08).

Exploratory analyses showed a strong correlation between the personality traits and the results of the urodynamic evaluation when the prostate was large, but not when it was small (Table 4). Social desirability contributed to the maximum urinary flow. Irritability and lack of assertiveness could partly explain the results of the detrusor pressure at maximum urinary flow. At different prostate sizes, the very low frequency power correlated with personality traits, such as guilt and the results of the biochemical analyses, such as blood glucose during the daytime. During day and night, such correlation was found for guilt and impulsiveness. Several personality traits contributed to biochemical markers: among others, urinary norepinephrine correlated with lack of assertiveness when the glands were small and large.

The score on groups of connected personality scales contributed to the values of biochemical markers and heart rate variability at different prostate sizes, such as "all anxiety" and urinary norepinephrine, all "impulsiveness" and serum cortisol and all "aggressiveness" and very low frequency power. Risk factors for cardiovascular diseases correlated with each other: Blood glucose correlated most strongly with the diastolic blood pressure, while the body mass index and S-HDL cholesterol served as significant independent predictors of S-insulin. A biochemical factor, B-glucose, contributed to the volume of the prostate when it was large, but no such correlation was found when it was small.

| Tested parameter | Correlates with | r | p | p<0.05 in subgroup |
|---|---|---|---|---|
| Maximum urinary flow | Social desirability | 0.34 | p<0.02 | Large |
| Detrusor pressure at maximum urinary flow | Irritability | −0.36 | p<0.01 | Large |
| Detrusor pressure at maximum urinary flow | Lack of assertiveness | 0.35 | p<0.01 | Large |
| Prostate volume | Blood glucose | 0.48 | p<0.001 | Large |
| Very low frequency power[1] | Blood glucose | −0.34 | p<0.02 | Large |
| Very low frequency power[1] | Guilt | −0.37 | p<0.01 | Small |
| Very low frequency power[2] | Guilt | −0.33 | p<0.01 | Small |
| Very low frequency power[2] | Impulsiveness | −0.39 | p<0.01 | Large |
| Urinary norepinephrine | Lack of assertiveness | −0.47 | p<0.001 | Both |
| All "anxiety" | Urinary norepinephrine | −0.37 | p<0.01 | Small |
| All "impulsiveness" | Serum cortisol | 0.36 | p<0.04 | – |
| All "aggressiveness" | Very low frequency power[2] | −0.29 | p<0.04 | Large |
| Blood glucose | Diastolic blood pressure | 0.48 | p<0.01 | – |
| Body mass index | Serum insulin | 0.56 | p<0.01 | – |
| HDL cholesterol | Serum insulin | −0.48 | p<0.001 | – |

[1]During daytime. [2]During day and night. HDL=high-density lipoprotein.

Table 4: **Significant relationships between urodynamics, personality, heart rate variability, and blood and urine chemistry as evaluated by stepwise multiple linear regression**

The strength of each relationship is expressed by its univariate correlation coefficient.

Although men with a large prostate had a higher detrusor pressure at maximum flow (86 *versus* 68 cm $H_2O$; p<0.02), they had similar IPSS (17.2 *versus* 17.9) and QOL (4.4 *versus* 3.8) scores and uroflow (4.6 *versus* 6.5 ml/s) before treatment. However, they reported more improvement of the IPSS (4.2 *versus* 10.4; p<0.003), QOL (1.2 *versus* 2.2; p<0.02) scores and uroflow (17.7 *versus* 11.4 ml/s; p<0.007) than men with a small gland. The overall improvement of these scores correlated with the increase in the urinary flow rate after surgery (r=0.52; p<0.005, and r=0.47, p<0.03) but not with the amount of resected tissue.

The operating time was longer for open surgery (Table 5), but more tissue was removed per minute. The amount of blood lost per gram of removed tissue was twice as large for TURP than for open surgery. During TURP the weight of the resected tissue correlated with the blood loss (p<0.002) and the operating time (p<0.04), but no such correlation was found for open surgery.

Open surgery was followed by the lowest IPSS (3.3; p<0.01) and QOL (0.8; p<0.02) score and the highest urinary flow rates (19.9 ml/s; p<0.01). Transurethral resection of the prostate produced intermediate results (6.0, 1.5 and 16.4 ml/s, respectively) and adrenergic alpha-antagonist treatment the poorest (9.4, 2.4 and 9.9 ml/s, respectively).

The prostate size was initially misjudged on clinical examination in 7 patients scheduled for TURP. The weight of the specimens subsequently obtained by open surgery averaged 137 g. Correlations between factors of morbidity in a previous series of 1100 transurethral resections of the prostate performed at our hospital suggest that the blood loss, operating time, and irrigating fluid absorption associated with a resection of 137 g would be 2.7 L, 150 min, and 1.1 L, respectively. The corresponding values in the 7 patients rescheduled for open surgery were 0.7 L, 100 min, and 0 L.

| | Surgical management | | |
|---|---|---|---|
| | TURP (n=18) | Open surgery (n=12) | ANOVA |
| **Prostate volume**, ml | 71  (23) | 136  (37) | p<0.001 |
| **Operating time**, min | 63  (26) | 101  (26) | p<0.001 |
| **Removed tissue** | | | |
| Total, g | 37  (20) | 123  (36) | p<0.0001 |
| Per unit operating time, g/min | 0.57 (0.27) | 1.29  (0.57) | p<0.001 |
| **Blood loss** | | | |
| Total, ml | 592  (421) | 858  (628) | |
| Per gram specimen, ml/g | 16.6 (8.3) | 7.3  (5.2) | p<0.002 |
| Per unit operating time, ml/min | 8.3  (3.9) | 8.0  (4.2) | |
| **Fluid absorption**, ml | 380[1] | | |

Data are means (SD). [1]75th percentile=510 ml.

Table 5: **Data on surgery performed to alleviate voiding symptoms**

# Paper II

Absorption of glycine 1.5 % caused more neurological symptoms than mannitol 3 % (Mann-Whitney U test, p<0.04). The average patient who absorbed more than 1000 ml of glycine had two neurological symptoms compared to 0.5 symptom for mannitol. Symptoms were twice as frequent after as during the operation. Bradycardia, acute arterial hypotension and nausea were most common. Nausea after the operation constituted half of the difference between the fluids.  The proportion was equal for short-lasting (less than 5 min) and long-lasting (up to 120 min) nausea. Other neurological symptoms were blurred vision, vomiting, uneasiness, confusion, and tiredness, but none of them alone reached statistical significance.

Circulatory symptoms were equally common in the two groups. During the operation, the incidence was 8% for bradycardia and 21% for hypotension and, after the operation, 17% and 25%, respectively.

There was a correlation between the volume of fluid absorbed and the incidence of symptoms, which was 0 to 25% at 500 to 1000 ml, 25 to 45% at 1001 to 1500 ml, and 50 to

60% at more than 1500 ml. Intravascular absorption was most dominant while extravascular absorption only occurred in one patient in the glycine (3000 ml) group and one in the mannitol (3150 ml) group.

Absorption of glycine 1.5% instead of mannitol 3% increased the likelihood of postoperative nausea by a factor of 5.5 and of all postoperative neurological symptoms by a factor of 4.8. An increase in the fluid volume absorbed from 1000 ml to 2000 ml increased the likelihood of postoperative bradycardia by a factor of 6.9 and of all postoperative neurological symptoms by a factor of 4.8.

| | Mannitol 3 % | | |
|---|---|---|---|
| **Fluid absorption range, ml** | **500-1000** | **1001-1500** | **>1500** |
| Number of patients | 13 | 8 | 5 |
| Age, years | 76 (62-85) | 76 (66-90) | 71 (65-87) |
| Operating time, min | 52 (33-105) | 70 (45-125) | 75 (45-170) |
| Blood loss, ml | 250 (10-750) | 665 (225-1300) | 1000 (400-3380) |
| Specimen weight, g | 21 (1-40) | 19 (11-27) | 32 (20-65) |

| | Glycine 1.5 % | | |
|---|---|---|---|
| **Fluid absorption range, ml** | **500-1000** | **1001-1500** | **>1500** |
| Number of patients | 13 | 8 | 5 |
| Age, years | 75 (68-87) | 76 (53-85) | 62 (55-79) |
| Operating time, min | 80 (51-90) | 73 (25-110) | 60 (50-65) |
| Blood loss, ml | 425 (90-1300) | 673 (200-1800) | 860 (300-1425) |
| Specimen weight, g | 15 (7-60) | 21 (10-71) | 37 (11-62) |

Data are medians (range).

Table 6: **Data on increasing ranges of fluid for 52 patients who absorbed more than 500 ml of mannitol 3 % (top) or glycine 1.5 % (bottom) during 394 transurethral resections of the prostate**

## Paper III

Infusion of glycine 1.5% gave a higher symptom score than infusion of mannitol 3% (median 2.0 *versus* 0.5; Wilcoxon's test p<0.006). The most common complaints were tiredness (n=7), headache (n=4), and prolonged problems involving prickling sensations in the skin (n=4). Cognitive function did not differ after the infusions.

The mean arterial pressure increased transiently at the end of the glycine infusion (p<0.001) and decreased at 3 hours (p<0.05), while it remained unchanged in the mannitol experiments. The 24-hour electrocardiographic recordings did not differ significantly from the control recording, but the fainting in one volunteer who had walked from the examination room to the lavatory to give a urine sample 50 min after the completion of the glycine infusion coincided with asystole lasting 6 seconds.

There was no difference between the fluids with respect to cerebral edema, which was reported by more than one radiologist only in 3 experiments (13%). Pronounced cerebral edema was not observed. The results of CT did not correlate with the symptom score.

At the end of the mannitol infusions, both B-Hb (from 142.5 down to 134.1 g/L) and S-Na (from 139.6 down to 132.2 mmol/L) was more reduced as compared to the glycine infusions (B-Hb from 142.2 to 136.5 g/L, S-Na from 139.4 to 133 mmol/L). B-Hb did not differ between the fluids at 1 and 3 hours, while S-Na was lower during the mannitol experiments (repeated-measures ANOVA, p<0.012). Glycine and mannitol significantly increased S-K, which increased more after glycine (p<0.01). Both infusions increased serum osmolality (S-osm from $283 \pm 5$ to $285 \pm 5$ mosmol/kg (p<0.03), but baseline levels were reached at 1 hour. Glycine infusion increased the median blood ammonia level from 36 (24-46) μmol/L to 46 (22-80) μmol/L (p<0.04).

The difference between the estimated infused volume as determined by the ethanol nomogram and the fluid volume infused was 132 ml at 10 min, 146 ml at 20 min and − 38 ml at 30 min. Mannitol infusion caused greater losses of water which exceeded the infused amount by 535 ml (median, p<0.01). The Na excretion was also higher after mannitol (p<0.04) and averaged 68 mmol during the 3 hours that urine was collected.

Infusions of mannitol expanded the blood volume more than glycine (336 *versus* 207 ml at 30 min; p<0.03), but both experiments resulted in slight hypovolemia (−165 versus −131 ml at 3 h), as indicated by the changes in B-Hb. Mannitol also hydrated the interstitial space

more than glycine (pooled data at 1 and 3 hours, p<0.03), but, for both fluids, the size of the interstitial fluid space was below baseline at 3 hours. Glycine significantly increased the volume of the intracellular fluid space at 1 and 3 hours, while no change was found after the mannitol infusions.

Glycine and mannitol decreased the extracellular fluid volume to below baseline at 1 and 3 hours. Glycine only significantly increased the intracellular fluid volume at 1 hour. The increased extracellular impedance in the leg indicated a reduction of the fluid volume, while the intracellular impedance did not change significantly.

## Paper IV

Cardiac output and the aortic and carotic blood flow rates increased significantly during the infusions. Cardiac output and the aortic blood flow rates fell promptly to about 50% of baseline 30 min after the infusions while the blood flow rates to the brain were well maintained. The heart rate decreased by approximately 20% during both experiments (p<0.001). The mean arterial pressures in both groups were below baseline after the infusions (p<0.02). The peripheral vascular resistance decreased during the mannitol infusions (p<0.001).

B-Hb decreased markedly during the infusions. S-Na decreased more during the infusions of mannitol 5% (from 140 to 98 mmol/L at 80 min; p<0.002) as compared to glycine (from 136 to 103 mmol/L at 80 min). S-K increased from 3.6 to 4.4 mmol/L in response to glycine while it decreased from 3.5 to 3.3 mmol/L during the mannitol 5% infusions. In the pigs that received mannitol 3%, S-Na decreased from 138 to 100 mmol/L at 80 min and S-K increased from 4 to 4.1 mmol/L, following the curve of isotonic mannitol. At the end of the experiments, 41%, 46% and 30% (n.s.) of the infused volume of glycine, mannitol 5% and mannitol 3%, respectively, had been recovered in the urine. Both glycine and mannitol 5% infusions progressively increased the excretion of sodium (p<0.001), while only glycine increased kaliuresis (p<0.001).

The whole-body oxygen delivery decreased after the glycine experiments (p<0.004) and oxygen consumption tended to decrease (p=0.12). No significant changes in oxygen delivery and consumption were found during the mannitol infusions.

S-osm decreased during the infusions of glycine (from 292 to 277.3 mosm/kg; p<0.02 *versus* mannitol 5%) and mannitol 3% (from 292.8 to 278.5 mosm/kg). The ICP increased slightly more during the infusions of glycine as compared to mannitol 3% (mean 170% versus 140% of baseline, respectively, at 90 min, which is not significant) but still more than during

the infusion of mannitol 5% (mean 28%, p<0.01). After the infusions, the ICP remained high only in the glycine group (p<0.001 when compared to baseline).

The two controls showed a slight spontaneous increase in ICP over a 110-min observation period from 7 to a maximum of 10 mm Hg and from 2 to 4 mm Hg respectively. The position of the catheters in the cerebral ventricles was verified by X-ray examination with contrast medium. Infusions of both glycine and mannitol 5% increased the oxygen delivery to the brain (p<0.005), but mannitol 5% also decreased oxygen consumption in the brain to about 50% of baseline (p<0.001). The pH and base excess values in jugular venous blood remained unchanged.

The blood volume increased more after the mannitol infusions than after glycine during the first 30 min (p<0.05). After the infusions, the interstitial volume was larger with mannitol (p<0.03). ICV expanded more after the glycine infusions (p<0.002).

Light microscopic investigations showed signs of interstitial dilation in all groups except the controls (Table 7). The highest scores for leakage of myoglobin, focal necrosis, and rupture of the histoskeleton were obtained for glycine 1.5%, whereas mannitol 5% had intermediate and mannitol 3% the lowest scores. There were significant linear correlations between myoglobin leakage, focal necrosis (p<0.02), and rupture of the histoskeleton (p<0.006), whereas interstitial dilation correlated only with rupture of the histoskeleton (p<0.04). Nearly all observed changes occurred both in the subendocardium and deeper in the myocardium. The ECGs showed that the heart rate-corrected QT time increased by 15-20% during both infusions (p<0.03). Mannitol 5% significantly increased the PQ time (+20%, p<0.05 *versus* glycine) and decreased the QRS amplitude (-20%), while glycine tended to prolong the QRS duration (+25%) and increase the T-wave amplitude (+50%).

|  | Glycine 1.5% (n = 4) | Mannitol 5% (n = 4) | Mannitol 3% (n = 5) | Control (n = 2) |
|---|---|---|---|---|
| Interstitial dilation | 0.75 | 1.0 | 1.0 | 0 |
| Myocardial hypoxia[a] | 1.75 | 1.5 | 0.4 | 1.0 |
| Focal necrosis | 1.5 | 1.0 | 0.8 | 0.25 |
| Rupture of the histoskeleton[b] | 1.75 | 1.25 | 1.0 | 0.25 |
| **Sum of all scores** | **5.75** | **4.75** | **3.2** | **1.5** |

[a]Evidenced by areas of myoglobin leakage from the myocytes. [b]Gordon and Sweet's silver impregnation method was used to visualize collagen and reticulum fibers.

Table 7: **Morphological observations made using light microscopy on the hearts of pigs receiving an intravenous infusion of irrigating fluid**

The scores used were 0 (normal), 1 (mild change), and 2 (severe change). The mean value for the group is shown.

## Paper V

The finasteride and placebo groups were well matched for age, weight, vital signs, IPSS, quality of life score, urine flow, prostate volume, and S-PSA at inclusion (Table 8). Finasteride pretreatment reduced the prostate volume, which remained unchanged in the placebo group. The mean reduction differed by 11.2 ml or 19% (p<0.001), with the greatest changes occurring in the largest prostates. Three months after TURP, the prostate volume did not differ between the groups. There was no difference between the groups in IPSS, quality of life score, or urine flow just before or three months after TURP.

Neither the total blood loss (Table 9), fluid absorption, weight of the resectate, resection time, nor the microvessel density differed between the groups. Moreover, no differences were found with respect to resource use and the evaluation, which includes the pretreatment period, hospitalization, and follow-up.

|  | Finasteride (n=26) | | Placebo (n=29) | |
| --- | --- | --- | --- | --- |
| **Age**, years | 69 | (56-78) | 68 | (54-76) |
| **International Prostate Symptom Score** | | | | |
| At inclusion | 19 | (12-29) | 18 | (10-27) |
| Just before TURP | 19 | (14-27) | 17 | (10-27) |
| 3 months after TURP | 4.5 | (1-13) | 5 | (1-11) |
| **Quality of Life assessment** | | | | |
| At inclusion | 4 | (3-5) | 4 | (2-5) |
| Just before TURP | 4 | (3-5) | 4 | (2-5) |
| 3 months after TURP | 1 | (0-3) | 1 | (0-3) |
| **Urine flow**, ml/sec[1] | | | | |
| At inclusion | 6.0 | (3.0-9.4) | 5.1 | (1.8-9.8) |
| Just before TURP | 6.3 | (2.8-10.1) | 5.9 | (2.2-11.6) |
| 3 months after TURP | 15.4 | (7.9-22.2) | 12.7 | (5.6-23.2) |
| **Prostate volume**, ml | | | | |
| At inclusion | 56 | (44-76) | 55 | (37-67) |
| Just before TURP | 50 | (35-68) | 54 | (36-92) |
| 3 months after TURP | 23 | (11-34) | 24 | (18-38) |
| **S-PSA**, µg/L | | | | |
| At inclusion | 3.0 | (2.0-5.2) | 2.3 | (2.0-5.8) |
| 3 months after TURP | 2.0 | $(2.0\text{-}2.0)^2$ | 2.0 | $(2.0\text{-}2.0)^2$ |
| **PSA density**, µg/L/g | | | | |
| At inclusion | 0.06 | (0.03-0.09) | 0.05 | (0.03-0.11) |

Data are the medians (10th-90th percentiles). [1]Calculated from the time micturition list. [2] The level of detection was 2.0 µg/L.

Table 8: **Age, IPSS, Quality of Life assessment, urine flow, prostate volume, S-PSA, and PSA density in patients who received finasteride or placebo daily during 3 months before transurethral resection of the prostate**

|  | Finasteride (n=26) | | Placebo (n=29) | |
|---|---|---|---|---|
| **Weight of resectate**, g | 20 | (12-30) | 17.5 | (10-31) |
| **Resection time**, min | 49 | (35-68) | 50 | (29-71) |
| **Blood loss** | | | | |
| Total, ml | 279 | (84-555) | 287 | (71-777) |
| Per gram resectate, ml/g | 14.5 | (6.6-26.8) | 16.4 | (7.1-29.3) |
| Per unit resection time,[a] ml/min | 5.2 | (2.3-10.0) | 5.9 | (2.1-10.9) |
| Per gram resectate per unit resection time,[a] ml/g/min | 0.24 | (0.13-0.47) | 0.32 | (0.19-0.61) |
| **Fluid absorption**, ml | 412 | (0-1117) | 405 | (0-1945) |
| **Blood hemoglobin concentration**, g/dl | 14.1 | (13.0-15.3) | 14.5 | (13.5-15.8) |
| **Microvessel density**, n/0.81 mm$^2$ | 24 | (15-34) | 22 | (11-35) |

Data are the medians (10th-90th percentiles). [a]Resection time was measured from the first cut to the completion of diathermy.

Table 9: **Weight of resectate, resection time, various indices of blood loss, fluid absorption, B-Hb, and microvessel density in patients given finasteride or placebo daily for 3 months before TURP**

In both groups, a correlation was found between blood loss during TURP and resectate weight and resection duration ($P \leq 0.002$) and between fluid absorption and blood loss (r=0.48; p<0.001). In patients with a resectate weight greater than or equal to 18.6 g (the median), finasteride was associated with less blood loss (median 324 ml, n=14) than in controls (median 547 ml, n=14, $P \leq 0.01$; Figure). The same trend was seen in the blood loss corrected for the resection time.

Finasteride may also reduce the percentage of men with high fluid absorption levels during TURP. The 75th percentile of fluid absorption in the finasteride group was 578 ml compared to 859 ml in the placebo group. Large-scale fluid absorption (>1500 ml) occurred in 1 finasteride patient and in 5 controls (Figure). In one of them, such absorption (1945 ml) prompted the surgeon to leave the left lobe intact (control group).

The microvessel density increased with the size of the prostate gland at inclusion (r = 0.32; $P \leq 0.02$) but did not correlate with the blood loss.
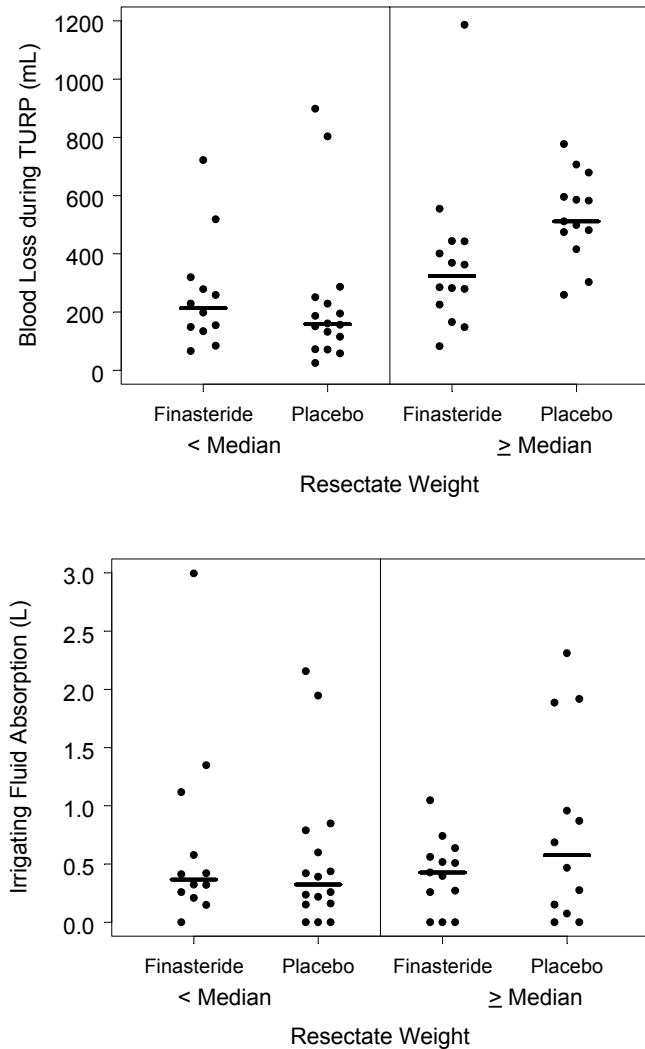


Figure 2: **The blood loss (top) and the fluid absorption (bottom) during TURP in finasteride-treated patients and controls, depending on resectate weight**

Finasteride was associated with a reduction of blood loss for resectate weights greater than or equal to 18.6 g (the median). Large-scale fluid absorption (>1500 ml) occurred in one finasteride patient and in five controls.

Two patients in the finasteride group reported decreased libido, impotence, or a semen abnormality. One unit of erythrocytes was transfused in one patient who had received

placebo. Postoperative bleeding required readmission of three finasteride and two placebo patients, one of whom had a repeat TURP. Three patients were found to have prostate cancer.

# DISCUSSION

## BPH and cardiovascular risk factors

Patients with a prostate larger than 54 ml were 3.5 years older and slightly heavier than men with a gland smaller than 45 ml, but these differences were not statistically significant. Their higher arterial pressures, fasting blood glucose concentrations and almost significantly higher serum cortisol concentrations indicate that men with a large gland are more prone to develop the metabolic syndrome which comprises insulin resistance, non-insulin-dependent diabetes mellitus, obesity, hypertension, blood lipid abnormalities, and atherosclerotic cardiovascular disease.[123] We also did additional statistics to test for the possibility that the main results can be explained by differences in age and body weight between the groups. Multiple linear regression revealed that both the size of the prostate (p<0.001) and body weight (p<0.01) served as independent predictors of the blood glucose level, while age was independent. Furthermore, deleting patients to obtain two matched groups of 20 matched pairs with respect to age and body weight, but with different prostate sizes, still demonstrated statistically significant differences in blood glucose and blood pressure. Hammarsten et al. investigated patients with LUTS and found that the prostates were larger in the group of men who had components of the metabolic syndrome.[124] The prevalence of this syndrome among patients with a large prostate might be higher than indicated by my data because men with a history of diabetes mellitus and AMI had been excluded in Paper I. It is possible that some of the patients with a large prostate in Paper I will show complications, such as diabetes and AMI, due to their higher B-glucose and higher arterial pressures within a few years. Further observations were that B-glucose showed a linear correlation with the prostate volume when the gland was large, but not when it was small, and B-glucose correlated with the diastolic blood pressure independently of prostate size (Table 4). Other observations on the relationships between risk factors for cardiovascular diseases revealed a complex picture. For example, the serum concentration of cortisol tended to be higher in men with a large gland. Cortisol, which is considered to be a stress hormone, stimulates gluconeogenesis, increases catabolism of protein in the cells and promotes mobilization of fatty acids from the adipose tissue.[125]

## Personality

The KSP questionnaire that I used in Paper I seems to produce stable results over time[126] and would therefore probably yield similar results if completed at the beginning of the development of BPH. It has previously been used to compare personality traits with biological markers for vulnerability to psychopathology, such as the activity of monoamine oxidase (MAO) in blood platelets.[110] Men with a small gland had lower score on the scale "lack of assertiveness", (Table 3) which indicates that they are more assertive in social situations than men with a large gland who resemble the control population. The "lack of assertiveness" scale belongs to a group of four other scales that describe anxiety, which influences eating behavior[127] and is a prognostic factor for mortality after AMI.[128] Serotonin might possibly be the common denominator influencing these functions. It is a transmitter substance found in the central nervous system, intestine and prostate[129] and might also participate in prostate growth control.[130] Our finding that men with a large gland tended to be overweight (body mass index 26.1 versus 24.9 kg/m$^2$) according to WHO's definition is supported by other studies comparing obesity and prostatectomy[131] and obesity and the weight of the resected tissue during TURP.[132] The prevalence of benign prostatic hyperplasia is increasing in China, perhaps due to the increased daily intake of total calories, fat, and animal protein, and the decreased daily intake of vegetables and whole grain, the sources of phytoestrogens.[133] A plausible explanation of the genesis of BPH could be that men who are less assertive choose food that contains a large proportion of animal products, which stimulate prostate growth, and avoid whole grain, which counteracts prostate growth.

## Heart rate variability

I also wanted to measure the function of the autonomic nervous system[134] in the patients because my hypothesis was that the increased long-term mortality after TURP was due to an increased sympathetic activity that damaged the heart and caused increased tension in the bladder neck and prostate capsule. Reduced HRV is associated with cardiovascular disease,[135] is a predictor of long-term survival after AMI,[136] and is associated with conventional risk factors before manifest disease develops,[114] as in our patients with no history of diabetes mellitus or AMI. The increased LF/HF ratio and the less HRV in all frequency bands in Paper I indicate that men with a large prostate have increased sympathetic activity. Furthermore, VLF power, a predictor of survival after myocardial infarction, was inversely correlated with

B-glucose when the gland was large, with a high excretion of epinephrine and a high diastolic blood pressure (Table 4).

## Age differences in Paper I

I do not think that the slight age difference between the groups might explain the differences in cardiovascular risk factors. The prostate only grows 1.6% per year[7] and the body mass index (BMI) decreased with age in our study. Urinary flow would probably be more similar at a standardized age because it decreases with age due to changes in the resistance of the urethra and not to changes in the infravesical pressure.[137] Personality seems to be stable over time.[126] The mean systolic pressure increases by 1 mm per year[138] and patients with diabetes mellitus were excluded in our study. We also made additional statistics to test for the possibility that the main results can be explained by differences in age and body weight between the groups. Multiple linear regression revealed that both the size of the prostate ($p<0.001$) and the body weight ($p<0.01$) served as independent predictors to the blood glucose level, while age was unimportant. Furthermore, deleting patients to obtain two matched groups of 20 matched pairs with respect to age and body weight, but with different prostate size, still showed statistically significant differences in blood glucose and blood pressure. Jensen-Urstad measured the effects of age on HRV by spectral analysis of 24-hour recordings.[139] I plotted her values and found that VLF and HF power as a function of age looked like exponential curves that leveled off toward more advanced ages. The total and LF power looked like regression lines. Due to the wide range of her results, however, I could not use them directly to correct the age difference between my groups. The LF/HF ratio is not correlated with age. I therefore conclude that men with a large prostate have a higher sympathetic tone than men with a small gland. This finding implies the importance of choosing the least traumatic and most cost effective management for their LUTS.

## Fluid absorption

### Symptoms

Glycine absorption during TURP (Paper II) or infusion (Paper III) produced more neurological symptoms than mannitol 3% did. Nausea after TURP constituted half of the difference between the fluids. Other neurological symptoms were blurred vision, vomiting, uneasiness, confusion, and tiredness, and the volunteers complained of tiredness, headache, and prickling sensations in the skin. Absorption of more than 1000 ml of glycine increases the risk of symptoms, and confusion is a frequent complication of TURP in old patients,[69] but

infusion of 1.25 L of glycine was not enough to impair the cognitive functions of our young, healthy volunteers. There are several case reports in the literature describing neurological symptoms such as coma,[140] blindness,[141] nausea,[142] and confusion[143] associated with the use of glycine 1.5% during TURP. Due to the absence of the ethanol method in these reports, many patients were misdiagnosed, and the right diagnosis was often made when a TUR reaction had already begun. The largest volumes absorbed in Paper II were limited to 3000 ml of glycine and 3150 ml of mannitol with no life-threatening symptoms, so that treatment with a hypertonic solution was not called for, which made it possible to study and compare the undisturbed development of symptoms in both groups.

## Ammonia toxicity

The mechanisms behind the neurological symptoms during and after glycine absorption are not fully understood, but ammonia toxicity, the action of glycine as an inhibitory transmitter on the nervous system and cerebral edema are possible explanations.

The major site of amino acid degradation in mammals is the liver. The $\alpha$-amino group of many amino acids is transferred to $\alpha$-ketoglutarate to form glutamate, which is then oxidatively deaminated to yield $NH_4^+$. In terrestrial vertebrates, $NH_4^+$ is converted into urea, which is then excreted.[144] In Paper III, the rise in the blood ammonia level was fairly small. The greatest change occurred in a 27-year-old male volunteer who complained of tiredness during and after the infusion. In another study on volunteers, the irrigating fluids, which contained glycine, produced hyperkalemia, prickling and burning skin sensations, and nausea. The severity of the symptoms correlated with the blood ammonia level, which increased significantly after the glycine infusions but not after mannitol.[145] Hyperammonemia after glycine absorption or infusion may be caused by a deficiency of the urea cycle enzyme argininosuccinate synthetase, which converts citrulline to argininosuccinate.[146] L-arginine is effective reducing the blood ammonia rise and associated coma that develops from intravenous glycine infusions.[147]

## Glycine as an inhibitory transmitter

Glycine, in contrast to mannitol, may cross the blood brain barrier[148] and function as an inhibitory transmitter in the spinal cord. It probably also acts at specific synapses in the medulla oblongata, pons, tectum, and retina.[149] There are many case reports in the literature describing blindness following TURP using glycine 1.5%. In one such patient who was also nauseous, the serum glycine level was 13,734 (normal 170-330) $\mu$mol/L.[58]

## Cerebral edema

Cerebral edema may follow an acute dilution of the blood and interstitial fluid volumes and urinary losses of sodium ions associated with osmotic diuresis,[72] which may decrease S-Na to less than 125 mmol/L during 1 to 4 hours.[150] These mechanisms underlying the decrease in S-Na are shown in Papers III and IV and, indirectly, also in Paper II since S-Na correlates closely with the absorbed fluid volume as indicated by the ethanol method. Fourteen patients went into coma or semicoma after absorption of 1.5-8.8 L of 1.5% glycine during TURP.[140] Their S-Na was 88-124 mmol/L, they were older (mean age 77 years), the average operating time longer (90 min) and the resection larger (41.5 g) as compared to the entire patient population undergoing TURP. The resectionist in 9 of the 14 cases saw a venous sinus or capsule perforation. All patients showed signs of cerebral edema such as dilated pupils, mild papilledema, decerebrate movements or posturing, clonus, and Babinski reflexes. Cerebral edema was not detectable by CT after infusion of 1.25 L of glycine 1.5% in the male volunteers (Paper III), but all of 5 women who absorbed 0.5-1.3 L of the same fluid during TCRE had nausea, and cerebral edema was detected by the same method as in Paper III in 4 of the women.[60] This sex difference[98] indicates that the limit for allowed fluid absorption during endoscopic surgery must be set lower in women to prevent brain damage and death. In the pigs (Paper IV), the hypotonic fluids glycine 1.5% and mannitol 3% caused the highest increase and isotonic mannitol 5% the smallest in ICP, which is consistent with the effects on S-osm. The ICP tended to be higher (170% versus 140% of baseline) during the infusions of glycine 1.5%, as compared to mannitol 3% and remained high during the observation period after the infusions, despite the same osmolality, probably because glycine increases the ICV more than mannitol (Papers III, IV). Our surprising finding that mannitol 5% decreased oxygen consumption in the brain would imply a protective effect of this fluid on the brain, which might be beneficial in cases of cerebral edema, due for example, to head injury and water intoxication. A further study is needed however, to examine this phenomenon. Edema of the occipital cortex might be a mechanism behind temporary blindness.[151]

## Hemodynamics and fluid distribution

The incidence of bradycardia and hypotension, which were common during, but even more common after the operation in Paper II, did not differ between glycine and mannitol 3%, which indicates the importance of using the ethanol method during endoscopic surgery. The two largest absorptions, 3000 ml of glycine and 3150 ml of mannitol 3 % were extravascular, which is not surprising, since the ethanol levels are lower and increase more slowly than when

the fluid enters the blood vessels directly.[52] Therefore, I suggest that the surgeon should not only blindly trust the ethanol method, but also, when it is time to empty the bucket, confirm with the nurse anesthetists that all the fluid used has been recovered. Palpation of the lower abdomen of the patient may disclose any stiffness indicating intra- or extraperitoneal absorption. If a volume of electrolyte-free water accidentally accumulates in the retroperitoneal space, it may act like a trap for extracellular ions for several hours, as long as the osmotic gradient persists, thus creating hyponatremia and a reduction of blood volume.[152]

The large intravenous fluid infusions in the pigs significantly increased CO and the aortic and carotic blood flow rates. Despite the overhydration of the animals, CO and the aortic blood flow rates fell promptly to about 50% of baseline after the infusions. The carotic blood flow rate remained normal, which implies that the body attempts to maintain normal blood circulation in the brain.[148] The pigs had a very high urine excretion rate during the infusions. After the infusions, the drop in the mean arterial pressure of about 20%, together with the decreased blood flow rates, showed that the animals were in a hypokinetic condition. Other authors have reported a very low CO[153,154] and hypovolemia[155] after large fluid absorption during TURP. Our calculations after the experiments in Paper IV showed that the hypokinetic circulation corresponded to large losses of sodium and a reduced blood volume. The combination of water and salt losses may explain the hypovolemia and the decreased S-Na at the end of the experiments in Papers III and IV. Both mannitol and glycine cause osmotic diuresis. Mannitol is not reabsorbed in the kidneys[156] and the resorptive mechanisms for amino acids soon become overwhelmed when glycine 1.5% is administered.[157]

A large blood loss may also explain why arterial hypotension occurs during TURP, but this factor was accounted for in Paper II by means of a logistic regression analysis.

S-K increased during the glycine infusions but decreased during both mannitol infusions in the pigs. In the volunteers, S-K increased significantly more after the glycine infusions. Glycine, but not mannitol, hydrated the cells in the volunteers. In the pigs, glycine increased the ICV significantly more than mannitol. After absorption of a hypotonic fluid, water enters the cells due to the higher osmolality of the intracellular fluid. Furthermore, glycine may also cross the cell membrane by using an amino acid transport mechanism and then bring water into the cells by osmotic diuresis. The explanation underlying the hyperkalemic effect of glycine is that the swollen cells decrease their volume by pumping out potassium.[158] Other authors have also demonstrated hyperkalemia caused by this mechanism in volunteers.[145]

## Morphology of the hearts, electrocardiograms

In the pigs, glycine solution showed the most harmful effects in the light microscopic examination of the myocardium and had a higher sum of all scores than the two mannitol solutions (Table 7). The glycine solution had the highest scores for leakage of myoglobin from myocytes and focal necrosis, which indicated myocardial hypoxia earlier than troponin T, whose blood concentration did not differ between the fluids. Mannitol5% had a higher score for myocardial hypoxia, focal necrosis, and rupture of the histoskeleton than mannitol 3%, probably because mannitol 5% expanded the blood volume more and exerted a greater load on the myocardium. A study in rabbits[159] showed that glycine had the highest scores for focal necrosis in subendocardial areas as compared to mannitol 3%. Analyses of the ECG[160] during and after the infusions showed bradycardia and prolongation of the PQ interval and the QRS duration, which are associated with death during an intravenous infusion of glycine 1.5% in the mouse.[161] Rabbits show bradycardia and an increase in the T-wave amplitude,[159] which was also seen in Paper IV. The prolongation of the QRS duration and the increase in the T-wave amplitude were glycine-specific.

Prolongation of the frequency-corrected QT interval occurred during infusions of both fluids and indicates an increased risk of sudden death in humans.[162] No pigs died during the infusions, but I think many of them would have died if the observation time had been longer, as was the case with dogs that received comparable volumes of glycine[163] and patients who had absorbed large amounts of fluid during TURP and TCRE.[164]

## Prevention of fluid absorption

The use of the ethanol method makes it possible to detect even small volumes of fluid absorption, obtain information about the main route of absorption and judge the effect of the attempts to decrease absorption. At my department, the urologist is informed when 1000 ml have been absorbed and is urged to stop the operation when 2000 ml have been absorbed,[52] as was the case with one patient in Paper V. Only looking for symptoms to appear is not safe enough because such symptoms are more common 30-60 min after the end of surgery than during the operation (Paper II). In Papers I, II, and V, the nursing staff measured the ethanol concentration in the patients' exhaled breath just before and every 10 min during the operation (Table 1). In case of absorption, the measurements were performed every 5 min and the absorption was estimated for clinical purposes by means of a nomogram,[100] which made it possible to shorten the operation and start treatment before a severe TUR syndrome developed.[165] For research purposes, the total absorption during each TURP was calculated

using a computer program[51] which is based on a study on resections in which the ethanol concentration in the expired breath was compared with the amount of fluid absorbed as determined by volumetric measurements. In Paper III, the breath ethanol concentration was measured every 5 min during the infusions. The values were expressed in the unit mg/L of air, with 0.1 corresponding to 0.230 g/L in blood. The nomogram usually gave too high values during the first 20 min of our infusions, probably because the breath tests were done during an ongoing infusion. In the clinic, however, breath samples are often taken when the surgeon empties the patient's bladder, resulting in a slight fall in the breath ethanol level due to a distribution effect. The new experience that finasteride might reduce the percentages of men with high fluid absorption levels (Paper V) and may also reduce the number of patients with large-scale fluid absorption (>1500 ml; Fig. 2, bottom) during TURP will be evaluated in a larger study. The use of TRUS in the preoperative evaluation makes it possible for the surgeon to schedule the patients with very large glands for open surgery instead of TURP, thus reducing the absorption to zero (Paper I; Table 5). The weights of the tissues obtained by TURP and open surgery correlated well with the volume of the prostate measured by TRUS (R=0.918, *P*=0.0001, Paper I; Table 5). The risk of large absorptions decreases if the resection is stopped after one hour.[52] The degree and incidence of absorption may also depend on experience and surgical technique. However, the finding that senior surgeons cause less absorption than residents[70] is not always consistent.[166] Attempts at reducing the pressure in the prostate cavity below 2 kPa, a critical limit where absorption occurs, have also been made. However, continuous flow irrigation, promoted fluid absorption which occurred at lower pressures than previously believed.[167] The capacity of the bladder was a statistically more important factor than the bag height in determining the intravesical pressure.[168] Monitoring the intravesical pressure allows a more consistent reduction of the absorption.[169,170]

## Treatment of fluid absorption

The key mechanism of the TUR syndrome when a hypo-osmolar solution has been absorbed is the initial dilution of the intravascular volume, leading to a decrease in S-Na and hypo-osmolality, followed by a hypokinetic condition due to losses of electrolytes and water. The late fall in arterial pressure[154] may be difficult to treat.[171] If the ethanol method is not used during endoscopic surgery when an electrolyte-free fluid is used, it may be easy to ascribe symptoms of the TUR syndrome to advanced age, AMI, medication, and excessive blood loss. Authors of medical textbooks and articles usually warn against the use of intravenous treatment after fluid absorption[71,172] because they consider the hypotonic condition to be

caused by dilutional hyponatremia. With this assumption as a base, they prescribe fluid restriction and injections of furosemide. However, the hypokinetic circulation (Paper IV) results from losses of water and electrolytes (Paper III, IV). Therefore, the supply of the deficient water and sodium is a more physiological treatment. The intravenous infusion of a 3-5% saline solution in a volume of 300-500 ml over 4 h may be a useful treatment, which assumption is supported by experimental[173] and clinical[140] studies. Cerebral demyelinating lesions[174] are not expected to develop if hypertonic saline is used to treat acute hyponatremia due to fluid absorption during endoscopic surgery. Hypertonic saline increases S-Na and S-osm. Moreover, it redistributes water from the cells to the extracellular space,[175] from where it may reach the kidneys. The use of furosemide only may worsen the condition due to the further losses of electrolytes and water. Retroperitoneal absorption may also be treated with hypertonic saline and drained with tubes[25] if large amounts have been absorbed.

## Blood loss

### Finasteride before TURP

Paper V showed that pre-treatment with finasteride, as compared to placebo, may help to reduce blood loss during TURP except in the smallest resections. For prostates with resectate weights equal to or more than 18.6 g (the median), finasteride was associated with less blood loss (median 324 ml, n=14) than in controls (median 547 ml, n=14, $p<0.01$; Fig. 2, top). A study in 2223 patients showed that 62% of the resectates weighed less than 20 g, which means that about 40% of the patients scheduled for TURP would benefit from preoperative finasteride treatment to reduce surgical blood loss. Large glands require hemostatic procedures more often during TURP and also carry an increased risk of symptoms caused by irrigating fluid absorption.[26] Finasteride decreases the incidence of surgery and acute urinary retention[35] and is most effective in men with large prostates. Men with small prostates may not be suitable candidates for finasteride therapy for BPH.[176]

Finasteride is a 4-azasteroid, a specific competitive inhibitor of the intracellular enzyme 5 α-reductase, which converts testosterone to the more potent androgen dihydrotestosterone (DHT).[177] Foley and Bailey found that the microvessel density was significantly greater in patients with BPH and hematuria than in patients with BPH only.[120] They also made a randomized study of the effect of finasteride on chronic hematuria in patients with BPH. In the control group, hematuria recurred in 63% of the patients within a year but in only 14% ($p<0.05$) in the finasteride group.[37]

We counted the microvessel density below the suburothelial tissue. Since we found no difference between the groups, we conclude that this might be due to involution of both the vessels and the interjacent prostate cells when finasteride was given.

We believe that the reduction of the blood loss in our resections was caused by a decreased blood flow. Finasteride might also reduce the risk of large-scale absorption due to reduced venous blood flow (Fig. 2, bottom).

## Transurethral and open surgery, operating time, weight of the tissue

In Paper I, the amount of blood lost per gram of removed tissue was twice as large for transurethral than for open surgery (Table 5). Although the operating time was longer for open surgery, more tissue was removed per minute. For TURP, the blood loss ($P<0.002$) and the operating time ($P<0.04$) correlated with the weight of the resected tissue, which has also been demonstrated by others.[82] No such correlation was found for open surgery (p=0.6 respectively, multiple regression). The choice between transurethral and open surgery, based on ultrasonography,[28] probably reduced the surgical trauma by decreasing the blood loss, operating time, and fluid absorption by 2.0 L, 50 min and 1.1 L, respectively, in seven patients scheduled for TURP but rescheduled for open surgery.

## Measuring versus estimating blood loss

We used the HemoCue photometer during TURP in Papers I, II, and V for both research and clinical purposes (Table 1) because technical methods for measuring blood loss are superior to visual estimation, which may result in underestimations of 100% or more or overestimations leading to over-transfusion rates.[81] In Paper I, during open surgery, the blood from the operating field and the squeezed compresses was collected in suction bottles and measured. The remaining blood content of each compress was estimated to be 25 ml. Since excessive blood loss during surgery tends to increase the hazards of the operation and influence postoperative morbidity,[79] it is a precautionary measure to determine the true blood loss before reaching a decision about whether to continue the resection on the intact lobe.

## Experience of the surgeon

The arterial supply to the prostate comes from branches of the inferior vesical and middle rectal arteries. The veins form the prostatic venous plexus, which is situated between the capsule of the prostate and the fibrous sheath.[178,179] The aim of TURP is to remove most of the adenomatous tissue in the prostatic cavity without damaging the capsule or the external sphincter. However, learning how to perform a radical resection, when the blood flow from cut vessels disturbs the visibility, takes years of training. If the surgeon accidentally enters the

capsule, large veins of the plexus may be damaged and excessive blood loss and fluid absorption may follow. The surgeon who had been a specialist in urology for 4 to 5 years performed all the resections in Paper V. Perkins and Miller reported data from 110 transurethral resections of the prostate done by 6 urology residents in their final year of training. Blood losses ranged from 5 to 1443 (mean 258) ml, averaged 22 ml/gram of tissue resected, and 4 ml/minute of resection time. The weight of the tissue resected ranged from 1 to 40 (mean 11.6) grams. The operating time ranged between 30 and 140 (mean 64) minutes. The average resection rate was 0.18 gram/minute.[180] The blood losses during TURP, reported in the literature, vary considerably,[181] but the difference is multifactorial.

## Other factors

In Paper V men were excluded who had coagulation disorders or were on treatment with anticoagulants during the past 3 months. Intake of NSAID and aspirin was discontinued 2 weeks prior to surgery. Prostate cancer was also an exclusion criterion due to the smaller blood loss as compared to BPH.[82] Spinal anesthesia was used in all but one patient, who received general anesthesia. The blood loss per gram of resected tissue is lower in the patients who receive general anesthesia due to the lower arterial pressure.[82] Other analyses in Paper V showed a correlation between fluid absorption and blood loss ($P<0.001$), which has also been demonstrated by others.[82]

# CONCLUSIONS

1. Patients with large prostates showed less assertiveness, tended to have a higher sympathetic tone, had more severe risk factors for cardiovascular diseases, had a more severe bladder outlet obstruction, required more invasive treatment, and reported more improvement after surgery than men with small prostates.

2. Neurological symptoms were more common when hypotonic glycine was absorbed, but there was no difference between hypotonic glycine and mannitol with respect to circulatory symptoms. There were twice as many symptoms after as during the operation.

3. Hypotonic glycine showed a greater tendency than hypotonic mannitol to cause symptoms. The urinary excretion of fluid and sodium was greater after mannitol, while only glycine hydrated the cells. With both fluids, the intravascular and interstitial volumes were below baseline after the experiment.

4. Very large volumes of hypotonic glycine and isotonic mannitol created a hypokinetic hypotensive state after infusion. Glycine increased the intracranial pressure and damaged the myocardium more than isotonic mannitol.

5. Pretreatment with finasteride may help to reduce blood loss in TURP, except in the smallest resections.

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# REFERENCES

1. Roos NP, Wennberg JE, Malenka DJ, Fisher ES, McPherson K, Andersen TF et al. Mortality and reoperation after open and transurethral resection of the prostate for benign prostatic hyperplasia. *N Engl J Med* 1989; **320**(17): 1120-4.

2. Hahn RG, Nilsson A, Farahmand BY, Ekengren J, Persson PG. Operative factors and the long-term incidence of acute myocardial infarction after transurethral resection of the prostate. *Epidemiology* 1996; **7**(1): 93-5.

3. Robbins SL, Cotran RS. Male genital system. Pathologic basis of disease. 2 ed. Philadelphia: W. B. Saunders Company; 1979. p. 1210-40.

4. Furuya S, Kumamoto Y, Yokoyama E, Tsukamoto T, Izumi T, Abiko Y. Alpha-adrenergic activity and urethral pressure in prostatic zone in benign prostatic hypertrophy. *J Urol* 1982; **128**(4): 836-9.

5. Meigs JB, Barry MJ. Natural history of benign prostatic hyperplasia. In: Kirby R, Mc Connell JD, Fitzpatrick JM, Roehrborn CG, Boyle P, editors. Textbook of benign prostatic hyperplasia. 1 ed. Oxford: Isis Medical Media Ltd; 1996. p. 125-35.

6. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984; **132**(3): 474-9.

7. Rhodes T, Girman CJ, Jacobsen SJ, Roberts RO, Guess HA, Lieber MM. Longitudinal prostate growth rates during 5 years in randomly selected community men 40 to 79 years old. *J Urol* 1999; **161**(4): 1174-9.

8. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. *Science* 1974; **186**(4170): 1213-5.

9. Doehring CB, Sanda MG, Partin AW, Sauvageot J, Juo H, Beaty TH et al. Histopathologic characterization of hereditary benign prostatic hyperplasia. *Urology* 1996; **48**(4): 650-3.

10. Griffiths K, Adlercreutz H, Boyle P, Denis L, Nicholson RI, Morton MS. Nutrition and cancer. Oxford: Isis Medical Media; 1996.

11. Hammarsten J, Hogstedt B. Hyperinsulinaemia as a Risk Factor for Developing Benign Prostatic Hyperplasia. *Eur Urol* 2001; **39**(2): 151-8.

12. Peehl DM, Wong ST, Stamey TA. Cytostatic effects of suramin on prostate cancer cells cultured from primary tumors. *J Urol* 1991; **145**(3): 624-30.

13. Krieg M, Bartsch W, Thomsen M, Voigt KD. Androgens and estrogens: their interaction with stroma and epithelium of human benign prostatic hyperplasia and normal prostate. *J Steroid Biochem* 1983; **19**(1A): 155-61.

14. Sherwood ER, Fong CJ, Lee C, Kozlowski JM. Basic fibroblast growth factor: a potential mediator of stromal growth in the human prostate. *Endocrinology* 1992; **130**(5): 2955-63.

15. Kaplan SA, Te AE, Pressler LB, Olsson CA. Transition zone index as a method of assessing benign prostatic hyperplasia: correlation with symptoms, urine flow and detrusor pressure. *J Urol* 1995; **154**(5): 1764-9.

16. Homma Y, Kawabe K, Tsukamoto T, Yamanaka H, Okada K, Okajima E et al. Epidemiologic survey of lower urinary tract symptoms in Asia and Australia using the international prostate symptom score. *Int J Urol* 1997; **4**(1): 40-6.

17. Jacobsen SJ, Jacobson DJ, Girman CJ, Roberts RO, Rhodes T, Guess HA et al. Natural history of prostatism: risk factors for acute urinary retention. *J Urol* 1997; **158** (2): 481-7.

18. Mebust WK, Holtgrewe HL, Cockett AT, Peters PC. Transurethral prostatectomy: immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3,885 patients. *J Urol* 1989; **141**(2): 243-7.

19. Harrison RH, III. Frequency and causes of fluid absorption: a comparison of three techniques for resection of the prostate under continuous pressure monitoring. *BJU Int* 1999; **84**(9): 1116-7.

20. Hahn RG, Sandfeldt L, Nyman CR. Double-blind randomized study of symptoms associated with absorption of glycine 1.5% or mannitol 3% during transurethral resection of the prostate. *J Urol* 1998; **160**(2): 397-401.

21. Hahn, R. G. Ethanol monitoring and economics. *Personal Communication* 2001.

22. Bellfield WT. Operations on the enlarged prostate with a tabulated summary of cases. *Am J Med Sci* 1890; **100**: 439.

23. Holtgrewe HL, Bay-Nielsen H, Carlsson P, Coast J, Echtle D, Fitzpatrick F et al. The economics of the management of lower urinary tract symptoms and benign prostatic hyperplasia. In: Denis L, Griffiths K, Khoury S, Cockett ATK, McConnell J, Chatelain C et al., editors. Proceedings of 4th international consultation on benign prostatic hyperplasia (BPH). 4 ed. S.C.I.; 1998. p. 63-81.

24. Badia X, Garcia-Losa M, Dal Re R. Ten-language translation and harmonization of the International Prostate Symptom Score: developing a methodology for multinational clinical trials. *Eur Urol* 1997; **31**(2): 129-40.

25. Holtgrewe HL, Valk WL. Factors influencing the mortality and morbidity of transurethral prostatectomy: a study of 2015 cases. *J Urol* 1962; **87**: 450-9.

26. Melchior J, Valk WL, Foret JD, Mebust WK. Transurethral prostatectomy: computerized analysis of 2,223 consecutive cases. *J Urol* 1974; **112**(5): 634-42.

27. Ohe H, Ohnishi K, Watanabe H, Itakura Y, Inaba T. Accuracy of digital palpation for size assessment of the prostate evaluated by transrectal sonography. *Tohoku J Exp Med* 1988; **154**(4): 323-8.

28. Terris MK, Stamey TA. Determination of prostate volume by transrectal ultrasound. *J Urol* 1991; **145**(5): 984-7.

29. Poulsen AL, Schou J, Puggaard L, Torp-Pedersen S, Nordling J. Prostatic enlargement, symptomatology and pressure/flow evaluation: interrelations in patients with symptomatic BPH. *Scand J Urol Nephrol Suppl* 1994; **157**: 67-73.

30. Elbadawi A. Functional pathology of urinary bladder muscularis: the new frontier in diagnostic uropathology. *Semin Diagn Pathol* 1993; **10**(4): 314-54.

31. Roehrborn CG, Oesterling JE, Auerbach S, Kaplan SA, Lloyd LK, Milam DE et al. The Hytrin Community Assessment Trial study: a one-year study of terazosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT Investigator Group. *Urology* 1996; **47**(2): 159-68.

32. Roehrborn CG, Siegel RL. Safety and efficacy of doxazosin in benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. *Urology* 1996; **48**(3): 406-15.

33. Lepor H. Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. *Urology* 1998; **51**(6): 892-900.

34. Djavan B, Marberger M. A meta-analysis on the efficacy and tolerability of alpha1-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic obstruction. *Eur Urol* 1999; **36**(1): 1-13.

35. McConnell JD, Bruskewitz R, Walsh P, Andriole G, Lieber M, Holtgrewe HL et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride Long-Term Efficacy and Safety Study Group. *N Engl J Med* 1998; **338**(9): 557-63.

36. Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 1999; **53**(3): 581-9.

37. Foley SJ, Soloman LZ, Wedderburn AW, Kashif KM, Summerton D, Basketter V et al. A prospective study of the natural history of hematuria associated with benign prostatic hyperplasia and the effect of finasteride. *J Urol* 2000; **163**(2): 496-8.

38. Roehrborn CG. Standard surgical interventions: TUIP/TURP/OPSU. In: Kirby R, McConnell J, Fitzpatrick J, Roehrborn CG, Boyle P, editors. Textbook of benign prostatic hyperplasia. 1 ed. Oxford: Isis Medical Media Ltd; 1996. p. 341-78.

39. Trockman BA, Gerspach J, Dmochowski R, Haab F, Zimmern PE, Leach GE. Primary bladder neck obstruction: urodynamic findings and treatment results in 36 men. *J Urol* 1996; **156**(4): 1418-20.

40. Dorflinger T, Jensen FS, Krarup T, Walter S. Transurethral prostatectomy compared with incision of the prostate in the treatment of prostatism caused by small benign prostate glands. *Scand J Urol Nephrol* 1992; **26**(4): 333-8.

41. Wasson JH, Reda DJ, Bruskewitz RC, Elinson J, Keller AM, Henderson WG. A comparison of transurethral surgery with watchful waiting for moderate symptoms of benign prostatic hyperplasia. The Veterans Affairs Cooperative Study Group on Transurethral Resection of the Prostate. *N Engl J Med* 1995; **332**(2): 75-9.

42. Riehmann M, Knes JM, Heisey D, Madsen PO, Bruskewitz RC. Transurethral resection versus incision of the prostate: a randomized, prospective study. *Urology* 1995; **45**(5): 768-75.

43. Heyns CF, Rittoo D, Sutherland GR, Davie IT, Scott NB, Chisholm GD. Intra-operative myocardial ischaemia detected by biplane transoesophageal echocardiography during transurethral prostatectomy. *Br J Urol* 1993; **71**(6): 716-20.

44. Koshiba K, Egawa S, Ohori M, Uchida T, Yokoyama E, Shoji K. Does transurethral resection of the prostate pose a risk to life? 22- year outcome. *J Urol* 1995; **153**(5): 1506-9.

45. Meier DE, Tarpley JL, Imediegwu OO, Olaolorun DA, Nkor SK, Amao EA et al. The outcome of suprapubic prostatectomy: a contemporary series in the developing world. *Urology* 1995; **46**(1): 40-4.

46. Ball AJ, Feneley RC, Abrams PH. The natural history of untreated "prostatism". *Br J Urol* 1981; **53**(6): 613-6.

47. Boyle P, Robertson C, Lowe F, Roehrborn C. Meta-analysis of clinical trials of permixon in the treatment of symptomatic benign prostatic hyperplasia. *Urology* 2000; **55**(4): 533-9.

48. Patel A, Fuchs GJ, Gutierrez-Aceves J, Andrade-Perez F. Transurethral electrovaporization and vapour-resection of the prostate: an appraisal of possible electrosurgical alternatives to regular loop resection. *BJU Int* 2000; **85**(2): 202-10.

49. Nesbit RM, Glickman SI. The use of glycine solution as an irrigating medium during transurethral resection. *J Urol* 1948; **59**: 1212-6.

50. Hulten JO, Jorfeldt LS, Wictorsson YM. Monitoring fluid absorption during TURP by marking the irrigating solution with ethanol. *Scand J Urol Nephrol* 1986; **20**(4): 245-51.

51. Hahn RG. Calculation of irrigant absorption by measurement of breath alcohol level during transurethral resection of the prostate. *Br J Urol* 1991; **68**(4): 390-3.

52. Hahn RG, Ekengren JC. Patterns of irrigating fluid absorption during transurethral resection of the prostate as indicated by ethanol. *J Urol* 1993; **149**(3): 502-6.

53. Creevy CD. Hemolytic reactions during transurethral prostatic resection. *J Urol* 1947; **58**: 125-31.

54. Madsen PO, Madsen RE. Clinical and experimental evaluation of different irrigating fluids for transurethral surgery. *Invest Urol* 1965; **3**(2): 122-9.

55. Hulten JO, Tran VT, Pettersson G. The control of haemolysis during transurethral resection of the prostate when water is used for irrigation: monitoring absorption by the ethanol method. *BJU Int* 2000; **86**(9): 989-92.

56. Harrison RH, III. A century of prostatic surgery. *BJU Int* 1999; **84**(7): 892.

57. Nilsson A, Randmaa I, Hahn RG. Haemodynamic effects of irrigating fluids studied by Doppler ultrasonography in volunteers. *Br J Urol* 1996; **77**(4): 541-6.

58. Kaiser R, Adragna MG, Weis FR, Jr., Williams D. Transient blindness following transurethral resection of the prostate in an achondroplastic dwarf. *J Urol* 1985; **133**(4): 685-6.

59. Hoekstra PT, Kahnoski R, McCamish MA, Bergen W, Heetderks DR. Transurethral prostatic resection syndrome--a new perspective: encephalopathy with associated hyperammonemia. *J Urol* 1983; **130**(4): 704-7.

60. Istre O, Bjoennes J, Naess R, Hornbaek K, Forman A. Postoperative cerebral oedema after transcervical endometrial resection and uterine irrigation with 1.5% glycine. *Lancet* 1994; **344**(8931): 1187-9.

61. Guyton AC. Renal disease, diuresis, and micturition. In: Wonsiewicz MJ, editor. Textbook of medical physiology. 8 ed. Philadelphia: W. B. Saunders Company; 1991. p. 344-54.

62. Lehman TH, Loomis RC, Moore RJ, Hodges CV. Intravenous mannitol during transurethral prostatectomy using distilled water as an irrigating medium. *J Urol* 1966; **95**(3): 396-406.

63. Baba T, Shibata Y, Ogata K, Kukita I, Goto T, Hamada Y et al. Isotonic hyponatremia and cerebrospinal fluid sodium during and after transurethral resection of the prostate. *J Anesth* 1995; **9**: 135-41.

64. Logie JR, Keenan RA, Whiting PH, Steyn JH. Fluid absorption during transurethral prostatectomy. *Br J Urol* 1980; **52**(6): 526-8.

65. Olsson J, Hahn RG. Survival after high-dose intravenous infusion of irrigating fluids in the mouse. *Urology* 1996; **47**(5): 689-92.

66. Hahn RG, Nilsson A, Stahle L. Distribution and elimination of the solute and water components of urological irrigating fluids. *Scand J Urol Nephrol* 1999; **33**(1): 35-41.

67. Olsson J, Hahn RG. Simulated intraperitoneal absorption of irrigating fluid. *Acta Obstet Gynecol Scand* 1995; **74**(9): 707-13.

68. Hahn RG. Ethanol monitoring of extravascular absorption of irrigating fluid. *Br J Urol* 1993; **72**(5 Pt 2): 766-9.

69. Olsson J, Nilsson A, Hahn RG. Symptoms of the transurethral resection syndrome using glycine as the irrigant. *J Urol* 1995; **154**(1): 123-8.

70. Checketts MR, Duthie WH. Expired breath ethanol measurement to calculate irrigating fluid absorption during transurethral resection of the prostate: experience in a district general hospital. *Br J Urol* 1996; **77**(2): 198-202.

71. Norris HT, Aasheim GM, Sherrard DJ, Tremann JA. Symptomatology, pathophysiology and treatment of the transurethral resection of the prostate syndrome. *Br J Urol* 1973; **45**(4): 420-7.

72. Hahn RG. Irrigating fluids in endoscopic surgery. *Br J Urol* 1997; **79**(5): 669-80.

73. Still JA, Jr., Modell JH. Acute water intoxication during transurethral resection of the prostate, using glycine solution for irrigation. *Anesthesiology* 1973; **38**(1): 98-9.

74. Landsteiner EK, Finch CA. Hemoglobinemia accompanying transurethral resection of the prostate. *N Engl J Med* 1947; **237**: 310.

75. Hjertberg H, Ekberg S, Hahn R, Hulten J, Jorfeldt L, Svedberg J. Absorption of irrigating fluid during transurethral prostatic resection as measured by ethanol, radioisotopes, and regular-interval monitoring. *Urology* 1991; **38**(5): 417-22.

76. Maluf NSR, Boren JS, Brandes GE. Absorption of irrigating solution and associated changes upon transurethral electroresection of prostate. *J Urol* 1956; **75**(5): 824-36.

77. Hahn RG. Dilution of blood proteins due to irrigant absorption in transurethral prostatic resection. *Scand J Urol Nephrol* 1989; **23**(2): 97-102.

78. Olsson J, Rentzhog L, Hjertberg H, Hahn RG. Reliability of clinical assessment of fluid absorption in transurethral prostatic resection. *Eur Urol* 1993; **24**(2): 262-6.

79. Nesbit RM, Conger KB. Studies of blood loss during transurethral prostatic resection. *J Urol* 1941; **46**: 713-21.

80. LeVeen HH, Rubricius JL. Continuous, automatic electronic determinations of operative blood loss. *Surg Gynecol Obstet* 1958; **106**: 368.

81. Desmond JW, Gordon RA. Bleeding during transurethral prostatic surgery. *Can Anaesth Soc J* 1969; **16**(3): 217-24.

82. Ekengren J, Hahn RG. Blood loss during transurethral resection of the prostate as measured by the HemoCue photometer. *Scand J Urol Nephrol* 1993; **27**(4): 501-7.

83. TU or not TU. *Lancet* 1989: 1361-2.

84. Malenka DJ, Roos N, Fisher ES, McLerran D, Whaley FS, Barry MJ et al. Further study of the increased mortality following transurethral prostatectomy: a chart-based analysis. *J Urol* 1990; **144**(2 Pt 1): 224-7.

85. Andersen TF, Bronnum-Hansen H, Sejr T, Roepstorff C. Elevated mortality following transurethral resection of the prostate for benign hypertrophy! But why? *Med Care* 1990; **28**(10): 870-81.

86. Taylor Z, Krakauer H. Mortality and reoperation following prostatectomy: outcomes in a Medicare population. *Urology* 1991; **38**(1 Suppl): 27-31.

87. Concato J, Horwitz RI, Feinstein AR, Elmore JG, Schiff SF. Problems of comorbidity in mortality after prostatectomy. *JAMA* 1992; **267**(8): 1077-82.

88. Hooten ME, Finstuen K, Thompson IM. Multivariate case-control study of survival following transurethral resection of prostate. *Urology* 1992; **39**(2): 111-6.

89. Seagroatt V. Mortality after prostatectomy: selection and surgical approach. *Lancet* 1995; **346**(8989): 1521-4.

90. Hargreave TB, Heynes CF, Kendrick SW, Whyte B, Clarke JA. Mortality after transurethral and open prostatectomy in Scotland. *Br J Urol* 1996; **77**(4): 547-53.

91. Holman CD, Wisniewski ZS, Semmens JB, Rouse IL, Bass AJ. Mortality and prostate cancer risk in 19,598 men after surgery for benign prostatic hyperplasia. *BJU Int* 1999; **84**(1): 37-42.

92. Hahn RG, Farahmand BY, Hallin A, Hammar N, Persson PG. Incidence of acute myocardial infarction and cause-specific mortality after transurethral treatments of prostatic hypertrophy. *Urology* 2000; **55**(2): 236-40.

93. Hahn RG. Smoking increases the risk of large scale fluid absorption during transurethral prostatic resection. *J Urol* 2001; **166**(1): 162-5.

94. Caine M, Raz S, Zeigler M. Adrenergic and cholinergic receptors in the human prostate, prostatic capsule and bladder neck. *Br J Urol* 1975; **47**(2): 193-202.

95. Appell RA, England HR, Hussell AR, McGuire EJ. The effects of epidural anesthesia on the urethral closure pressure profile in patients with prostatic enlargement. *J Urol* 1980; **124**(3): 410-1.

96. Verrier RL, Thompson PL, Lown B. Ventricular vulnerability during sympathetic stimulation: role of heart rate and blood pressure. *Cardiovasc Res* 1974; **8**(5): 602-10.

97. Hahn RG, Essen P. ECG and cardiac enzymes after glycine absorption in transurethral prostatic resection. *Acta Anaesthesiol Scand* 1994; **38**(6): 550-6.

98. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992; **117**(11): 891-7.

99. Hahn RG, Shemais H, Essen P. Glycine 1.0% versus glycine 1.5% as irrigating fluid during transurethral resection of the prostate. *Br J Urol* 1997; **79**(3): 394-400.

100. Hahn RG. Ethanol monitoring of irrigating fluid absorption. *Eur J Anaesthesiol* 1996; **13**(2): 102-15.

101. Guyton AC. The body fluid compartments: extracellular and intracellular fluids; interstitial fluid and edema. In: Wonsiewicz MJ, editor. Textbook of medical physiology. 8 ed. Philadelphia: W.B. Saunders Company; 1991. p. 274-85.

102. Nadler SB, Hidalgo JU, Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962; **51**: 224-32.

103. Hahn RG. A haemoglobin dilution method (HDM) for estimation of blood volume variations during transurethral prostatic surgery. *Acta Anaesthesiol Scand* 1987; **31**(7): 572-8.

104. Hannan WJ, Cowen SJ, Fearon KC, Plester CE, Falconer JS, Richardson RA. Evaluation of multi-frequency bio-impedance analysis for the assessment of extracellular and total body water in surgical patients. *Clin Sci (Colch )* 1994; **86**(4): 479-85.

105. De Lorenzo A, Andreoli A, Matthie J, Withers P. Predicting body cell mass with bioimpedance by using theoretical methods: a technological review. *J Appl Physiol* 1997; **82**(5): 1542-58.

106. Jansen H, Berseus O, Johansson JE. A simple photometric method for determination of blood loss during transurethral surgery. *Scand J Urol Nephrol* 1978; **12**(1): 1-5.

107. Abrams PH, Griffiths DJ. The assessment of prostatic obstruction from urodynamic measurements and from residual urine. *Br J Urol* 1979; **51**(2): 129-34.

108. Jensen KM, Jorgensen JB, Mogensen P. Urodynamics in prostatism. I. Prognostic value of uroflowmetry. *Scand J Urol Nephrol* 1988; **22**(2): 109-17.

109. Rollema HJ, van Mastrigt R. Improved indication and followup in transurethral resection of the prostate using the computer program CLIM: a prospective study. *J Urol* 1992; **148**(1): 111-5.

110. Schalling D, Asberg M, Edman G, Oreland L. Markers for vulnerability to psychopathology: temperament traits associated with platelet MAO activity. *Acta Psychiatr Scand* 1987; **76**(2): 172-82.

111. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**(3): 189-98.

112. Anthony JC, LeResche L, Niaz U, Von Korff MR, Folstein MF. Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. *Psychol Med* 1982; **12**(2): 397-408.

113. Shapiro BA, Peruzzi WT. Interpretation of blood gases. In: Ayres SM, Shoemaker WC, editors. Textbook of critical care. 3 ed. Philadelphia: Saunders; 1995. p. 278-94.

114. Jensen-Urstad M, Jensen-Urstad K, Ericson M, Johansson J. Heart rate variability is related to leucocyte count in men and to blood lipoproteins in women in a healthy population of 35-year-old subjects. *J Intern Med* 1998; **243**(1): 33-40.

115. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; **17**(3): 354-81.

116. Bigger JT, Jr., Fleiss JL, Rolnitzky LM, Steinman RC. Stability over time of heart period variability in patients with previous myocardial infarction and ventricular arrhythmias. The CAPS and ESVEM investigators. *Am J Cardiol* 1992; **69**(8): 718-23.

117. Eriksson BM, Wikstrom M. Determination of catecholamines in urine by liquid chromatography and electrochemical detection after on-line sample purification on immobilized boronic acid. *J Chromatogr* 1992; **593**(1-2): 185-90.

118. Kent SP. Diffusion of myoglobin in the diagnosis of early myocardial ischemia. *Lab Invest* 1982; **46**(3): 265-70.

119. Leadbeatter S, Wawman HM, Jasani B. Further evaluation of immunocytochemical staining in the diagnosis of early myocardial ischaemic/hypoxic damage. *Forensic Sci Int* 1990; **45**(1-2): 135-41.

120. Foley SJ, Bailey DM. Microvessel density in prostatic hyperplasia. *BJU Int* 2000; **85**(1): 70-3.

121. Armitage P, Berry G. Statistical methods in medical research. 3ed. Oxford: Blackwell Science; 1994.

122. Hosmer DW, Lemeshow S. Applied Logistic Regression. 1ed. New York: John Wiley & Sons; 1989.

123. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; **14**(3): 173-94.

124. Hammarsten J, Högstedt B, Holthuis N, Mellström D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. *Prostate Cancer and Prostatic Diseases* 1998(1): 157-62.

125. Guyton AC. The adrenocortical hormones. In: Wonsiewicz MJ, editor. Textbook of medical physiology. 8 ed. Philadelphia: W. B. Saunders Company; 1991. p. 842-54.

126. Kampe T, Edman G, Hannerz H. Ten-year follow-up study of personality traits in adults with intact and restored dentitions. *J Oral Rehabil* 1996; **23**(7): 443-9.

127. Lucki I. The spectrum of behaviors influenced by serotonin. *Biol Psychiatry* 1998; **44**(3): 151-62.

128. Januzzi JL, Stern TA, Pasternak RC, DeSanctis RW. The influence of anxiety and depression on outcomes of patients with coronary artery disease. *Arch Intern Med* 2000; **160**(13): 1913-21.

129. di Sant'Agnese PA, Mesy Jensen KL, Churukian CJ, Agarwal MM. Human prostatic endocrine-paracrine (APUD) cells. Distributional analysis with a comparison of serotonin and neuron-specific enolase immunoreactivity and silver stains. *Arch Pathol Lab Med* 1985; **109**(7): 607-12.

130. Cockett AT, di Sant'Agnese PA, Gopinath P, Schoen SR, Abrahamsson PA. Relationship of neuroendocrine cells of prostate and serotonin to benign prostatic hyperplasia. *Urology* 1993; **42**(5): 512-9.

131. Giovannucci E, Rimm EB, Chute CG, Kawachi I, Colditz GA, Stampfer MJ et al. Obesity and benign prostatic hyperplasia. *Am J Epidemiol* 1994; **140**(11): 989-1002.

132. Daniell HW. Larger prostatic adenomas in obese men with no associated increase in obstructive uropathy. *J Urol* 1993; **149**(2): 315-7.

133. Gu F. Changes in the prevalence of benign prostatic hyperplasia in China. *Chin Med J (Engl )* 1997; **110**(3): 163-6.

134. Guyton AC. The autonomic nervous system; the adrenal medulla. In: Wonsiewicz MJ, editor. Textbook of medical physiology. 8 ed. Philadelphia: W. B. Saunders Company; 1991. p. 667-78.

135. Van Hoogenhuyze D, Weinstein N, Martin GJ, Weiss JS, Schaad JW, Sahyouni XN et al. Reproducibility and relation to mean heart rate of heart rate variability in normal subjects and in patients with congestive heart failure secondary to coronary artery disease. *Am J Cardiol* 1991; **68**(17): 1668-76.

136. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; **59**(4): 256-62.

137. Von Garrelts B. Micturition in the normal male. *Acta Chir Scand* 1957; **114**: 197-210.

138. Landahl S, Bengtsson C, Sigurdsson JA, Svanborg A, Svardsudd K. Age-related changes in blood pressure. *Hypertension* 1986; **8**(11): 1044-9.

139. Jensen-Urstad K, Storck N, Bouvier F, Ericson M, Lindblad LE, Jensen-Urstad M. Heart rate variability in healthy subjects is related to age and gender. *Acta Physiol Scand* 1997; **160**(3): 235-41.

140. Henderson DJ, Middleton RG. Coma from hyponatremia following transurethral resection of prostate. *Urology* 1980; **15**(3): 267-71.

141. Gillett W, Grossman HB, Lee R. Visual disturbances in TUR reaction. *Urology* 1985; **25**(6): 573-5.

142. Hoyt HS, Goebel JL, Lee HI, Schoenbrod J. Types of shock-like reaction during transurethral resection and relation to acute renal failure. *J Urol* 1958; **79**(3): 500-6.

143. Thomas D, Hales P. Overhydration during transurethral resection of the prostate using glycine as an irrigating solution. *Anaesth Intensive Care* 1984; **12**(4): 366-9.

144. Stryer L. Amino acid degradation and the urea cycle. Biochemistry. San Francisco: W. H. Freeman and company; 1975. p. 432-55.

145. Hahn RG, Stalberg HP, Gustafsson SA. Intravenous infusion of irrigating fluids containing glycine or mannitol with and without ethanol. *J Urol* 1989; **142**(4): 1102-5.

146. Ryder KW, Olson JF, Kahnoski RJ, Karn RC, Oei TO. Hyperammonemia after transurethral resection of the prostate: a report of 2 cases. *J Urol* 1984; **132**(5): 995-7.

147. Fahey JL. Toxicity and blood ammonia rise resulting from intravenous amino acid administration in man: the protective effect of L-arginine. *J Clin Invest* 1957; **36**: 1647-55.

148. Guyton AC. Cerebral blood flow, the cerebrospinal fluid and brain metabolism. In: Wonsiewicz MJ, editor. Textbook of medical physiology. 8 ed. Philadelphia: W. B. Saunders Company; 1991. p. 679-85.

149. Pycock CJ, Kerwin RW. The status of glycine as a supraspinal neurotransmitter. *Life Sci* 1981; **28**(24): 2679-86.

150. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine (Baltimore)* 1976; **55**(2): 121-9.

151. Defalque RJ, Miller DW. Visual disturbances during transurethral resection of the prostate. *Can Anaesth Soc J* 1975; **22**(5): 620-1.

152. Hahn RG. Transurethral resection syndrome from extravascular absorption of irrigating fluid. *Scand J Urol Nephrol* 1993; **27**(3): 387-94.

153. Reiz S, Duchek M, Kerkoff Y, Olson B. Non-cardiogenic pulmonary oedema. A serious complication of transurethral prostatectomy. A case report. *Acta Anaesthesiol Scand* 1981; **25**(2): 166-8.

154. Singer M, Patel M, Webb AR, Bullen C. Management of the transurethral prostate resection syndrome: time for reappraisal? *Crit Care Med* 1990; **18**(12): 1479-80.

155. Hahn RG. Fluid and electrolyte dynamics during development of the TURP syndrome. *Br J Urol* 1990; **66**(1): 79-84.

156. Anderson P, Boreus L, Gordon E, Lagerkranser M, Rudehill A, Lindquist C et al. Use of mannitol during neurosurgery: interpatient variability in the plasma and CSF levels. *Eur J Clin Pharmacol* 1988; **35**(6): 643-9.

157. Hahn RG. Amino acid concentrations in serum and urine after intravenous infusion of 1.5% glycine in prostatectomy patients. *Prostate* 1992; **21**(3): 173-81.

158. Hirose M, Hashimoto S, Nose H, Morimoto T, Itoh T, Natsuyama T et al. Mechanism underlying the changes in plasma potassium concentration during infusion of isosmotic nonelectrolyte solution. *Anesthesiology* 1992; **77**(2): 336-41.

159. Hahn RG, Nennesmo I, Rajs J, Sundelin B, Wroblewski R, Zhang W. Morphological and X-ray microanalytical changes in mammalian tissue after overhydration with irrigating fluids. *Eur Urol* 1996; **29**(3): 355-61.

160. Guyton AC. The normal electrocardiogram. In: Wonsiewicz MJ, editor. Textbook of medical physiology. 8 ed. Philadelphia: W. B. Saunders Company; 1991. p. 118-23.

161. Olsson J, Hahn RG. Glycine toxicity after high-dose i.v. infusion of 1.5% glycine in the mouse. *Br J Anaesth* 1999; **82**(2): 250-4.

162. Algra A, Tijssen JG, Roelandt JR, Pool J, Lubsen J. QTc prolongation measured by standard 12-lead electrocardiography is an independent risk factor for sudden death due to cardiac arrest. *Circulation* 1991; **83**(6): 1888-94.

163. Drinker HR, Jr., Shields T, Grayhack JT, Laughlin L. Simulated transurethral resection reaction in the dog: early signs and optimal treatment. *J Urol* 1963; **89**: 595-602.

164. Ayus JC, Arieff AI. Glycine-induced hypo-osmolar hyponatremia. *Arch Intern Med* 1997; **157**(2): 223-6.

165. Hulten JO, Hahn RG. Monitoring irrigating fluid absorption during transurethral resection of the prostate (TURP); a comparison between 1 and 2% ethanol as a tracer. *Scand J Urol Nephrol* 1989; **23**(2): 103-8.

166. Hjertberg H. The use of ethanol as a marker to detect and quantify the absorption of irrigation fluid during transurethral resection of the prostate. *Scand J Urol Nephrol Suppl* 1996; **178**: 1-64.

167. Ekengren J, Hahn RG. Continuous versus intermittent flow irrigation in transurethral resection of the prostate. *Urology* 1994; **43**(3): 328-32.

168. Ekengren J, Zhang W, Hahn RG. Effects of bladder capacity and height of fluid bag on intravesical pressure during transurethral resection of the prostate. *Eur Urol* 1995; **27**(1): 26-30.

169. Hjertberg H, Pettersson B. The use of a bladder pressure warning device during transurethral prostatic resection decreases absorption of irrigation fluid. *Br J Urol* 1992; **69**(1): 56-60.

170. Hubert J, Cormier L, Gerbaud PF, Guillemin F, Pertek JP, Mangin P. Computer-controlled monitoring of bladder pressure in the prevention of 'TUR syndrome': a randomized study of 53 cases. *Br J Urol* 1996; **78**(2): 228-33.

171. Osborn DE, Rao PN, Greene MJ, Barnard RJ. Fluid absorption during transurethral resection. *Br Med J* 1980; **281**(6254): 1549-50.

172. Pierce JM, Jr. The treatment of water intoxication following transurethral prostatectomy. *J Urol* 1962; **87**(2): 181-3.

173. Bernstein GT, Loughlin KR, Gittes RF. The physiologic basis of the TUR syndrome. *J Surg Res* 1989; **46**(2): 135-41.

174. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. *N Engl J Med* 1987; **317**(19): 1190-5.

175. Hahn RG, Nilsson A, Hjelmqvist H, Zhang W, Rundgren M. Renal function during intravenous infusion of urological irrigating fluids in the sheep. *Acta Anaesthesiol Scand* 1996; **40**(6): 671-8.

176. Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology* 1996; **48**(3): 398-405.

177. McConnell JD. Finasteride therapy for benign prostatic hyperplasia. In: Kirby R, McConnell JD, Fitzpatrick JM, Roehrborn CG, Boyle P, editors. Textbook of benign prostatic hyperplasia. 1 ed. Oxford: Isis Medical Media Ltd; 1996. p. 259-65.

178. Snell RS. The pelvis: Part II The pelvic cavity. Clinical anatomy for medical students. 1 ed. Boston: Little, Brown and Company; 1973. p. 291-327.

179. Sobotta J, Becher H. Nerves and vessels of abdominal and pelvic cavities, of perineum and genital organs. In: Ferner H, Staubesand J, editors. Atlas of human anatomy. 9 ed. München: Urban & Schwarzenberg; 1975. p. 259-77.

180. Perkins JB, Miller HC. Blood loss during transurethral prostatectomy. *J Urol* 1969; **101**(1): 93-7.

181. Mackenzie AR, Levine N, Scheinman HZ. Operative blood loss in transurethral prostatectomy. *J Urol* 1979; **122**(1): 47-8.

# PAPERS I–V