A Laparoscopic Approach in Gastro-Oesophageal Surgery

Experimental and Epidemiological Studies

BY

RUNE SANDBU
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ABSTRACT

The extension of laparoscopic procedures into the chest may induce specific pathophysiologic effects.

In pigs, we have demonstrated how devastating a combined thoraco-laparoscopic approach can be for gas exchange. Furthermore, the transmission of elevated pressure intra-cranially is a potential danger. The application of positive end-expiratory pressure (PEEP) was found to improve gas exchange and, more importantly, hypoxemia could be avoided. The application of PEEP did not increase intra-cranial pressure further; nor did it adversely affect cerebral circulation.

Even before the introduction of the laparoscopic technique, there was a substantial increase in the annual number of antireflux procedures. Therefore, the threefold increase of the incidence of antireflux surgery recorded during the past decade cannot solely be explained by the introduction of minimal access surgery. However, a clear shift in the preferred methodology took place. This change was not scientifically supported at the time of the transition and, surprisingly, it is still not supported today. In comparison with open surgery, patients do not seem to derive significant long-term benefits from having the antireflux procedure done laparoscopically. As was demonstrated, laparoscopy might even be an inferior approach in some patients. Nevertheless, it is reasonable to assume that laparoscopy can yield equally good results as open surgery despite our failure to confirm that in our studies. Determination of the effectiveness of minimal access surgery in the treatment of GORD is critical, before minimal access techniques become the standard for antireflux surgery in the community.

Key words: Gastro-oesophageal surgery, fundoplication, laparoscopy, long-term results, pneumothorax, intra-cranial pressure, positive end-expiratory pressure.

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V. R Sandbu, H Khamis, S Gustavsson, U Haglund. Laparoscopic antireflux surgery in routine hospital care. Accepted for publication, Scand J Gastroenterol.

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# Table of contents

**Abbreviations** ............................................................................................................................ 5  
**Introduction**  
  Historical background .................................................................................................................. 7  
  Technical principles of minimal access surgery ........................................................................ 8  
  Potential benefits of minimal access surgery ............................................................................ 10  
  Anatomical considerations ........................................................................................................ 11  
  Pathophysiology  
    Pneumothorax and positive end-expiratory pressure (PEEP) .............................................. 12  
    Insufflation pressure and intracranial pressure (ICP):  
      Pneumothorax and PEEP ....................................................................................................... 13  
    Gastro-oesophageal surgery and minimal access approach: An overview ............................. 14  
**Aims of the thesis** ...................................................................................................................... 20  
**Material and Methods**  
  A. Experimental studies (Studies I and II)  
    Ethical considerations and animals ....................................................................................... 21  
    Method of anaesthesia ............................................................................................................ 21  
    Technique for separate lung intubation and differential lung ventilation ............................ 22  
    Model for combined positive pressure pneumoperitoneum  
      and unilateral pneumothorax .................................................................................................. 23  
    Experimental design .............................................................................................................. 24  
    Monitoring ............................................................................................................................... 26  
  B. Epidemiological studies and survey of long-term results on antireflux surgery  
    (Studies III-V)  
    Methods of survey ................................................................................................................. 29  
    Study design ........................................................................................................................... 30  
    Patients and ethical considerations (Studies IV and V) ....................................................... 32  
  **Statistical methods** ................................................................................................................. 33  
**Results and discussion**  
  Study I ......................................................................................................................................... 35  
  Study II ....................................................................................................................................... 39  
  Study III ..................................................................................................................................... 42  
  Study IV ..................................................................................................................................... 47  
  Study V ....................................................................................................................................... 51  
**General discussion** .................................................................................................................... 58  
**Conclusions** ............................................................................................................................. 66  
**Acknowledgements** .................................................................................................................. 67  
**References** ................................................................................................................................ 68  

4
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>CO</td>
<td>cardiac output</td>
</tr>
<tr>
<td>c-pH</td>
<td>pH in cerebral cortical tissue</td>
</tr>
<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
</tr>
<tr>
<td>C stat</td>
<td>static lung compliance</td>
</tr>
<tr>
<td>EpC</td>
<td>Centre for Epidemiology</td>
</tr>
<tr>
<td>ETCO₂</td>
<td>end-tidal partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>GORD</td>
<td>gastro-oesophageal-reflux-disease</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>LDF</td>
<td>Laser-Doppler flow signal</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
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<tr>
<td>PCWP</td>
<td>pulmonary capillary wedge pressure</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end-expiratory pressure</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>partial pressure of carbon dioxide in arterial blood</td>
</tr>
<tr>
<td>PcCO₂</td>
<td>partial pressure of carbon dioxide in cerebral cortical tissue</td>
</tr>
<tr>
<td>PcO₂</td>
<td>partial pressure of oxygen in cerebral cortical tissue</td>
</tr>
<tr>
<td>PjvO₂</td>
<td>partial pressure of oxygen in venous blood from the brain</td>
</tr>
<tr>
<td>PPI</td>
<td>proton-pump inhibitors</td>
</tr>
<tr>
<td>SaO₂</td>
<td>oxygen saturation in arterial blood</td>
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<tr>
<td>SjvO₂</td>
<td>oxygen saturation in venous blood from the brain</td>
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<tr>
<td>VCO₂</td>
<td>CO₂ elimination</td>
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Introduction

Historical background

In 1901, Georg Kelling, a surgeon from Dresden, demonstrated a method he called “koelioscopie.” The surgeon punctured the peritoneal cavity with a needle and expanded it with filtered air. He then inserted a trocar into the abdominal wall and used the trocar to introduce a cystoscope (laparoscope). This procedure was performed on a live canine during the 73rd Congress of German Naturalists and Physicians. It was the beginning of the field of laparoscopy (1-3).

The first major clinical contribution is attributed to the Swedish physician, Hans Christian Jacobaeus (1910) (4). His initial experience with the technique was restricted to patients with ascites. He was able to diagnose syphilis, tuberculosis, cirrhosis and malignancies. Later, Jacobaeus expanded the limits to include the thoracic cavity (thoracoscopy) (5).

For more than half a century, however, laparoscopy had limited use in clinical practice. It was chiefly applied in gynaecology as a diagnostic tool and for tubal ligation. A major problem at that time concerned optics and light transmission. It was not just a coincidence that the development of general laparoscopic surgery occurred shortly after the introduction of the computer chip TV camera. The first reports of successful laparoscopic cholecystectomy emanated from France in 1987 (6,7).

After 1987, everything happened with incredible speed and a veritable explosion of laparoscopy into general surgical practice followed. Within a few years, there was hardly any open intra-abdominal procedure that had not been attempted laparoscopically (3,8). Enthusiasts predicted by the turn of the 20th century that the majority of general surgery would be performed using this new approach (9,10). Certainly, for procedures such as cholecystectomy and Nissen fundoplication, laparoscopy has become the “gold standard”
The matter of securing adequate training and credentialing of laparoscopic surgeons has become widely debated (13). By contrast, the question of evaluation of outcomes was virtually bypassed for all procedures (9,10,14).

When laparoscopy is adopted in the upper abdomen, in particular when the dissection is extended to the mediastinum, there is substantial risk of pneumothorax (15-17). The positive insufflation pressure applied in the abdomen may then be transmitted to the intra-thoracic structures and fundamentally change the patophysiologic conditions.

This thesis is an attempt to address some of those issues that arise when laparoscopy is applied in gastro-oesophageal surgery.

**Technical principles of minimal access surgery**

The denotation “minimal access surgery” refers to all surgical procedures that apply visualisation through video-endoscopy and limited access, often through trocars, to perform all or part of the intended procedure. In this thesis, I will focus on laparoscopy as it is performed at the gastro-oesophageal junction.

Basic laparoscopic principles and equipment are outlined below:

- The main prerequisite for abdominal exposure is establishment of **pneumoperitoneum**. Different techniques can be used to gain prime entrance to the peritoneal cavity: Verres needle, Hasson trocar or minilaparotomy.
• **Insufflation of carbon dioxide (CO₂)** is utilised to maintain pneumoperitoneum. CO₂ is a common product of metabolism and its major advantage is the rapid dissolution in the event of venous gas embolus. It is also low in cost and highly inflammable. Other gases have been evaluated (air, O₂, He and N₂O), but for different reasons they are less suited for laparoscopy (18-20).

• Optimal exposure of the operative field depends on the **insufflation pressure**; “the higher pressure, the better view.” However, increased intra-abdominal pressure is of potential danger to the patient’s safety. Undesired, but unavoidable side effects, are reduction of the respiratory minute volume and compression of the vena cava with obstruction of venous blood return to the heart. Therefore, it is not advisable to apply pressure higher than **12-15 mm Hg** (20-22).

• One or several **trocars** are used to make easy access for the **endoscope** and **surgical instruments**.

• Light is transmitted from the light source to the endoscope through **light cables**.

• **Video imaging equipment** allows all members of the surgical team to view the operative field simultaneously.

Most standard abdominal procedures have been translated into equivalent laparoscopic procedures. Ideally, the difference should be the abdominal access not the surgical principles.
Potential benefits of minimal access surgery

Minimal access surgery offers possibilities to reduce tissue damage because of the operation. The reduction of surgical stress has been demonstrated in a decreased inflammatory cytokine response in the early post-operative course (23-26). The development of post-operative infectious complications (i.e. wound infections) may be attenuated (27-29).

Patients often experience less pain after laparoscopic procedures and a quick mobilisation allows for shorter hospital stay. Earlier return to normal activities and thereby a shorter period of sick leave has repeatedly been reported for different laparoscopic procedures, i.e. cholecystectomy (12,30,31), appendectomy (27-29,32,33) and inguinal hernia repair (34-37). However, when prospective, randomised single-blind comparisons of laparoscopic versus small-incision cholecystectomy or of laparoscopic versus open fundoplication have been undertaken, no significant advantages were found in terms of post-operative recovery (38,39).

A reduced risk of incisional hernia (40,41) and a more acceptable, cosmetic result may be further arguments in favour of the laparoscopic approach. In patients in whom one has had the opportunity to inspect intra-peritoneal a second time, sparse general adhesions have been observed; however, the local adhesions have often been dense (42,43). It is not known whether the laparoscopic approach will reduce the risk of post-operative ileus and make subsequent laparotomy easier. Scientific support for these arguments is inconclusive.

Economic considerations regarding laparoscopic techniques are not included in the present thesis.
Anatomical considerations

The diaphragm constitutes the boundary between thoracic and abdominal cavities. On the thoracic side, the diaphragm is lined by the pleura and on abdominal side by the peritoneum. Although these membranes are extremely delicate, they define the different anatomic compartments. Several important organs pass between the thorax and abdomen, i.e. the aorta, the caval vein and the oesophagus. The opening in the diaphragm where the oesophagus passes into the abdomen is called the hiatus and the slings of diaphragm muscle, which curves around the oesophagus from right and left to support the hiatus, is called the right and left crus. With age, the hiatus often becomes wider and the gastro-oesophageal junction looses its anchoring in the crura. The proximal part of the stomach may slide up into the mediastinum, with a hiatal hernia being the result (Figure 1).

Figure 1: Schematic illustration of the gastro-oesophageal junction and hiatal hernia.
During gastro-oesophageal operations, the surgeon regularly opens the peritoneum in the hiatal region in order to extend the dissection into the mediastinum. The proximity of surgical manipulations to cardiac and pulmonary structures is challenging cardiopulmonary functions and the risk of peri-operative complications increases. In particular, the mediastinal pleura might be ruptured during dissection (16,44-47).

Pathophysiology

Pneumothorax and positive end-expiratory pressure (PEEP)

If the pleura is opened and communication to the peritoneal cavity established, inadvertently or as part of the procedure, a pneumothorax will result and the negative intra-pleural pressure found during normal inspiration cannot be maintained. In open surgery this does not normally constitute a problem because the intra-pleural pressure will be equal to the pressure in the operating room (atmospheric or zero pressure) and application of a minimal PEEP will force the lungs to inflate fully. By contrast, the intra-pleural pressure of a pneumothorax (or, to be precise, a capnothorax) created during laparoscopy may equalise the positive intra-peritoneal insufflation pressure and thereby prevent full inflation of the lung during inspiration. Such an event may harm the gas exchange.

The application of PEEP has been suggested to counterbalance the insufflation pressure (16,48). Theoretically, PEEP can improve the ventilation of collapsed and poorly ventilated alveoli, decrease intra-pulmonary shunt volumes and, finally, increase systemic oxygen saturation (49). On the other hand, compliance can be reduced during PEEP because of over-distension of alveoli, alveolar rupture and surfactant inactivation (49). PEEP induced
increase in lung volume may cause compression of the small intra-alveolar vessels, thereby increasing pulmonary resistance (50,51) and decreasing cardiac output (CO).

It has not been established which combination of insufflation pressure and PEEP is least harmful for the circulation and gas exchange.

**Insufflation pressure and intracranial pressure (ICP): pneumothorax and PEEP**

During laparoscopy, positive-pressure gas insufflation is applied to establish abdominal distension. This application also induces a significant increase in intracranial pressure (ICP), a phenomenon which has not been widely recognised (52-54).

ICP is normally held within narrow limits. The four intracranial compartments (cerebrospinal fluid, blood, parenchyma, and bone) respond to changes in one or more of the compartments with reciprocal changes in the non-osseous compartments to maintain a stable ICP (Monro-Kellie doctrine) (55). Nevertheless, during rapid increase in one or more compartments, compensation by the remaining compartments is usually inadequate and ICP rises. Furthermore, the cranial cavity is not isolated from changes in pressure of other compartments. Blood and cerebrospinal fluid movements will transmit changes in intra-abdominal and intra-thoracic pressure intracranially. Elevated intra-abdominal pressure will compress lumbar and abdominal veins, as well as impair venous return. Central venous pressure will rise and hence impede venous drainage from the central nervous system (CNS) with a resulting increase in ICP (53,54,56).

As described in the previous section, application of PEEP is recommended to correct the negative effects of pneumothorax, if encountered during laparoscopy. However, potential deleterious effects on the CNS because of PEEP have been described, though the results from different studies were
inconsistent (57-61). In head-injured patients, PEEP resulted in reduction of mean arterial pressure (MAP) and elevation of ICP, and consequently reduced cerebral perfusion pressure (CPP) (58). PEEP is thought to increase intrathoracic pressure and thereby impair venous return and cardiac filling, which can lead to reduction of CO and MAP (58-60). These observations were made in patients or animals with cerebral lesions, where the brain’s ability to withstand pressure elevations was already challenged.

However, if a communicating pneumothorax is faced during a laparoscopic procedure in a healthy subject, with reduction of lung compliance and oxygen saturation, it is not known whether application of PEEP to promote pulmonary gas exchange would lead to a further increase in ICP and thereby impairment of cerebral blood flow.

Gastro-oesophageal surgery and minimal access approach: An overview

- Antireflux surgery

Of all gastro-oesophageal surgical procedures, antireflux surgery is at present the most commonly performed. For this reason, antireflux surgery is best suited to study how the new technique was implemented in routine hospital care. The surgical treatment of hiatal hernia is, in principal, the same as for severe gastro-oesophageal-reflux-disease (GORD). Thus, many of the following paragraphs can also include the treatment of hiatal hernia.

Two major changes in the management of severe GORD have occurred during the past decade. For many years, surgical therapy was regarded as superior (62,63), but with the introduction of proton-pump inhibitors (PPI) in 1989, an alternative and often equally effective medical treatment became
available (64-66). The introduction of the laparoscopic technique for antireflux surgery provided an alternative option. The laparoscopic Nissen fundoplication was first described in 1991 by both Dallemagne (67) and Geagea (68). In Sweden, antireflux procedures employing minimal access surgery were first employed in 1992.

The principles of fundoplication operations include mobilising the lower oesophagus and to wrapping the fundus of the stomach either partially or totally around the oesophagus. When the oesophageal hiatus is enlarged, it is narrowed by sutures in order to preclude the possibility for para-oesophageal herniation and to prevent the wrap from being pulled up into the chest (Figures 2A and 2B). The specific techniques for different kinds of fundoplication and crural closure used in open surgery, i.e. partial anterior (Watson) or posterior (Toupet) and total fundoplication (Nissen, Nissen-Rosetti) have been translated into equivalent laparoscopic techniques.

Figure 2: 360° (total) Nissen fundoplication with crural closure (A), and 180° (partial, posterior) Toupet fundoplication (B).
Heading (69) estimated a fundoplication rate (number of antireflux operations per 100,000 inhabitants) of 10 for Scotland for the 5-year period between 1982 and 1986. The remarkable increase in antireflux surgery in recent years, noted in several European countries, is often attributed to the change in surgical modality (70). In contradiction, it is generally held that the indications for surgery remain unchanged, regardless of the surgical technique (71). Nevertheless, current trends indicate that laparoscopic fundoplication is being used increasingly as an alternative to maintenance therapy with proton PPI (11).

Numerous studies have concluded that the short-term outcome after laparoscopic antireflux procedures is at least as good as for open procedures. Accelerated painless recovery is achieved without compromising the efficacy and clinical outcome of the procedure (11). However, published reports are almost exclusively from specialised centres (72-79), making it difficult to draw any firm conclusions from these data and applying them to routine hospital care. The widespread adoption of laparoscopic antireflux surgery by generalists without special interests in reflux disease can possibly have a negative impact on the outcome. It has been repeatedly demonstrated that laparoscopic antireflux surgery has a long learning curve (80-84). Therefore, it may be hard to achieve the necessary experience and surgical training in low-volume hospitals.

To our knowledge, there have only been published results from six controlled randomised trials comparing the outcome after the two techniques. The Dutch multicentre study was discontinued because of a high incidence of early dysphagia in the laparoscopic group (85). In a Swedish study with blind evaluation of the recovery and discharge periods, patients in both groups stayed a median of three days post-operatively at hospital and no significant differences were found in the duration of sick leave (39). Good short-term results after both laparoscopic and open procedures have been reported from
different Finnish groups in three prospective, randomised studies. They compared complications, outcome, quality of life and patient satisfaction. In one study, the patients (n=42) were followed for 2 years; the other reports were based on a 12-month follow-up (86-88). The different procedures seem to be equally effective, but the number of patients in each study is too small to allow any firm conclusions. Both Heikkinen and Loustarinen report that new on-set dysphagia tended to be more frequent among patients who had had the antireflux procedure made laparoscopically. A similar finding was reported in a randomised Swedish study (89).

To our knowledge, long-term follow-up studies have not been done. Surgeons, as well as patients, seem to prefer the laparoscopic technique and take it for granted that the effectiveness of laparoscopic and conventional open approach is comparable (43,90,91).

The goal of antireflux surgery is resolution of all symptoms of gastro-oesophageal reflux with negligible side effects and no further need for medical therapy (92,93). To evaluate outcome of antireflux surgery it is therefore paramount to ask the patients whether they are symptom-free and satisfied with the results. Exclusion of heartburn, which is the cardinal symptom of GORD, correlates well with post-operative normalisation of 24-hour pH monitoring (94). Many patients, however, refuse to participate in post-operative 24-hour pH monitoring. Moreover, this test is both elaborate and expensive. The absence of heartburn is fairly reliable in predicting normal acid exposure on pH testing (94). Several investigators have proposed disease-specific questionnaires as a tool for follow-up surveys after antireflux surgery (93-95).
• **Cardiomyotomy**

The minimal access technique has replaced open surgery in the treatment of oesophageal achalasia. Laparoscopic Heller myotomy and partial fundoplication have emerged as the procedure of choice (96,97). From specialised centres, excellent results have been reported (96,98,99). However, the disease is seldom occurring and few, if any, units in Sweden will have enough patients to perform this procedure routinely.

• **Oesophagectomy**

Different techniques for endoscopic oesophagectomy have been employed. The mediasinoscopic approach to the oesophageus was developed by Buess and colleagues (100), but its diffusion has remained limited. Several investigators have reported their experience of oesophagectomy with thoracoscopy-assisted techniques combined with laparotomy for gastric mobilisation (101-103). This technique was also adopted at our clinic, but for the same reasons as reported by others, we abandoned it after a few years because no reduction in morbidity or mortality could be demonstrated (104-107). Refinements in technical equipment, i.e. the introduction of a hand-port system, have made dissection and gastric mobilisation easier to perform laparoscopically (108). A combined thoracoscopic and laparoscopic technique was therefore a logical development (109,110). However, contrary to other advanced surgical endoscopic procedures, endoscopic oesophagectomy has not yet been convincing and few clinics have included the technique in their standard repertoire (111).
Concerning the oncological issue, we now know that performing a radical lymphadnectomy by the minimal access technique takes longer operating time and may increase morbidity (111,112).

- **Gastric resections**

Laparoscopic partial gastrectomy for benign diseases and for palliation has been accepted as an effective surgical option (113). Laparoscopically assisted resections for malignancies, however, deserve a word of caution. The CO₂ insufflation may stimulate tumour proliferation and the risk for port site metastases has been addressed in several reports (19,114,115). Further standardisation is needed as well as the definition of correct indications based on long-term results. In Sweden, the laparoscopic approach is seldom used for gastric resections (for benign as well for malign disease).

- **Bariatric methods**

Laparoscopic methods for gastric banding and Roux-en-Y gastric bypass are widely adopted and the new technique has generated further refinements in the surgical treatment of obesity.

Prospective, randomised studies comparing equivalent open and laparoscopic methods are few and the little results available are inconclusive (116,117). In obese patients morbidity, caused by parietal trauma after laparotomy, occurs in up to 30% (infections and incisional hernias) of the patients (41). These complications have been encountered only infrequently when applying minimal access techniques.

In Sweden, obesity surgery is mostly performed at specialised clinics; all of these clinics have extensive experience in employing the laparoscopic approach.
Aims of the thesis

This thesis deals with two principally disparate issues.

First, in part one of the thesis pathophysiology specific for the application of laparoscopic techniques in gastro-oesophageal surgery is investigated. We evaluated two possible therapeutic actions (differential lung ventilation and PEEP) to correct for potential harmful effects (Studies I and II). Second, in part two the widely applied laparoscopic approach for antireflux surgery is surveyed as regards implementation and outcome (Studies III-V).

The specific aims of part 1 were to study the following issues during combined pneumoperitoneum and unilateral pneumothorax in anaesthetised pigs:

- investigate the effects on cardiopulmonary function (Study I)
- determine whether differential ventilation with varying PEEP on each lung was beneficial (Study I)
- to evaluate the effects of PEEP on ICP and cerebral blood flow (Study II)

The specific aims of part 2 were as follows:

- analyse whether the new therapeutic options (i.e. the introduction of proton pump inhibitors (PPI) in 1989 and the laparoscopic technique in 1992) altered the surgical treatment of GORD. Specifically, we sought to study the change in the frequency of antireflux procedures (Study III)
- to compare the long-term results after conventional open and laparoscopic procedures (Study IV)
- to compare the long-term results after laparoscopic antireflux procedures at low- and high-volume hospitals (Study V)
Material and Methods

A. Experimental studies (Studies I and II)

Ethical considerations and animals

The experimental protocols were reviewed and approved by the Institutional Review Board of Uppsala University. The animals were treated in conformity with the Helsinki convention for the use and care of animals (“Principles of Laboratory Animal Care” and “Guide for the Care and Use of Laboratory Animals,” National Institute of Health Publication No. 80-23, revised 1985). Thirty male and female Swedish Landrace piglets 11-14 weeks of age, with a mean weight of 24 ± 2 kg (range 21-30 kg), were studied. The animals were fasted overnight with free access to water and delivered by the same supplier directly to the laboratory on the morning of the experiment. After the completion of the experiment, when the animals still were anaesthetised, cardiac arrest was induced with intravenous injection of potassium chloride.

Method of anaesthesia

Anaesthesia was accomplished with an intramuscular injection of 3mg/kg tiletamine + 3mg/kg zolazepam (6 mg/kg Zoletil®, Virback Lab., France), 2mg/kg xylazine (Rompun®, Bayer, Germany) and atropine 0.04mg/kg combined with an intravenous bolus injection of 1 mg/kg morphine. Anaesthesia was maintained with a continuous infusion of 20 mg/kg/h
ketamine and 0.48 mg/kg/h morphine (118). Muscular blockade was maintained by continuous intravenous infusion of pancuronium bromide, 0.24 mg/kg/h. Tracheotomy was performed and mechanical ventilation initiated with an I:E ratio of 1:1, F\textsubscript{O}\textsubscript{2} of 0.4, respiratory rate 25 per minute and PEEP 5 cm H\textsubscript{2}O (Servo ventilator 900C, Siemens-Elema, Sweden). Minute ventilation was adjusted to maintain PaCO\textsubscript{2} between 5.0 and 5.5 k Pa. To compensate for fluid losses throughout the study, an intravenous bolus of 50-200 ml dextran 70 (Macrodex®, Fresenius Kabi AB, Sweden) was administered before commencement of the interventions, aiming at a pulmonary capillary wedge pressure (PCWP) of 8-10 mm Hg. This was followed by a continuous intravenous infusion of a balanced crystalloid solution with 2.5% glucose, 10 ml/ kg/h.

**Technique for separate lung intubation and differential lung ventilation (Study I)**

Each lung was intubated separately. In the pig, the bronchial tree differs from human anatomy (119). Pigs have a separate bronchial branch to the right upper lobe, and this branch goes directly from the trachea, proximal to the carina.

First, the larger 8 mm endotracheal tube was positioned with its tip immediately above the bronchial branch to the right upper lobe. To achieve separate intubation and differential ventilation, the left bronchus was intubated through the wide bore tube with a 5 mm outer diameter endotracheal tube. This tube was advanced over a 3.5 mm bronchoscope to ensure optimal placement (Figure 3). After the cuffs were inflated, both tubes were connected to separate ventilators.
Model for combined positive pressure pneumoperitoneum and unilateral pneumothorax (Studies I and II)
Two trocars (5 mm) were introduced: one intraperitoneally and the other into the right pleural space to accommodate gas insufflation. The trocars were connected to a common gas insufflator (Pelvi-Pneu CO₂, WISAP, Germany) and the pressure was monitored with an aneroid manometer. During the experimental intervals, CO₂ was insufflated with a common pressure applied to both trocars in the abdomen and in the right haemithorax, and thereby pneumoperitoneum and unilateral pneumothorax under equal positive pressure were achieved (Figure 4).
Experimental design

Study I

The model for combined positive pressure pneumoperitoneum, unilateral pneumothorax and differential lung ventilation was used. Different combinations of PEEP on right and left lung were evaluated. The rationale for the application of PEEP was to decrease the pressure gradient between the peritoneal and pleural cavities during inspiration and expiration so that the lungs inflate completely. We hypothesised that the optimal respiratory technique would be differential lung ventilation. We assumed that PEEP applied in the lung with pneumothorax had to be equal to or exceed the CO₂ insufflation pressure. To avoid harmful effects that might be related to prolonged and elevated PEEP, we decreased PEEP on the lung without pneumothorax.

An experimental cycle was initiated by insufflating CO₂ with a pressure of 10 mm Hg applied to both trocars. During this period, right and left PEEP settings of 10(right)/5(left), 10/10, 15/5, 15/10 cm H₂O were used by random assignment. The same PEEP setting was applied for the next 20 minutes with no adjustments of the ventilators. Measurements were recorded at the end of each interval. The gas insufflation was then turned off. The pneumothorax and the pneumoperitoneum were evacuated and a period of haemodynamic and respiratory stabilisation was allowed. Thereafter, a new experimental cycle was started with another combination of PEEP.

In a pilot study, with a PEEP setting of 5/5 cm H₂O, extremely high airway pressures, exceeding 90 cm H₂O, were recorded. This resulted in severe deterioration of blood gases, which was hard to overcome despite long recovery periods. Therefore, the PEEP combination of 5/5 was always applied at the end of the experiment. During the study, it became clear that a higher PEEP on both lungs was favourable, and for the last four animals, an additional cycle with a PEEP setting of 15/15 was inserted before 5/5.
Study II

In this study we examined the changes in ICP and cerebral circulation in a similar model as described above but without differential lung ventilation. We hypothesised that application of PEEP to counterbalance the insufflation pressure would be beneficial for pulmonary gas exchange, but increase ICP and consequently impair cerebral blood flow.

In the control group (n=11) we analysed changes in ICP, cerebral circulation and blood gases. Carbon dioxide insufflation pressures of 5, 10, 15 or 20 mm Hg were randomly assigned and applied for 20 minutes during the intervention period. PEEP was kept at 5 cm H₂O.

In another eight piglets the experiment was similar, except PEEP was adjusted to a value equal to the insufflation pressure of CO₂ during the intervention periods (PEEP group, n=8).
In all animals the experiment consisted of four test intervals with intermediate recovery periods.

**Monitoring**

**Haemodynamic monitoring (Studies I and II)**

Intra-vascular catheters were placed surgically. A catheter (16 G) was inserted via a branch of the right external carotid artery into the aortic arch for recording of MAP and sampling for arterial blood gas analysis. A pulmonary artery catheter (7 Fr) was introduced via the right external jugular vein into the pulmonary artery for measurements of CO and PCWP. Intra-vascular pressures and ECG were monitored continuously (Solar 8000, Marquette Hellige, USA). Blood samples were analysed in a blood gas analyser (ABL5, Radiometer, Denmark) and in a Haemoxymeter (OSM3, Radiometer, Denmark). In Study II a catheter (20 G) was also inserted into the left internal jugular vein and passed retrogradely into the jugular bulb for blood sampling, for measurements of oxygen saturation and for partial pressure (SjvO₂ and PjvO₂).

**Respiratory monitoring (Studies I and II)**

A respiratory profile monitor (CO₂SMO+, Novametrix Medical Systems, Inc., Wallingford, Connecticut, USA) was connected to the ventilator for monitoring of end-tidal carbon dioxide levels (ETCO₂), CO₂ elimination (VCO₂) and static compliance (C stat).

In Study I two ventilators with two separate respiratory profile monitors were used.

**Intracranial monitoring (Study II)**

Paratrend® catheter: The probe incorporates optical fibres for the measurements of PCO₂ and pH, an electrochemical sensor for PO₂, and a
thermocouple for measurements of temperature (Paratend-7®, Biomedical Sensors LTD, High Wycombe, England). The cylindrical construction of the sensor allows measurements over the entire surface of the probe, the diameter of which is 0.5 mm. The four sensor components are located at intervals along the distal 4 cm of the polyethylene probe, which is permeable to O₂ and CO₂. The outer surface of the probe is coated with covalently bonded heparin to prevent deposition of fibrin. The monitor continuously displays pH, PCO₂, PO₂ and temperature. Although originally designed for measurement of arterial blood gases, Paratrend-7® has also been validated for measurements in cerebral tissue (120-122).

The Paratrend® catheter was inserted through a Camino® bolt (Camino laboratories, San Diego, USA) fitted into a right parietal burr hole and positioned 4 cm into the brain for measurement of cerebral cortical tissue PO₂, PCO₂, and pH (PcO₂, PcCO₂ and c-pH) (Figure 5).

**Camino® pressure transducer:** ICP was measured by a Camino® pressure transducer inserted through a 2-mm burr hole approximately 1 cm anterior to the Paratrend® probe (Figure 5).

**Periflux® laser-Doppler flowmetre:** For continuous measurement of cerebral cortical blood flow, a Laser-Doppler flow probe (Flexible Straight Probe 320, Periflux® laser-Doppler flowmetre PF 2B, Perimed, Stockholm, Sweden) was introduced through a 2-mm burr hole 1 cm anterior to the coronal suture. The probe was placed on the surface of the brain cortex (Figure 5).

The flow estimate with this technique is based on the Doppler effect induced by moving erythrocytes to low-power laser light. Light (with a wavelength of 632.8 nm) from a 2-mV helium neon laser is guided to the tissue by a light conductor, which also serves to transmit the back-scattered light to the photodetector system. There is a frequency shift when the laser light has interacted with moving tissue elements. The bandwidth of the Doppler-shifted
frequencies increases proportionally to the velocity of erythrocytes. The signal amplitude reflects the microcirculation.

The Laser-Doppler probe has been validated for flow measurements in the CNS; good correlation was reported with flow changes detected by the microsphere technique (123,124). Its accuracy in monitoring changes in cerebral cortical blood flow has also been validated during the low flow state after induction of cerebral ischaemia (125).

The Laser-Doppler flow signal (LDF) was registered as online printout. The measurements of each animal were recorded as a fraction of the steady state baseline level, which was designated as 1.0.

Cerebral perfusion pressure (CPP) was calculated as the difference between MAP and ICP (MAP-ICP = CPP).

**Figure 5:** Schematic illustration of the placement of the Paratrend® catheter (A), Camino® pressure transducer (B) and Periflux® laser-Doppler flowmetre (C).
B. Epidemiological studies and survey of the long-term results of antireflux surgery

Methods of survey
EpC (Studies III-V)
The Centre for Epidemiology (EpC) at the Swedish National Board of Health and Welfare administers a register of all in-patient public hospital care in Sweden (126). This register, which is updated each year, became fully comprehensive in 1987. Data of all surgical procedures are publicly available while patient identification numbers are protected. The ICD-9 (WHO) classification of diagnoses is applied and operations are coded according to the Swedish Classification of Surgical Procedures.

Questionnaire to the heads of all surgical departments (Study III)
To validate the information obtained from EpC we mailed a questionnaire on antireflux surgery to the heads of all surgical departments in Sweden. The question was whether the department performed any antireflux surgery, and, if so, the number of open and laparoscopic procedures for 1995 and 1996. Pre-operative evaluation and indications for surgery were not addressed in this study.

Questionnaire to patients (Studies IV and V)
A questionnaire devised to identify typical symptoms of GORD and post-operative side effects of antireflux surgery was mailed to all patients included in the studies.
The questionnaire included items on heartburn, acid regurgitation, medical treatment, dysphagia, gas bloat, ability to belch and vomit, as well as an
overall estimate of satisfaction. We specifically asked about revision surgery and complaints that could be related to the scars. The usefulness of the questionnaire was validated on 136 patients before the study was undertaken (127).

**Study design**

**Study III**

Age, gender, county of residence for each patient, information regarding the numbers and the kind of antireflux procedures, the duration of hospital stay and the post-operative mortality rate were analysed for the period from 1987 to 1997 using data obtained by the EpC. We have compared the surgical activity in different health service regions (counties) and among different hospitals over the years. Fundoplication rates for each county are calculated and adjustments are made for variations in the population. Information from the questionnaire that was sent to heads of all surgical departments was compared with data obtained from EpC in order to validate the latter.

**Study IV**

Long-term outcome after laparoscopic and conventional open antireflux procedures were compared by administering a questionnaire to the patients 4 years after surgery. We hypothesised that the open and the laparoscopic techniques were equally effective in controlling symptoms and providing patient satisfaction. The success rate was estimated to be 85-95% (77). Sample sizes of approximately 180 patients were necessary to detect a difference of 10% in failure rate in a two-tailed test with a significance level of 5% and statistical power of 85%. The response rate was estimated to be between 80 and 90%.
The study period took place between 1995 and 1996. In an effort to have uniform study groups we selected those hospitals where more than 50 patients had been operated on by one of the techniques. Two random samples of approximately 230 patients in each group were thus identified for study purposes.

**Study V**

Long-term results after laparoscopic antireflux procedures performed at low- and high-volume hospitals were compared using a questionnaire 4 years after surgery. The study period was the same as in the previous study, i.e. 1995 and 1996.

We hypothesised that the long-term results were equally good for patients operated on at low- and high-volume hospitals. Calculation of sample size was similar to study IV. All 220 patients operated on at low-volume hospitals and a computerised random sampling of 225 patients operated on at high-volume hospitals was identified for study purposes.

**Definition of treatment failure (Studies IV and V)**

The main endpoints in Studies IV and V were treatment failure and patient satisfaction. Treatment failure was defined by the presence of one or more of three criteria:

- a new antireflux procedure had been required to control symptoms or to relieve side effects
- medication was taken at least once a week specifically to relieve heartburn or acid regurgitation
- patient dissatisfaction with the result of surgery
Patients and ethical considerations (Studies IV and V)

The study protocol was approved by the local ethics committee in science at Uppsala University. Permission to obtain the identification numbers and addresses was provided by the Centre for Epidemiology (EpC). None of the patients included in Studies IV and V were treated at the authors’ department. The questionnaires were treated anonymously and confidentially. The patients were also informed of their freedom to choose to participate in the study and that no financial compensation would be given. Non-responders received a second survey. Heads of those surgical departments that took part were informed about and approved of the study.
Statistical methods

Study I
A Two-way, Randomised Block design was performed for each outcome variable to determine if the mean outcomes of the four randomised treatments differed significantly from one another.
In addition, comparisons were made between the mean outcome averaged over the four randomised procedures, the mean outcome at baseline and the mean outcome for procedure “5/5.”
For treatment “15/15,” which was applied only for the four last animals, a purely descriptive comparison of the average outcomes was employed.

Study II
A multivariate repeated measures analysis of variance (MANOVA) was used, with the different settings of insufflation pressure serving as a within factor and PEEP serving as a between factor. For SaO₂, the standard analysis was inappropriate because of severe skewness of the data. Therefore, a repeated measures analysis of variance was performed on the ranks of the SaO₂ values, and the Wilcoxon rank sum test for two independent samples was subsequently used to compare the median SaO₂ values between the two groups.

Studies I and II: A residual analysis was performed to confirm that the underlying model assumptions were met by the data. P values of less than 0.05 were defined as significant. The Bonferroni correction was used to ensure that the overall Type 1 error rate did not exceed 0.05.
Study III

In Study III, simple descriptive methods were used, i.e. number, percent, proportion and median.

Studies IV and V

Comparison of questionnaire items between the groups was conducted using a logistic regression with sex, age, and body mass index (BMI) serving as the covariates. The Bonferroni correction was used to control the overall Type 1 error rate at 0.05. Comparisons of age, sex and BMI between the groups were conducted using t tests and the chi-squared test.
Results and discussion

Study I

Results

When a communicating pneumo-pleuro-peritoneum was established with CO₂ insufflation pressure of 10 mm Hg in anaesthetised pigs, the following major observations were noted:

- increased PCWP
- hypercarbia, respiratory acidosis and increased CO₂ elimination
- hypoxemia

The hypoxemia could be corrected and the acidosis considerably reduced if adequate PEEP was applied on both lungs (Figures 6 and 7). The blood gases were close to normal when PEEP in both lungs exceeded the CO₂ insufflation pressure. If there was a difference in PEEP between the lungs, there was a tendency to simultaneous decrease in C stat, ETCO₂ and VCO₂ in the lung with the lower PEEP, even in the presence of hypercarbia as measured by blood gas analysis. Haemodynamic outcomes were relatively stable.
Figure 6: Arterial oxygen saturation (SaO$_2$) at baseline and at different combinations of PEEP in right and left lung (dx/sin).

Figure 7: pH at baseline and at different combinations of PEEP in right and left lung (dx/sin).
Discussion
It is well known that CO$_2$ is absorbed transperitoneally during laparoscopy (128,129). The degree of hypercarbia and acidemia that is induced depends on CO$_2$ insufflation pressure, peritoneal area available for gas exchange and respiratory compensation (49). At an insufflation pressure of 10 mm Hg, the changes are usually moderate and are clinically well tolerated both in humans (49) and in pigs (130). With a communicating pneumo-pleuro-peritoneum, a larger surface area will be exposed. More CO$_2$ may be absorbed with a concomitant increase in hypercarbia and acidosis. With positive pressure in the pleural cavity, as in our model, a pneumothorax may further aggravate the condition because of collapse of lung parenchyma and impaired gas exchange. Shunting of blood in the collapsed lung parenchyma may result in hypoxemia and CO$_2$ retention (130,132). CO$_2$ is more soluble and crosses from the blood into the alveoli 25 times faster than oxygen (49). Impaired gas exchange is therefore first noted in reduced oxygenation rather than increasing hypercarbia, even in the presence of an abnormal amount of systemically dissolved CO$_2$. We observed a significant difference in \( \text{PaO}_2 \) between the four randomised treatments, but not in \( \text{PaCO}_2 \).

Tension pneumothorax refers to a pneumothorax characterised by an increased intra-pleural pressure that is caused by an opening through the pleura allowing air to pass in but not out. An increasing intra-thoracic extra-pulmonary pressure can cause the lung to collapse and even push the structures in mediastinum to the other side (mediastinal shift). In a strict sense the pneumothorax of our model is not a tension pneumothorax, but it has a positive intra-thoracic pressure and thus a tension-like pathophysiology may result.

It is unclear whether cardiovascular collapse observed during tension pneumothorax is secondary to a direct compressive effect on central venous structures with reduced preload to the heart, or secondary to grave hypoxemia.
that is caused by lung parenchymal collapse with shunting of desaturated blood, or a combination (49,131). In our study severe hypoxemia, hypercarbia and respiratory acidosis developed without significant changes in HR and MAP. This finding led us to conclude that hypoxemia is an early sign of impaired gas exchange in ventilated pigs with pneumothorax. This position is in accordance with the findings of Barton and colleagues in an experiment with progressive pneumothorax, where $\text{SaO}_2$ decreased immediately and continued to decline to levels below 50% before cardiovascular collapse (131).

We initially hypothesised that the optimal respiratory technique during laparoscopy with communicating unilateral pneumothorax would be differential lung ventilation with different PEEP on left and right lungs. On the side of the pneumothorax, we thought that PEEP had to equal or exceed the CO$_2$ insufflation pressure to avoid lung parenchymal collapse and poor oxygenation. To minimise harmful side effects we tried to keep a lower PEEP on the contra-lateral lung.

Our hypothesis, however, was not completely supported. To counterbalance the positive insufflation pressure it seemed correct to apply an equal or larger PEEP. However, this PEEP had to be applied to both lungs to avoid deterioration of gas exchange. No beneficial effects of differential application of PEEP were documented.
Study II

Results

- This study demonstrated that the establishment of positive pressure pneumo-pleuro-peritoneum resulted in immediate elevation of ICP. The magnitude of the increase in ICP was proportional to the increase in insufflation pressure (Figure 8).

- CPP decreased, but LDF remained unchanged (Figures 8 and 9). There were no obvious metabolic signs of cerebral ischaemia. However, arterial and venous jugular bulb desaturation developed unless PEEP was matched to counterbalance the insufflation pressure (Figure 10).

- Application of PEEP prevented arterial hypoxemia and hypercapnia; moreover, a less pronounced decrease in pH was observed (Figures 10 and 11).

- Changes in ICP, CPP, and cerebral oxygen extraction ratio did not differ significantly between the study groups. Hence, PEEP did not adversely affect ICP or cerebral circulation (Figure 8).

We did not succeed in obtaining reliable and reproducible measurements of PcO₂. The variation between initial baseline values in different animals and between baseline measurements at different times during the same experiment was pronounced and unsystematic, often yielding no measurement at all. The problem with the oxygen sensor of the Paratrend® probe has also been experienced in similar experiments in our laboratory (133). Nevertheless, because of regular blood sampling from the left jugular bulb catheter, we obtained measurements of saturation and partial pressure of oxygen in venous blood from the brain (SjvO₂ and PjvO₂). We could then calculate the cerebral
oxygen extraction ratio as the ratio of the arterial jugular bulb oxygen content difference to the arterial oxygen content $[(\text{CaO}_2 - \text{CjvO}_2)/\text{CaO}_2]$

The Laser-Doppler probe was found sensitive to adjustments in location. In five animals measurements of cortical blood flow were inaccessible because we were unable to establish stable baseline values.
Figure 8

ICP and CPP in control (-) and PEEP group (+)

Figure 9

Laser-Doppler flow (LDF) in control (-) and PEEP group (+)
Figure 10

SaO\textsubscript{2} and SjO\textsubscript{2} control (-) and PEEP group (+)

Figure 11

a-pH and c-pH in control (-) and PEEP group (+)
Discussion

In our study the increase of ICP was immediate and proportional to the increase in insufflation pressure. The difference in PaCO₂ between the control and the PEEP group was significant, but LDF remained at the same level and the elevation in ICP did not differ between the groups. These results verify the observations of Halvorsen and co-workers. In their study baseline ICP was 14 (±2) and increased to 30 (±5) mm Hg at 15 mm Hg pneumo-peritoneum. This increase was independent of changes in PaCO₂ and pH (54). It is also in accordance with the data from Schöb and his colleagues who tested different insufflation gases in pigs (134). The increase in ICP with increasing insufflation pressure has been described during laparoscopy in humans (135,136).

Although the increased ICP constitutes a sign of warning, in clinical practice the most important factor is whether the cerebral circulation is compromised. Specifically, brain tissue oxygenation must be ensured. Even a brief period of inadequate perfusion of brain tissue leads to intense production of lactic acid (metabolic acidosis) (137). In an experimental study of cardiopulmonary resuscitation five minutes of cardiac arrest resulted in c-pH of 6.3-6.6 though a-pH was not below 7.4 (133). In our study the acid-base buffering capacity of the brain was not exhausted. No cortical metabolic acidosis was detected because cortical oxygenation was probably sufficient to meet local demands.

Autoregulation of cerebrovascular resistance to blood flow can prevent large fluctuations in cerebral circulation despite large variations in systemic blood pressure (137). In the normal cerebrovascular bed cerebral blood flow can be maintained in the face of rising ICP until the difference between MAP and ICP falls to about 40 mm Hg (137-139). Moreover, because oxygen supply is usually superfluous and the cerebral extraction ratio is low, the brain can, during periods of compromised circulation, increase the oxygen extraction
Recent studies suggest that $S_jvO_2$ correlates better with cerebral oxygenation than CPP (140-143). Our study verified that cortical cerebral blood flow could be maintained despite a reduction in CPP. Nevertheless, in the control group (pneumo-pleuro-peritoneum without compensatory PEEP), $S_jvO_2$ was extremely low and the oxygen extraction ratio was close to its upper limit when insufflation pressures of 15 and 20 mm Hg were applied. Jugular venous oxygen saturation below 50% can be interpreted as a sign of global brain hypoxia (144), indicating that the compensatory mechanisms were nearly exhausted. PEEP enhanced arterial oxygenation and thereby could augment the oxygen supply to the brain.

This study was conducted on young and healthy pigs. However, one should be careful in interpreting the results and then applying them in clinical situations. Our patients are often elderly with cardiopulmonary impairment, a condition that renders them far more sensitive to an insult such as combined pneumo-pleuro-peritoneum. The study verifies that the acute problem of pneumothorax during ongoing laparoscopic surgery (i.e. fundoplication, cardiomyotomy, oesophageal resection and bariatric procedures) may be corrected by application of PEEP. PEEP may help to ensure good oxygenation, CO$_2$ elimination and avoidance of cerebral hypoxemia.

**Study III**

**Results**

A good correlation was found between data obtained from EpC and the answers to the questionnaire from the heads of the surgical departments that participated in the study. We concluded that the data in EpC were reliable. Therefore, data collected exclusively from EpC are used in the following analysis.
The increase in the annual number of antireflux procedures was almost threefold during the study period (Figure 12). In 1987, 456 antireflux procedures were performed. Ten years later, this figure had risen to 1,303. The fundoplication rate rose from an average of 5.5 to 12.3/100,000 inhabitants during a 10-year period.

The variation in operative volume among hospitals was also pronounced; we found that most hospitals operated on fewer than 15 patients during the study period.

The length of hospital stay has decreased for both open and laparoscopic procedures. Mean hospital stay was 12.2 days in 1987, whereas in 1997 it was 3.0 days for laparoscopic and 7.9 days for open surgery. Furthermore, we observed a large variation among hospitals regarding the length of hospital stay.

GORD was registered as the diagnosis in 270 procedures (43.9%) among those patients who had an antireflux procedure or a hiatal hernia repair carried out in 1987; 406 procedures (66.0%) were diagnosed as hiatal hernia. Thus, the diagnosis of hiatal hernia was more frequently adopted than GORD. Ten years later, 1,143 patients (84.4%) were given a diagnosis of reflux and 242 (17.8%) were classified as hiatal hernia. Only one (0.03%) laparoscopic antireflux procedure has been associated with a fatal outcome since its introduction in 1992.
Figure 12: Annual numbers of antireflux procedures in Sweden, 1987-1997.

Discussion

The annual numbers of surgical procedures performed to correct GORD and hiatus hernia have changed dramatically and inversely during the study period. The explanation is more likely a shift in nomenclature than an actual change in the frequencies of the different diseases.

The increase in the fundoplication rate started before the introduction of proton-pump inhibitors and continued even more pronounced during the following few years. The development of laparoscopic antireflux surgery did not alter the course of this increase. The present study shows that soon after its introduction the laparoscopic technique replaced the open procedure as the
preferred method. This change occurred before the proposed benefits of laparoscopy were clearly documented.

The length of hospital stay has also been considerably reduced during the study period for open surgery, from 12.2 to 7.9 days, on average, illustrating the problem with historical controls.

The fundoplication rates varied greatly among health service regions. However, there is no reason to believe that the prevalence of GORD is different (145). On the other hand, no one can define the most optimal or even a reasonable fundoplication rate. It might be that the often quoted annual number of 10 antireflux operations/100,000 (69) is far too low.

Study IV

Results

Failure and dissatisfaction were significantly more common in the laparoscopy group than in the laparotomy group. Treatment failure rates were 29.0% in the laparoscopy group and 14.6% in the laparotomy group (p<0.004). The dissatisfaction rates were 15.0 and 7.0% in the laparoscopy and laparotomy group, respectively (p<0.005). We could not recognise any item in which the patients receiving the open technique had an overall significantly worse outcome.

An estimated 19.5% of the patients in the laparoscopy group and 8.6% in the open group reported that they used medication at least once a week specifically to relieve heartburn or acid regurgitation (p<0.02). Most of them used medication every day, and in case of medication, 75% used PPI.

Gas bloat or flatulence was reported as the most bothersome abdominal complaint by 39.7% of all the patients. Only 2.1% (8 patients) considered
dysphagia as their most bothersome symptom, although 9.0% (33 patients) reported daily episodes of difficulties in swallowing food.

Discussion

In this study the high overall failure rate is primarily a result of the high proportion of patients who continue to use medication to relieve heartburn or who are dissatisfied. It is obvious that the definition of treatment failure has influenced the reported results. This is discussed in more detail in a later section (General Discussion). A more restrictive definition of failure will reduce the number of procedures that are classified as failures; however, there will still be a marked difference between the results after laparoscopic and open procedures.

The results in the laparoscopic group are worse than most of the literature suggests (72-74,78,79,146), but they are not extreme (43,147-149). It should also be noted that the results obtained from population-based studies, as ours, are often inferior to what is reported from selected specialised centres.

At a 2-year follow-up after laparoscopic fundoplication, Soper reported that 26% of the patients had symptoms suggestive of persisting gastro-oesophageal reflux (43). Anatomic failure of the procedure was documented in 7% and in 2.8% surgical revision was required. The incidence of redo after a primary laparoscopic approach is usually about 2-6% at short-term follow-up (11). Most remarkably, the group at Adelaide University noted 12.7% repeat operations in their 5-year follow-up of 178 consecutive laparoscopically operated patients (148). More than half of the surgical failures were due to intra-thoracal herniation. This complication is seldom reported after open surgery, but is frequently encountered after laparoscopic procedures (42,150). The design of the present study does not allow us to explore the findings at
redo procedures and thus we cannot determine whether intra-thoracal herniation is a usual cause for surgical failure in Sweden. There are no data available in the literature to suggest that the surgical failure rate is higher after laparoscopic fundoplication than after the open approach. In the present study revision surgery was reported in 5-6% in both groups.

The long learning curve of laparoscopic antireflux surgery may be a confounding factor (80-83). However, laparoscopic antireflux surgery had been performed for more than 3 years in Sweden and 950 procedures were accomplished before the study period (Study III). In addition, the patients were selected only from those hospitals with high activity in laparoscopic antireflux surgery. Even though this was an inclusion criteria of the study, it may also be a bias. An increasing incidence of antireflux surgery may tend to lower the threshold for accepting patients for surgery (78,90,151). In their enthusiasm over the new approach, surgeons undertaking laparoscopic procedures may have operated on patients with less convincing symptoms of GORD. In the 1990s, it was a trend to focus more on technical skills in laparoscopic handicraft than on the experience of antireflux surgery. Thus, laparoscopic surgeons at many hospitals took over antireflux surgery from specialised thoracic and oesophageal surgeons (91). In the beginning, surgeons may have found it difficult to accomplish an equivalent antireflux procedure by laparoscopy as in open surgery (152). “Minor” adjustments of the antireflux procedure could have been made, i.e. omission of hiatal repair and insufficient mobilisation of the gastric fundus. If so, this may also have had an impact on outcome after laparoscopic antireflux surgery.

Dysphagia is one of the most troublesome complications of antireflux surgery. However, there is no standardised and uniformly applied scoring system and the incidence of persisting dysphagia, as recorded in the literature, is extremely variable. In several reports laparoscopic fundoplication has been associated with obstructive complaints such as dysphagia and bloating.
These consequences are believed to be associated with the lack of tactile feedback and other factors inherent in the laparoscopic technique (77,153). In a prospective, randomised multicentre trial from the Netherlands (85), 7 out of 57 patients had persistent dysphagia at a 3-month follow-up after laparoscopic fundoplication. The dysphagia was severe enough to require intervention. By comparison, none of the 46 patients having open surgery experienced dysphagia of this severity. This substantial difference led to discontinuation of the trial on ethical grounds. Others have not reported such frequent and severe dysphagia after undergoing laparoscopic surgery. This observation may be an indication of the impact the individual surgeons have on the occurrence of dysphagia rather than the specific technique used. In the present study there was no significant difference in the incidence of dysphagia or gas bloat among the study groups. Furthermore, severe dysphagia was seldom encountered. An incidence of approximately 2% of this problem is exactly the same as Bessell reported in a study on 846 consecutively laparoscopically operated patients (154). In fact, occurrence of dysphagia among the patients who responded to the questionnaire was comparable to that found in a normal population (145) and much less common than that found among patients with GORD (155,156).

Our study does not support the presumption that laparoscopic antireflux surgery is to be preferred to open procedure. It does suggest, however, that patients do not derive significant benefit from having the antireflux procedure made laparoscopically.
Study V

Results

Treatment failures were more common among patients operated on at high-volume hospitals than those operated on at low-volume hospitals. Estimated treatment failure rates after adjusting for age, sex and BMI were 29.0 and 19.7% at high- and low-volume hospitals, respectively ($p<0.0314$). However, because of the number of items that was tested, the $p$ value for the difference in treatment failure rates was not statistically significant at an overall 0.05 level (Bonferroni correction).

Nevertheless, with each question regarding the effectiveness of the procedure to suppress reflux, the patients operated on at low-volume hospitals tended to have a more favourable outcome. They experienced heartburn and acid regurgitation less often, needed less medication to relieve such complaints and revision surgery was undertaken less frequently among these patients.

Gas bloat and flatulence were considered as the most bothersome abdominal complaints by 46.8% of all patients. Although 7.8% (32 of 408 patients) reported daily episodes of difficulties in swallowing, only 2.7% (eleven patients) identified dysphagia as their most troublesome post-operative symptom. Further, among patients who reported daily episodes of difficulty in swallowing, gas bloat and flatulence were more often considered as their worst symptom.

We could adjust for three confounding factors: age, gender and BMI; however, the difference between the groups was not significant for any of these variables. Neither age nor gender had a significant influence on outcomes of the different items. Yet, BMI seemed to have an impact on outcome. As BMI increased, the more satisfied was the patient with his or her experience after
the operation. The correlation was statistically significant (p<0.0006), but the magnitude of the correlation was small, with a Spearman correlation coefficient of $-0.14$. In addition, BMI was almost identical in the high- and low-volume groups.

The results of Studies IV and V are summarised in Tables 1 and 2.
Table 1: The study groups and reasons for exclusion. * The high-volume laparoscopic group is compared with the open procedure group.

<table>
<thead>
<tr>
<th></th>
<th>Open procedure</th>
<th>Laparoscopic procedure</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low-volume</td>
<td>High-volume</td>
</tr>
<tr>
<td>Patients identified in</td>
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<tr>
<td>Died</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Moved, could not be</td>
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<td>5</td>
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<td></td>
</tr>
<tr>
<td>Excluded</td>
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<td>1</td>
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<td>previous surgery</td>
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</tr>
<tr>
<td>not able to answer</td>
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<td>1</td>
<td>1</td>
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<td>217</td>
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<tr>
<td>Response rate</td>
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<td>Women</td>
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<tr>
<td>Mean age</td>
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<tr>
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<td>26.4</td>
<td>26.3</td>
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<td>Median follow-up</td>
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Table 2: Results of the patient questionnaire. For details, refer to manuscripts IV and V.
* The high-volume laparoscopic group is compared with the open procedure group.

<table>
<thead>
<tr>
<th></th>
<th>Open procedure (n = 185) %</th>
<th>Laparoscopic procedure</th>
<th>P value*</th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td>Low-volume (n = 208) %</td>
<td>High-volume (n = 200) %</td>
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<td>A. Effectiveness of the antireflux procedure</td>
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<td></td>
</tr>
<tr>
<td>No improvement</td>
<td>2.0</td>
<td>5.3</td>
<td>6.0</td>
</tr>
<tr>
<td>Revision surgery</td>
<td>5.4</td>
<td>2.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Acid regurgitation</td>
<td>3.7</td>
<td>5.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Heartburn</td>
<td>6.0</td>
<td>6.8</td>
<td>11.0</td>
</tr>
<tr>
<td>Medication</td>
<td>8.7</td>
<td>11.1</td>
<td>19.5*</td>
</tr>
<tr>
<td>Failure</td>
<td>14.6</td>
<td>19.7</td>
<td>29.0*</td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>7.0</td>
<td>13.9</td>
<td>15.0*</td>
</tr>
<tr>
<td>B: Procedure related side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulties in swallowing food &gt;once a day (&gt;5 times a day)</td>
<td>9.8 (1.6)</td>
<td>7.7 (1.4)</td>
<td>8.0 (2.0)</td>
</tr>
<tr>
<td>Difficult or unable to belch</td>
<td>33.1</td>
<td>46.0</td>
<td>29.0</td>
</tr>
<tr>
<td>Gas bloat, flatulence (daily complaints)</td>
<td>27.7</td>
<td>39.1</td>
<td>31.8</td>
</tr>
<tr>
<td>Suspicion of incisional hernia</td>
<td>4.0</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Would recommend the operation</td>
<td>92</td>
<td>90</td>
<td>92</td>
</tr>
</tbody>
</table>
Discussion:
Because of the great variation in operating volume of laparoscopic antireflux surgery among hospitals (Study III), we considered Sweden well suited for studying the impact of operative volume on outcome. To our surprise, the results suggest that procedures performed at high-volume hospitals were less successful than procedures done at low-volume hospitals. Different explanations could help to account for these results. For instance, an increasing incidence of antireflux surgery may tend to lower the threshold for accepting patients for surgery, as also was discussed in the previous section. Furthermore, whereas university and large, county hospitals are educational institutions with a high number of surgical trainees, the staff at the smaller, regional hospitals doing fewer procedures may be more experienced. In a recent report from the USA (VA National Surgical Quality Improvement Program) it was concluded after assessing the outcomes of eight commonly performed operations that volume of surgery cannot be used as an alternative measure of quality in surgical care (157). Moreover, outstanding results can also be obtained by regional hospitals, despite a low-volume of patients (158). Nevertheless, a larger hospital volume can provide excellent facilities for specialisation and refinements in every particular step of treatment and patient care (79,159). It should be a challenge for units with an interest in laparoscopic antireflux surgery to demonstrate that the potential advantage of high-volume is also reflected in better outcome.
When considering the results of the present study, it should be kept in mind that there are some methodological weaknesses. For instance, this study was not randomised. However, it is unlikely that patients would submit themselves to randomisation between high- and low-volume hospitals. It may even be argued that, despite the relatively large difference between the median volumes of the hospital groups, neither of the study groups were frankly high-volume hospital groups in an international context. Other factors
may influence the long-term results: in particular, the indication for surgery, the selection of different techniques, differences in hospital routines and the experience of the surgeon. These circumstances could not be adjusted for by other means than a large sample size. Furthermore, the result of a questionnaire may be different from that obtained by clinical examination on the same issue. It is then difficult to predict which one is more accurate. Moreover, because the questionnaires in the present study were handled anonymously and confidentially and did not involve any of the authors’ patients, there is no danger of the kind of bias that can result when researchers query their own patients.

Inability to belch or vomit, gas bloat and increased flatulence are often perceived as surgical side effects but are difficult to evaluate (93), especially when a pre-operative comparison is lacking as in our study. Interestingly, 47% of the patients regarded gas bloat or increased flatulence as their most bothersome post-operative symptom. Among the dissatisfied patients 29% complained above all of gas bloat and increased flatulence. Surgical side effects are therefore not to be underestimated when indications for surgery and different therapeutic options are considered.

We have tried to assess the effectiveness of laparoscopic antireflux surgery. If our results mirror the reality of the situation, laparoscopic antireflux surgery is questionable as the method of choice for treatment of serious GORD. The substantial increase in the incidence of antireflux surgery seen in Sweden during the past few years may not have optimised the treatment of GORD patients. Medical maintenance therapy with PPI could perhaps be the better option for some patients and open surgery may have been better than laparoscopic for others. Results of laparoscopy may also improve if the indications for antireflux surgery are restricted. A prospective, randomised
study to identify different sub-groups of patients who are more likely to benefit from laparoscopic surgery than PPI is recommended.
General discussion

The uncritical acceptance of laparoscopic technique among patients and surgeons, enthusiastically supported in mass media, made possible a revolution in surgical practice within less than a decade. The quick and wide acceptance occurred despite the fact that it was weakly supported by solid data (10). The technical equipment of this approach may be ultra-modern, but the way it was implemented violated traditional scientific principles. At the time when this approach already was regarded as the method of choice, minimal access surgery was not modern medicine in the meaning that it was not evidence-based (160).

Laparoscopy had been applied in gynaecology for decades. Moreover, substantial knowledge had been collected from experimental and clinical studies regarding the effect of positive pressure pneumoperitoneum. However, communicating pneumo-pleuro-peritoneum represents a more complicated and challenging condition. The experimental work of this thesis was an attempt to explore that specific pathophysiologic condition in light of the new surgical approach applied during dissection in the diaphragmatic hiatus.

In pigs we have demonstrated how devastating a combined thoraco-laparoscopic approach can be for gas exchange. PEEP may then help to optimise respiratory function. The application of PEEP was found to improve gas exchange and, more importantly, hypoxemia could be avoided. Yet, no beneficial effects of differential lung application of PEEP were documented. To achieve optimal ventilation application of PEEP to both lungs had to counterbalance the insufflation pressure.

The transmission of elevated pressure intra-cranially during positive pressure pneumo-pleuro-peritoneum is a potential danger. However, application of
PEEP does not seem to increase ICP further; nor does it seem to adversely affect cerebral circulation. Because PEEP can help to ensure good systemic oxygenation and CO₂ elimination, it may also help to avoid cerebral hypoxemia.

Pneumothorax, which is a potential complication to laparoscopic surgery in the upper abdomen (i.e. antireflux procedures, operations for large hiatal hernia and cardiomymotomies) may be much more frequent than realised (16,45,161). Many instances of pneumothorax are subclinical (16). Despite an endoscopical and radiological verified pneumothorax, the clinical symptoms are often moderate with an increase in airway pressure and ETCO₂, as well as reduced lung compliance. If more pronounced symptoms develop, hypoxemia will also be present (16,44,47,132). Joris et al. have demonstrated the therapeutic value of the application of PEEP in patients with pneumoperitoneum and communicating pneumothorax. What this implies is that the operative procedure can often be continued without performing tube thoracostomy or conversion to open surgery (16).

Before applying PEEP, it is necessary to assess the nature of the pneumothorax and consider differential diagnosis, i.e. endobronchial intubation, obstruction of the tracheal tube or a bronchus and bronchospasm. Fiberoptic bronchoscopy and x-ray of the chest can be helpful but such examinations are often not readily available. Auscultation can reveal unilateral decreased breath sounds, and combined with increased airway resistance, elevated ETCO₂ and an abrupt decrease in compliance, the diagnose is fairly reliable. Moreover, the surgical procedure itself can give an indication of the reason of acute respiratory insufficiency. One should also keep in mind that the lesion of pleura can operate as a “check-valve,” whereby tension pneumothorax can develop (162,163). This is a potentially life-threatening complication and if impairment of cardiopulmonary functions is encountered, the pneumothorax should immediately be evacuated. Simple
desufflation of the abdomen cannot be relied upon in tension pneumothorax; instead, managing the patient with a chest drain is indicated.

If pneumothorax is encountered during such standard laparoscopic procedures as fundoplication and hypoxia develops, the first step recommended is an increase of oxygen concentration in inspired air, followed by increased ventilation and application of PEEP. The results from Study I indicate that optimal PEEP is equal to or higher than the abdominal insufflation pressure. The insufflation pressure should be kept as low as possible because the negative effects on respiratory function tend to worsen with increasing pressure (162,164). A tube thoracostomy during the operation may interfere with maintenance of pneumoperitoneum and hence make it difficult to expose the surgical field. However, it is paramount that if there are signs of cardiopulmonary compromise, laparoscopy should be discontinued. After the operation, when the abdomen has been desufflated, any residual gas will be quickly absorbed and the pneumothorax will disappear. Therefore, chest drain is seldom indicated. In any event, a chest X-ray should be routinely performed post-operatively to rule out any suspicion of tension pneumothorax.

Diagnostic laparoscopy in trauma patients has proven successful in detection of occult diaphragmatic lacerations, particular in patients with lower chest stab wounds (165,166). Such injuries are notoriously difficult to detect by chest roentenography, computed tomography or diagnostic lavage. Wiedeman et al. have demonstrated that tension pneumothorax may develop when pneumoperitoneum is created in the face of a diaphragmatic injury and that the risk of its development increases with increasing insufflation pressure (162). Hypoxemia provided an early clue of the pneumothorax, even when chest X-ray was still normal. The lines of action given above can be applied during short diagnostic procedures, but if a diaphragmatic lesion were
diagnosed, we would not recommend the repair to be done laparoscopically because of the substantial risk of tension pneumothorax. Further, the lesion is seldom encountered and a conventional method is to be preferred.

In major oesophageal surgery, i.e. oesophageal resection, one is confronted with longer operating times and more extended dissection in the mediastinum. Harmful effects of excessive PEEP applied for too many hours may predispose for overdistention of lung parenchyma with post-operative inflammatory reaction and atelectases as a result. Moreover, the patients are often elderly with cardiopulmonary impairment, rendering them far more sensitive to an insult such as a combined pneumo-pleuro-peritoneum. At present, we do not think that a thoraco-laparoscopic approach is to be recommended for oesophageal resection.

This thesis has demonstrated that the advent of the laparoscopic technique had a profound impact on the practice of antireflux surgery. However, there was a substantial increase in the annual number of antireflux procedures even before the introduction of the laparoscopic technique. The threefold increase of the incidence of antireflux surgery recorded during the past decade therefore cannot solely be explained by the advent of the minimal access technique. Nevertheless, a clear shift in the preferred methodology took place. This change was not scientifically supported at the time of the transition and, surprisingly, it is still not supported today. As was demonstrated, laparoscopy might even be an inferior approach in some patients. However, it is reasonable to assume that laparoscopic technique can yield equally good results as open surgery despite our failure to confirm that in this series of studies. Controlled prospective, randomised studies with adequate patient enrolment to secure statistical power are needed to settle this issue conclusively.
The development of the minimal access technique has stimulated numerous innovations of new surgical instruments that can also be utilised in open surgery, i.e. the Harmonic scalpel technology. In combination with advancements in the treatment of post-operative pain, this development has even changed the practice of conventional open surgery. However, before new trials are undertaken, it is important that properly defined measures to evaluate short- and long-term outcome are agreed upon.

For instance, one problem is that the criteria to evaluate success or failure are not well defined (90,93). To equalise reflux control with success rate can give a false impression (91,92). In a number of reports it is not stated how many patients are still on antireflux medication (43,72-74,78,95) but if reported, continuous medical therapy in about 6-8% is usual (77,91,167). There is no agreement today whether continued use of medication is a sign of failure, as in this thesis (Studies IV and V), or not. Even patients with objectively demonstrated anatomical failure of the fundic wrap often do well on PPI (43).

The definition of failure in the present studies was rather demanding, but was defined in order to achieve the goals of antireflux surgery. For a disease in which an alternative and often similarly effective medical therapy exists (168), one has to aim at optimal surgical results and patient satisfaction is therefore crucial. After all, most patients who submit themselves to surgery do it because of exacerbating symptoms and not because of objective signs, i.e. endoscopic findings or results from 24-hour pH monitoring. The Genval panel of experts accepted the statement, “reflux disease is likely present when heartburn occurs on two or more days a week on the basis of the negative impact of this symptom frequency on the health related well being (quality of life)” (169). It is therefore logical that reasonable symptom control without the need of frequent medication should be an indicator for surgical success or failure. Although we are aware that indiscriminate use of acid suppression therapy does not necessarily represent a technically failed antireflux
procedure, we still regard it as a treatment failure because cessation of medication to suppress the symptoms of GORD is an important aim of surgery. The questionnaire applied in Studies IV and V was also designed to detect medication used specifically to suppress reflux symptoms.

Moreover, because the questionnaires were handled anonymously and confidentially and did not involve any of the authors’ patients, there was no danger for the kind of bias that can result when researchers query their own patients.

This thesis did not study the indications for antireflux surgery. The treatment of severe GORD is unique because medical maintenance therapy with PPI and antireflux surgery are similarly effective options for most patients. Surgical indications that were sound before the advent of PPI do not necessarily stand for trial today. Likewise, the apparently attractiveness of the laparoscopic approach may influence the patients and doctors’ choice of treatment. In this respect, we had better have solid knowledge for our recommendations, rather than merely relying on presumptions. Therefore, a large prospective, randomised study on the optimal treatment of severe GORD should ideally compare maintenance therapy with PPI in adequate doses to surgical treatment with open or laparoscopic procedure. Such a study should be of national interests; the pharmaceutical industry or medical suppliers should not fund such a study because the treatment of GORD has strong implications for the national health economy. Except for the rarely occurring syndrome of Zollinger-Ellison, GORD is the only commonly accepted indication for maintenance PPI therapy (FASS). Every year the Swedish people buy PPI for approximately one hundred million dollars (170). At the same time, approximately 1,300 patients will be operated on at a cost of 4,000-7,000 dollars per patient, including sick leave (171).
The argument in favour of surgery has been that it offers a definitive treatment. However, as this thesis has proven, this is a presupposition that has not been verified. Many patients continue to use antisecretory medication regularly despite surgery. Furthermore, patients often complain of what they believe to be side effects of the surgical treatment. In contrast, patients who never have had the opportunity to discuss different treatment options and chosen to continue with maintenance therapy may regret they never have been offered surgery.

A study that compares outcome of medical and surgical treatments will of course demand close collaboration between surgeons and internists. That may be as challenging as the problem of funding. The patients will benefit in the long term when both surgeons and internists can agree upon the treatment. Depending on what speciality the patients’ doctor happens to promote, the indications for different therapeutic options should not differ that greatly (9,11,90,172).

Generally, the laparoscopic approach is also appealing because it offers a completely new “costume” to old surgical solutions. In particular, younger surgeons may feel attracted by new technology because it is easy for them to adopt and in a single, giant leap they may suddenly surpass their “master.” The ”master,” on the other hand, may feel a regained youthful vigour when he or she is still able to cope with the new trend. Yes, the fairy tale of HC Andersen, “The Emperors new cloths” is worth remembering. Why is it that new surgical techniques can move from “innovations” to widespread use on the basis of little more than intuition (10,14,173)?

The laparoscopic approach is a major complement of the surgical technique. There is no reason to deny that fact, but in terms of patient outcome and overall management of abdominal disease, it has been a small advance relative to the huge financial investments (10). We need to determine when it should be used and for whom it would benefit most.
When confronted in the future with new therapeutic options, medical societies, community health care systems and legal authorities should make a common effort to guarantee that the evaluation and introduction take place with maintained quality control. Before a new drug is accepted for legal prescription, it is scrutinised through long and cumbersome experimental and clinical evaluation. Similarly, there should be a more demanding attitude toward general implementation of new surgical methods in routine hospital care. The instrument manufacturers should not be allowed to have any consequential influence on that process. At an early stage, new techniques have to undergo clinical testing, and a long time is often needed for follow-up before a complete picture of risks, side effects and outcomes are known. It should not be acceptable to let the individual surgeon determine the utility of new surgical techniques. It is more effective and honest if data on the usefulness of the techniques were collected systematically and collectively. A national consulting board for research and supervision of the implementation of new surgical methods would be welcomed.
Conclusions

- During laparoscopy, pneumothorax may induce deleterious effects on the respiratory function.
- Application of PEEP may help to ensure good oxygenation and CO₂ elimination when accidental pneumothorax is encountered during laparoscopy (pneumoperitoneum). PEEP did not adversely affect ICP or cerebral circulation.
- To achieve optimal ventilation the PEEP applied to both lungs has to counterbalance the insufflation pressure. No benefit of differential lung ventilation was encountered.

- Surgical treatment for GORD has increased threefold in 1997 as compared with 1987.
- The laparoscopic approach has replaced the open technique as the method of choice in antireflux surgery.
- In comparison with open surgery, patients do not seem to derive significant long-term benefits from having the antireflux procedure done laparoscopically.
- Better results after laparoscopic surgery, particularly at hospitals with larger operating volumes, have to be demonstrated before the method can be recommended as routine treatment for severe GORD.
- We strongly recommend carrying out a randomised controlled trial between maintenance treatment with adequate doses of PPI and conventional open or laparoscopic techniques.
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86


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