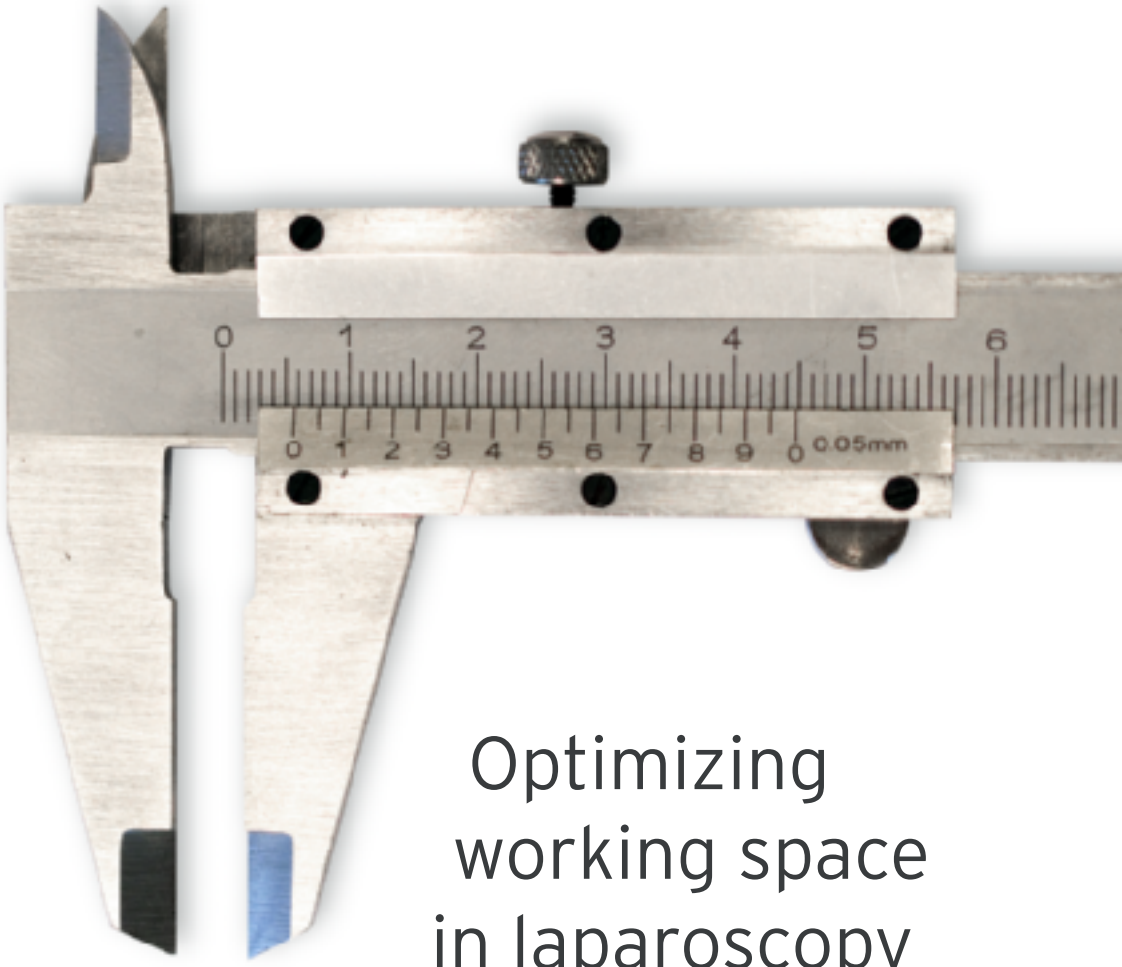
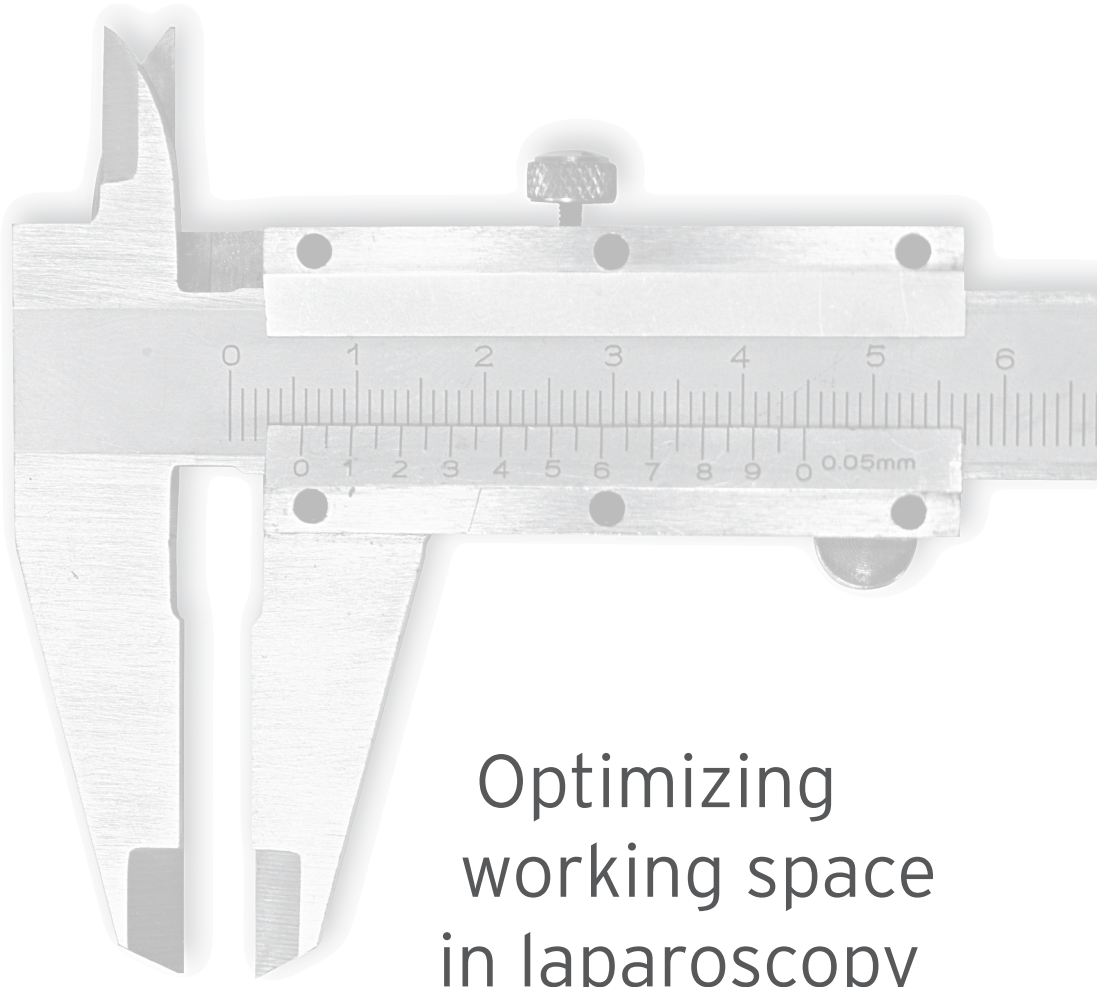


Optimizing working space in laparoscopy

Studies in a porcine model

John Vlot



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Optimizing Working Space in Laparoscopy
Studies in a porcine model

Het optimaliseren van laparoscopische werkruimte
Studies in een varkensmodel

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. H.A.P. Pols

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Overige leden: Prof.dr. J.F. Lange
Prof.dr. R.J. Stolker
Prof.dr. B.M. Ure

CONTENTS

PREFACE

As far back in time as Hippocrates (460-375 BC), interest in studying the inside of the human body existed. Lighting and optics had to evolve to enable adequate visualization. In 1805 Philippe Bozzini used light from a wax candle to look into the bladder and rectum [1]. Bruck, a dentist, was the first to use an electrically overheated platinum wire as a light source. In 1879 Max Nitze, a urologist, added cooling by water circulation and a lens system to create the first usable modern endoscope.

Georg Kelling performed the first recorded laparoscopy in a dog in 1901 using pneumoperitoneum with filtered air. At about the same time Hans Christian Jacobeaus published the first report of what he called "laparoscopy" in humans. The insufflator was invented in 1921 by Otto Goetze. Carbon dioxide (CO_2) pneumoperitoneum was introduced by Richard Zollikofer in 1924. In present-day endoscopic surgery, CO_2 insufflation has become commonplace as a way of creating working space.

The transition from diagnostic to operative laparoscopy started in 1933 with laparoscopic adhesiolysis using electrocautery by Fervers, a gynecologist.

In 1952 Harold Hopkins introduced the rod-lens sytem. Karl Storz in 1960 added a cold light source to the armamentarium. Bipolar coagulation, clips and improving optics and instruments allowed ever increasing complexity of laparoscopic surgery. In 1986 CCD-technology started video-laparoscopy using monitors leading to the first laparoscopic cholecystectomy in 1987 by Philippe Mouret .

The first case of pediatric laparoscopy was published by Stephen Gans in 1971 [2]. Also in 1971, Izabella Klimkovich reported the first pediatric thoracoscopic procedures [3].

Nowadays, minimal access surgery has become the standard approach for many disorders that were traditionally managed by laparotomy or thoracotomy [4, 5]. The problems pediatric endoscopic surgeons are faced with are different from those encountered by endoscopic surgeons dealing with adult patients. Pathology often differs, e.g. gastrointestinal tract atresias, requiring procedures specifically devised for neonates. But even when pathology is the same, e.g. gastrointestinal reflux in an older child, the smaller size of the patient requires adaptation of the techniques used in adults.

Pediatric patients are smaller, limiting working space for surgery. Also, physiologic reactions to surgical trauma and CO_2 insufflation differ from those in adults [6-9]. This poses major challenges in minimal access surgery for pediatric surgeons and pediatric anesthesiologists.

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OUTLINE OF THE THESIS

In **chapter 1**, the physiologic reactions to insufflation of CO_2 into the abdominal cavity and the strategies to overcome the negative side effects this induces are reviewed. Special attention is paid to factors that can be influenced to increase working space in laparoscopy whilst minimizing side-effects. Objective assessment of working-space dimensions is recognized as a problem in clinical research. In an experimental animal model however, this can be achieved with (computed) tomography.

In **chapter 2**, the effect of CO_2 insufflation pressure on working-space dimensions (linear working-space distances and working-space volume) is measured in 20 kg pigs using computed tomography (CT) under a strictly protocolized anesthesiologic regime with constant cardiorespiratory monitoring.

In **chapter 3**, the outcome of a national survey amongst Dutch laparoscopic surgeons researching the perceived benefits and indications for mechanical bowel preparation (MBP) prior to laparoscopic colorectal surgery is presented.

In **chapter 4**, the effect of MBP on working space is measured in a porcine laparoscopy model.

In **chapter 5**, the effect of pre-stretching of the abdominal wall on working space is measured in a porcine laparoscopy model.

In **chapter 6**, the effect of neuromuscular blockade (NMB) on working space is measured in a porcine laparoscopy model.

In **chapter 7**, the effect of CO_2 pneumoperitoneum pressure, pre-stretching of the abdominal wall and NMB is measured in 6 kg pigs.

In **chapter 8**, the results presented in this thesis are contemplated. Recommendations are made based on the review of literature concerning laparoscopic working space and on the experimental findings from this thesis. Plans for future research are presented.

Chapter 9 summarizes this thesis in English and in Dutch.

CHAPTER 1

How can working space in laparoscopic surgery be optimized?

A REVIEW OF LITERATURE

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ABSTRACT

Aims

Adequate working space is essential for safe and effective laparoscopic surgery. However, the factors that determine working space have not been sufficiently studied. Working space can be very limited, especially in children. A literature review was undertaken to search for factors that can be influenced to increase working space in laparoscopy.

Methods

MEDLINE and reference lists from relevant articles were searched. The search strategy used the following MeSH index terms: Laparoscopy [adverse effects, complications], Artificial Pneumoperitoneum [adverse reactions, complications], Anesthesia [drug effects], Hemodynamics, Artificial Respiration, Hypercapnia, Hypothermia, Physiological Stress, Elective Surgical Procedures [adverse effects], Neuromuscular Blockade, Cathartics and Patient Positioning. Additionally, "working space" and equivalent terms like "surgical site exposure" and "surgical conditions" were included in the search.

Results

Many factors affect laparoscopic working space. Some of these e.g. body size, cannot be influenced. Other factors such as intra-abdominal carbon dioxide (CO_2) pressure, bowel content, positioning of the patient, and muscle tone can be influenced to increase working space. Many factors are co-responsible for muscle tone e.g. depth of anesthesia, the use of neuromuscular blocking agents and loco-regional anesthesia. Also different anesthetic drugs may either increase (e.g.opioids) or decrease (e.g. propofol) muscle tone. Unfortunately, an accurate method to assess muscle tone is lacking. Most attention in literature has focused on the unwanted effects of CO_2 pneumoperitoneum on the body and on strategies to minimize these. Much less attention has been paid to working space itself. This may be related to the absence of a reliable clinical method for measuring working space. Most studies have used surgeon's satisfaction, subjective assessment of surgical conditions, or duration of the operation as primary outcome.

Conclusions

Working space in laparoscopic surgery, although essential, has not been adequately researched. Working space is especially limited in small children. Here, small gains in working space could be of major benefit. Research on CO_2 pneumoperitoneum has mainly concentrated on its side effects and on strategies to avoid these. Working space itself has received much less attention. Moreover, most research on working space during laparoscopic surgery has used subjective or surrogate measures as primary outcome. Assessment of changes in working space asks for a more precise, quantitative method

of evaluation. In experimental work this can be computed tomography. This method is of course not applicable in endoscopic surgery in humans. However, 3D camera technology may be able to provide similar distance and volume information in the near future.

INTRODUCTION

Since the advent of endoscopic surgery around 1990, many open operations have been replaced by minimal access endoscopic procedures [1]. This evolution has also taken place in pediatric surgery [2]. In traditional open surgery, access to the region of interest in body cavities is obtained through sizable incisions in the body wall and retraction of the wound edges. Through this access, structures are manipulated not only with instruments, but also by the gloved hands and fingers of the surgeon with or without interposition of gauzes. Trauma is caused to both the body wall and to intra-cavitary structures. Trauma to the body wall is caused by the incision, by retraction of the wound edges, by dehydration and local hypothermia, and by exposing the wound to ambient air [3-5]. Long lasting effects are scar formation with cosmetic consequences, paresthesia and chronic pain as a result of trauma to sensory nerves, and muscle weakness as a result of trauma to motor nerves. The longer the incision, the higher the likelihood of wound-related problems such as infection and incisional hernia [6, 7]. Likewise, trauma to the intra-cavitary structures is caused by local dehydration and hypothermia, by exposure to ambient air, and by manipulation. The use of gauzes traumatizes the parietal and visceral peritoneum, as demonstrated by the appearance of petechiae intraoperatively. Both trauma to the body wall and local tissues lead to adhesions and related complications such as volvulus and obstruction [8-10]. By evaporation, systemic dehydration and hypothermia may occur. Open surgical procedures are followed by profound changes in endocrine metabolic function and various host defense mechanisms, impaired pulmonary function, and hypoxemia. These physiologic changes are supposed to be involved in the pathogenesis of postoperative morbidity [11].

In endoscopic surgery access to the region of interest is gained through relatively small incisions and separation of tissue layers either by mechanical lifters or by insufflation of a gas under pressure. Endoscopic surgery is generally believed to cause less trauma than does open surgery, and many publications proclaim its advantages such as less postoperative discomfort, faster mobilization, earlier resumption of oral intake, lower incidence of postoperative respiratory complications, improved cosmesis and shorter hospital stay [12-17]. Many of these claims have remained difficult to prove [18]. Endoscopic surgery, when compared with similar open surgery, has no different effects on classic endocrine metabolic responses but may slightly reduce inflammatory responses and various immune functions, although the data are not consistent [3, 18-

30]. In contrast, most data show improvement of postoperative pulmonary function and less hypoxemia with endoscopic operations [11]. Because wound tension is proportional to the square of the incision-length, conventional incisions are subject to more total tension than any combination of trocar incisions of equal total length [31]. Endoscopic surgery seems also to induce fewer adhesions [32-34]. Despite the limited hard evidence, there is a general belief that endoscopic surgery is minimally invasive – and the term minimally invasive surgery (MIS) is therefore widely used. As minimal invasiveness has not been firmly proven, we prefer to use the term minimal access surgery (MAS), which emphasizes the smaller body wall incisions to gain access to the surgical region of interest.

Unfortunately endoscopic surgery has several disadvantages as well. In current general practice, the view is mostly two-dimensional. There is less tactile feedback, the operation takes longer, the learning curve is more pronounced, and the equipment is expensive [35-39]. In addition, the pressurized carbon-dioxide (CO_2) environment used to create working space has negative effects. Physiology varies nonlinearly with body mass, which makes some of these effects more prominent in children, such as the effects of abdominal CO_2 insufflation on the cerebral, respiratory, hemodynamic and renal system [40, 41]. Size of the patient is a prominent distinguishing factor between endoscopic surgery in children and adults. Laparoscopic working space varies with the cube (third power) of body size [41].

Although abdominal wall lifting results in fewer pathophysiologic changes, it has no clinical advantages above a low pressure CO_2 pneumoperitoneum [42]. Moreover endoscopic surgery using abdominal wall lifting is more difficult for the surgeon [18]. As most MAS is performed in a pressurized CO_2 environment we will consider working space in this context only. Many factors influence the dimensions of laparoscopic working space, but key factors are: size of the patient, CO_2 pneumoperitoneum pressure, and depth of anesthesia (table 1).

Most clinical and experimental research has focused on the side effects of the CO_2 pneumoperitoneum and on strategies to avoid these, but not on working space itself. Hence the question arises: How can working space in (pediatric) laparoscopic surgery be optimized?

In section I of this article, the known pathophysiologic sequelae of CO_2 insufflation are reviewed. Section II reviews literature on strategies to minimize the negative side-effects of CO_2 insufflation. Section III focuses on working space during laparoscopic surgery, how it is determined and how it can be influenced.

Table 1. Factors determining laparoscopic working space

Patient factors	
Key factor	Age/size of the patient
Other factors	Body wall thickness (obesity)
	Body habitus e.g. low lying costal arch, scoliosis
	Organomegaly and space occupying lesions
	Bowel content
	Muscular weakness or rigidity (cerebral palsy)
Pneumoperitoneum factors	
Key factor	Pressure
Other factors	Patient positioning
Anesthesiologic factors	
Key factor	Depth of anesthesia
Other factors	Neuromuscular blocking agents
	Drugs affecting muscle tone
	Opioids ↑
	Propofol ↓
	Ketamine ↑
	Nitrous oxide as inhalation gas (bowel distension)
	Locoregional anesthesia (decreased muscle tone)
	Artificial ventilation
	Respiratory rate
	Minute volume
	PEEP
	(Laryngeal) mask ventilation/endotracheal tube leakage
Technical factors	
Key factors	Intra-abdominal trocar length
	Optical system and instruments size

METHODS

MEDLINE and reference lists from relevant articles were searched. The search strategy used the following MeSH index terms: Laparoscopy [adverse effects, complications], Artificial Pneumoperitoneum [adverse reactions, complications], Anesthesia [drug effects], Hemodynamics, Artificial Respiration, Hypercapnia, Hypothermia, Physiological Stress, Elective Surgical Procedures [adverse effects], Neuromuscular Blockade, Cathartics and Patient Positioning. Although "laparoscopic working space" is not a MeSH term, we included it in our search, which also included equivalent terms like "surgical (-site) exposure" and "surgical conditions".

RESULTS

Section I Consequences of pressurized CO_2 in the abdomen (table 2)

Georg Kelling performed the first recorded laparoscopy in a dog in 1901 using filtered air. In 1924, Richard Zollikofer introduced a CO_2 pneumoperitoneum [43]. It is understandable that CO_2 was eventually chosen as gas for insufflation: CO_2 is readily available, cheap, not combustible and is easily removed from the body through the lungs. CO_2 is less prone to cause gas embolism when it accidentally enters the blood stream, in contrast to inert gasses like helium and argon [44, 45]. However, CO_2 pneumoperitoneum causes profound pathophysiologic changes, which have to be considered in the search for ways to enlarge working space. These changes are related on the one hand to the biological effect of CO_2 and on the other hand to the mechanical effect of increased intra-abdominal pressure (IAP). These effects are difficult to separate.

Table 2. Influences associated with pressurized CO_2 in the abdomen

Hypercapnia	
Intra-peritoneal CO_2 and elevated IAP	Systemic hemodynamics
	Local hemodynamics and microcirculation
	– Peritoneal pH and circulation – Gastro-intestinal hemodynamics – Hepatic blood flow – Renal hemodynamics – Testicular circulation – Femoral venous flow
	Intracranial pressure and cerebral blood flow
	Respiratory system
Duration of the CO_2 pneumoperitoneum	
Retro- vs. intra peritoneal CO_2 insufflation	
Patient positioning	
– Head up tilt – Head down tilt – Prone versus supine position	
Hypothermia	

- ***Consequences of hypercapnia***

Insufflated CO_2 is absorbed by the body [46-48]. Hypercapnia per se causes acidosis and a hyper-dynamic circulation with increased cardiac output, decreased systemic vascular resistance and an increase in mean arterial blood pressure [49-54]. It also has an important effect on cerebral hemodynamics as it causes vasodilation and increased cerebral blood flow [55-57].

- ***Consequences of intra-peritoneal CO_2 and elevated IAP***

  Effects on systemic hemodynamics

At an IAP of 12-15 mm Hg, venous return, preload, and cardiac output are reduced due to mechanical effects of higher IAP, whilst heart rate, mean arterial pressure, as well as systemic and pulmonary vascular resistance are increased due to increased sympathetic tone [18]. These hemodynamic changes resemble chronic heart failure [58].

Several studies comparing the effects of CO_2 pneumoperitoneum with the effects of a pneumoperitoneum created with another gas have shown that the effects on hemodynamics are mainly caused by the biological effect of CO_2, at least up to an IAP of about 12 mm Hg [59-65]. CO_2 absorption increases up to an IAP of 15 mm Hg and declines at higher pressures [66]. At a higher IAP, pressure induced changes become more important than the type of gas used [67]. The guidelines on CO_2 pneumoperitoneum of the European Association for Endoscopic Surgery advocate the use of the lowest IAP that provides adequate exposure and consider an IAP < 14 mm Hg safe in a healthy non-pediatric patient [18]. The guidelines state that low pressure CO_2 pneumoperitoneum – defined as a pressure of 5-7 mm Hg – reduces adverse effects on physiology but clinical relevance of the use of this lower IAP has been doubted [18]. In a laparoscopic cholecystectomy study in humans, Dexter et al. found that heart rate and mean arterial blood pressure increased in the high pressure group but that stroke volume and cardiac output were depressed by a maximum of 26% and 28%. In contrast, insufflation in the low pressure group produced a rise in mean arterial pressure and a rise in both stroke volume and cardiac output of 10% and 28% respectively [39]. In a RCT in humans undergoing laparoscopic cholecystectomy, Kanwer et al. concluded that a lower IAP resulted in a lower intensity of postoperative shoulder pain but not in improved hemodynamics [68]. A similar conclusion was drawn in a Cochrane study comparing low pressure versus standard pressure CO_2 pneumoperitoneum in laparoscopic cholecystectomy [69]. Because of the high risk of bias due to incomplete outcome data in seven trials, it was not possible to conclude about the safety of low pressure CO_2 pneumoperitoneum. The authors arbitrarily took 12 mm Hg as the limit between low and high pressure.

In children similar hemodynamic changes have been reported [70], most prominently in small children [18, 71, 72]. This could be related to a higher CO_2 absorption in small children [48]. Low pressure CO_2 pneumoperitoneum (≤ 8 mm Hg) during laparoscopic fundoplication in a series of 13 children aged 6-36 months did not decrease cardiac index [73].

Effects on local hemodynamics and microcirculation

o Peritoneal pH and circulation

CO_2 is an acid which causes local acidosis when insufflated into the pleural or peritoneal cavity [61, 74, 75]. It increases peritoneal blood flow [64, 76].

o Gastrointestinal hemodynamics

CO_2 insufflation decreases splanchnic circulation [77-80]. Most studies were performed with a relatively high IAP. Blobner at al. showed in a porcine model that a CO_2 pneumoperitoneum at a pressure under 12 mm Hg resulted in moderate splanchnic hyperemia. Splanchnic blood flow decreased at a higher IAP [67]. Similarly Knolmayer et al. demonstrated in a porcine model that gastric blood flow was not reduced at an IAP of 8 mm Hg [79]. Windberger et al., also in a porcine model, demonstrated that CO_2 pneumoperitoneum resulted in a decrease in splanchnic perfusion at an IAP of 14 mm Hg, with only a minimal effect at 7 mm Hg [81]. Schilling et al. concluded that laparoscopic procedures with a CO_2 pneumoperitoneum should be performed at a pressure of 10 mm Hg or lower to avoid splanchnic microcirculatory disturbances [38].

o Hepatic blood flow

Hepatic blood flow is reduced during CO_2 pneumoperitoneum [37, 82, 83]. A decreased hepatic perfusion has also been shown by a decreased indocyanine green removal [84]. Jakimowicz et al. found an IAP-related decrease in portal venous flow [37]. The higher the IAP, the lower the hepatic tissue blood flow, which could protect against embolism [85].

o Renal hemodynamics

Several studies have reported a significant decrease in renal blood flow associated with CO_2 pneumoperitoneum [82, 86, 87]. Sassa et al. studied erythrocyte velocity in the cortical peri-tubular capillary (CPC) with a magnifying endoscope during CO_2 pneumoperitoneum in humans, as well as in a porcine model. Erythrocyte velocity in the CPC was significantly lower in all kidneys at an increase of IAP from 8 to 12 mm Hg. The renal artery flow was not affected by IAP. After stopping the CO_2 pneumoperitoneum, the erythrocyte velocity in the CPC recovered immediately. From these findings, the authors concluded that the most suitable IAP for maintaining renal microcirculation is 8 mm Hg [88]. In children undergoing laparoscopy, urine output drops within 45 minutes. Especially in children below one year of age anuria develops. This is a fully reversible phenomenon with no apparent renal hypoxia present [89, 90].

o Testicular circulation

Istanbulluoglu found adverse effects of CO_2 pneumoperitoneum on testicular circulation in a porcine model [91]. However, IAP in this study was 20 mm Hg and the CO_2 pneumoperitoneum lasted for 4 hours. Schier et al. found no changes in tissue oxygen saturation and microcirculatory measurements in the testis during laparoscopic inguinal hernia repair [92]. IAP during the procedure was not mentioned in the publication.

o Femoral venous flow

Femoral flow is decreased during CO_2 pneumoperitoneum [93-95]. Head-up tilt further reduces femoral flow. One would expect more thromboembolic complications during laparoscopic surgery using CO_2 pneumoperitoneum but the opposite has been reported [96-98].

Intracranial pressure (ICP) and cerebral blood flow

It has long been known that a CO_2 pneumoperitoneum causes an increased ICP [99]. As mentioned before, hypercapnia on its own causes vasodilation and hyper-perfusion of the brain, which may increase ICP [56]. When CO_2 as an insufflation gas was replaced with helium or nitrous oxide, ICP raised concomitantly with IAP as well, but significantly less than when CO_2 was used [100]. The strong relationship between ICP and IAP has been reported on several occasions [87, 101]. In a porcine study in which IAP was increased in 5 mm Hg steps from 0 to 5, 10 and 15 mm Hg, ICP increased from 14 mm Hg to 19, 24 and 29 mm Hg respectively. The ICP at 15 mm Hg IAP increased further in the head-down tilt up to 39 mm Hg. Head-up tilt did not change ICP [101]. Other studies also showed that head-down tilt increased ICP, but the regional oxygen saturation remained unaffected unless there was hypercapnia [102, 103].

Both in adults and children, CO_2 leads to an increase in middle cerebral artery blood flow velocity [104, 105]. Even at low IAP, CO_2 insufflation in children caused considerable increases in $ETCO_2$ and $PaCO_2$ with concomitant increases in regional cerebral oxygenation saturation and cerebral blood volume, even when superimposed on a baseline of mild hypocapnia [106].

Effects on the respiratory system

CO_2 pneumoperitoneum has a pronounced impact on the respiratory system [18, 107]. Potential respiratory consequences of abdominal CO_2 insufflation, resulting in increased IAP, include impaired diaphragmatic motion, decreased pulmonary functional residual capacity and -compliance, increased airway resistance and decreased tidal volume and minute ventilation [108]. Windberger et al. found in parallel with the increase of IAP, an increase in the mean trans-mural pulmonary artery pressure while arterial oxygenation

decreased [81]. These changes may lead to intrapulmonary shunting, increased alveolar-to-arterial oxygen gradient and possible hypoxemia.

- ***Impact of the duration of the CO_2 pneumoperitoneum***

Not only IAP and the kind of gas used for the pneumoperitoneum play a role in physiologic derangements, but also the duration of the pneumoperitoneum is important [38, 41]. Even with a low IAP of 8 mm Hg, important hemodynamic and acid-base changes occur in rabbits during prolonged (210 minutes) CO_2 pneumoperitoneum [109]. Duration of surgery is a risk factor for the occurrence of negative events in neonatal endoscopic surgery [72]. Jacobs et al. found a relationship between hypothermia and the duration of the operation [110]. Oxidative stress induced by the CO_2 pneumoperitoneum is considered time dependent [111-113].

- ***Retro- versus intra-peritoneal CO_2 insufflation***

Whether retro-peritoneoscopy leads to a higher degree of hypercarbia has been a matter of debate. A higher degree of CO_2 absorption was found during total extra-peritoneal hernia repair (TEP) compared with trans-abdominal pre-peritoneal hernia repair (TAPP) in one study [114], but no difference was found in another [115]. A higher CO_2 absorption rate was found when trans-peritoneal cholecystectomy was compared with retroperitoneal hernia repair [116]. Bannenberg et al. found fewer hemodynamic consequences when using retro-peritoneal CO_2 insufflation in a porcine model [117]. A possible explanation for the differences in results could be related to differences in insufflation pressure [118]. When using CO_2 insufflation for maintaining subcutaneous spaces, low insufflation pressure seems of paramount importance in avoiding large area subcutaneous emphysema and related high CO_2 absorption [119]. In a study in 10 kg pigs using an insufflation pressure of 10 mm Hg, cardiorespiratory changes and a rise in $ETCO_2$ occurred in the peritoneal insufflation group, whereas the retro-peritoneal group remained stable [120]. In a retrospective study about urologic MAS in children, both the trans-peritoneal and the retro-peritoneal approach resulted in important hemodynamic changes [121].

- ***Effect of patient position***

  Head-up tilt (reverse Trendelenburg position)

Both head-up tilt and elevated IAP independently reduce venous return from the lower extremities [18, 95]. Intermittent compression of the lower limbs during laparoscopic surgery can partly counteract the negative effect of an increased IAP on the venous return from the lower limbs [122, 123]. In a porcine model, Klopfenstein et al. showed that a 20 degree head-up tilt in the absence of CO_2 pneumoperitoneum decreased mean arterial pressure, cardiac output, and both hepatic arterial flow and total hepatic blood

flow (THBF)[124]. When a 15 mm Hg CO_2 pneumoperitoneum was added, only cardiac output and portal venous blood flow decreased.

Head-down tilt (Trendelenburg position)

Trendelenburg position increases venous return from the lower body, but increases also ICP [102, 125]. In contrast to what would be expected, extreme head-down tilt e.g. during laparoscopic prostatectomy is remarkably well tolerated despite elderly age [126,127]. Lee et al. found that regional cerebral oxygen saturation, measured with near-infrared spectroscopy, remained unaffected during gynecological procedures in Trendelenburg position [103].

In porcine experiments, Klopfenstein et al. showed that the head-down tilt increased MAP and THBF in the absence of CO_2 pneumoperitoneum, whereas no change was observed in the presence of CO_2 pneumoperitoneum [124].

Head-down tilt displaces the diaphragm and mediastinum in a cephalad direction, further limiting diaphragmatic excursion. Hypercarbia may occur due to CO_2 absorption across the peritoneum and due to induced alterations in respiratory mechanics. The magnitude of change correlates directly with intra-peritoneal pressure [128]. Head-down tilt reduces pulmonary compliance by 30% and leads to ventilation perfusion mismatch [18, 129, 130]. In 10 pediatric patients, head-down tilt resulted in a 17% decrease in lung compliance. Insufflation of CO_2 up to an IAP of 12 mm Hg resulted in a 27% further decrease in lung compliance [131].

Prone versus supine position

In a porcine CO_2 pneumoperitoneum model, Bannenberg et al. did not find differences in hemodynamics or oxygen transport between the prone or supine position [132].

- ***Hypothermia***

Hypothermia during surgery commonly occurs. Anesthetic agents disturb the bodies thermoregulatory control [133]. The core body temperature can drop as a result of low room temperature or the use of cold irrigating and intravenous fluids [134-136] , leaving patients at a greater risk for wound infections and coagulation disorders [137-139]. This may result in longer hospitalization with a concomitant increase in cost [140] [18]. It has often been assumed that laparoscopy, in comparison with laparotomy, decreases the risk for heat loss because the abdominal cavity is sealed during laparoscopic surgery, preventing the dissipation of heat. However, from the beginning of the endoscopic surgical era, researchers have warned against hypothermia during laparoscopy [110, 141-143]. In neonatal MAS, low body temperature is a significant risk factor [41, 72].

Most of the literature on this subject has focused on heating and humidification of insufflated CO_2 and not on the relationship between hypothermia and the amount of gas

used as a result of peritoneal resorption and external leakage. Jacobs et al. found that hypothermia was positively correlated with the amount of gas used, as well as with the duration of the operation [110]. In a retrospective multicenter study with 218 patients, Kalfa et al. therefore pleaded for a maximal effort to avoid gas leakage in neonatal MAS [72]. Pediatric thoracoscopy may paradoxically lead to hyperthermia. The small working space, the low insufflation pressure, the low leakage rate, and the high temperature of the endoscope all play a role [144, 145].

The majority of commercially available insufflators deliver dry CO_2 at approximately 21°C and 0% relative humidity [146]. During laparoscopic procedures, especially in adult gastric bypass surgery where volumes of up to 200 liters of CO_2 are used, patients are exposed to large volumes of relatively cool insufflation gas. This can lower the body temperature considerably [147-149]. Bessell et al. showed that not warming but humidification protected against hypothermia [142]. The use of insufflated gas that is only heated provides limited protection against changes in core temperature during laparoscopic surgery due to the small amount of heat required to warm the gas to body temperature. The latent heat required to saturate the insufflated gas with water vapor has a much greater cooling effect [142, 150].

In a clinical study, Bäcklund et al. reported that only warming the insufflation gas resulted in a significantly higher urinary output in patients undergoing prolonged laparoscopic procedures, but this coincided with a lower IAP in the heated gas group [151]. Puttick et al. showed in a clinical study that insufflation of CO_2 at body temperature resulted in a reduced postoperative intra-peritoneal cytokine response [149]. Mouton et al. reported that humidification of the insufflation gas reduced postoperative pain in patients undergoing laparoscopic cholecystectomy, a finding that they attributed to less peritoneal irritation by the CO_2 [152].

In a scanning electron microscopy study in mice, Volz et al. showed that the integrity of the parietal peritoneum is temporarily disturbed by insufflation with dry CO_2 [153]. In the experimental study of Hazebroek et al., a CO_2 leakage rate of 0.3L/min was created in 300 gram rats [154]. A close correlation between core temperature and intra-peritoneal temperature was found. Warm humidified CO_2 prevented the decrease in intra-peritoneal temperature but the morphologic alteration of the peritoneum persisted. Size of the peritoneal intercellular clefts did not differ between the insufflated groups and the animals undergoing gasless laparoscopy. In the gasless group, either the mechanical effects of lifting on the basal membrane or the air entering the abdominal cavity during lifting could explain for this [3] [154]. Recently Papparella et al. showed in a rat model that the degree of disruption of the mesothelial lining of the peritoneum depended on the CO_2 pneumoperitoneum pressure. Low CO_2 pressure caused minor peritoneal changes as opposed to high pressure and air insufflation [155].

Hypothermia has also been found in experimental thoracoscopy [156]. The discussion whether the insufflated CO_2 should be humidified and heated in MAS is ongoing [157, 158]. Prevention of CO_2 leakage seems the simplest measure to take, especially in pediatric endoscopic surgery.

Section II Strategies to minimize the side effects of the CO_2 pneumoperitoneum

- ***Modulating IAP***

Section I delineated the profound effects of CO_2 pneumoperitoneum on hemodynamics and lung function, both in adults and in children. IAP seems especially important above 12-15 mm Hg, but most studies were performed in adult humans or adult animals. Whether this pressure level is also safe in children is doubtful. Blood pressure in children is strongly correlated with age [159, 160]. The 50th percentile for systolic/diastolic blood pressure two weeks after term birth is 80/50 mm Hg [161], while at 10 years of age systolic/diastolic blood pressure is about 105/63 mm Hg and at 18 years it is 124/72 mm Hg [160]. These reference values are derived from non-anesthetized, healthy individuals. Hypotension is very common during pediatric anesthesia [162]. From a survey among members of the Society for Pediatric Anesthesia (SPA) and the Association of Paediatric Anaesthetists of Great Britain and Ireland, thresholds for hypotension were determined. The threshold systolic blood pressures reported by the 367 SPA members who responded to the survey are listed in table 3. A 20-30% decrease in systolic blood pressure was considered to be significant by 78% of the respondents [163]. During laparoscopy in children blood pressure has a tendency to increase [73, 108, 164, 165]. In a series of 52 children below 6 months of age undergoing laparoscopic surgery, mean maximum systolic blood pressure was 78 mm Hg with a mean arterial pressure (MAP) of 55 mm Hg [164]. De Waal and Kalkman measured a MAP of 63 mm Hg during laparoscopic gastrointestinal reflux surgery in a group of children 6-36 months of age [73]. In a study of prolonged 10 mm Hg CO_2 pneumoperitoneum in neonatal and adolescent pigs, Metzelder et al. found hypotension in both groups, but more pronounced in the neonatal group [71]. A French multicenter assessment of the safety of neonatal MAS revealed substantial morbidity [72]. The authors suggest that the sensitivity to CO_2 insufflation during the first month of life is higher.

Table 3. Published data on normal and abnormal systolic blood pressure according to age in children

Age **mm Hg**	**normal systolic blood pressure** [160]	**perioperative hypotension threshold** [163]	**hypertension threshold** [159, 161]
2 weeks	80	46	98
2 years	92	55	100
12 years	105	67	115
15 years	115	78	120

Pulmonary mechanics in children change significantly during CO_2 pneumoperitoneum, directly correlating with IAP. At least one ventilatory intervention to restore baseline tidal volume and $ETCO_2$ was required in 16 out of 17 children undergoing laparoscopy under 1 year of age in a study by Bannister et al [128]. Fujimoto et al. reported large increases in the minute-volume in newborn infants undergoing laparoscopic surgery to return $PaCO_2$ levels to a normal level [165]. Children and infants who have a low functional reserve capacity, high closing capacity, and high oxygen consumption are more prone to develop hypoxemia during increased IAP [166]. Because there is a non-linear relationship between tidal volume and CO_2 production, children require not only higher baseline respiratory rates, but also disproportionately larger increases in respiratory rate and minute volume to compensate for CO_2 insufflation than adults [41]. Both in adults and children the lowest possible IAP providing sufficient working space should be used, as IAP is the factor exerting the greatest effect on hemodynamics and pulmonary mechanics. Also, the longer the CO_2 pneumoperitoneum lasts, the more pronounced its effects will be, making expedient surgery a second important factor in minimizing the effects of CO_2 pneumoperitoneum [41, 167, 168].

- ***Volume loading***

Since the effects of CO_2 pneumoperitoneum on hemodynamics are dependent on intravascular volume, adequate preoperative intravascular fluid loading is essential [18]. Volume load increased portal blood flow but not renal blood flow in pigs in all body positions [169]. Junghans et al. found that increasing intra-thoracic blood volume improved hemodynamic function in all body positions [122]. Cardiac preload can also be increased by using intermittent sequential pneumatic compression of the legs [123].

- ***Medication***

  Medication affecting hemodynamics

  - *Esmolol (β_1 blocker)*

Beta-adrenergic blockade can be used to control the acute sympathetic response to CO_2 pneumoperitoneum. In a porcine study, esmolol did not alter the measured hemodynamic parameters in any position [169]. In another porcine study, esmolol reduced cardiac output and myocardial contractility [122]. The authors recommended not to use β_1 blockers because they compromise myocardial contractility and suppress sympathetic compensatory mechanisms. However, a clinical RCT in 45 healthy women undergoing gynecologic laparoscopy found faster emergence times and a decreased need for postoperative analgesics with esmolol [170].

o Nitroprusside

In one study in pigs, nitroprusside reduced renal blood flow in supine and head-up tilt [169] but in another, nitroprusside did not affect hemodynamic function in any body position [122]. In contrast Feig et al. reported a positive effect on hemodynamics of the use of nitroglycerine in 15 adult ASA III or IV patients undergoing laparoscopic procedures, but pre-existing diastolic cardiac dysfunction might play a role in this patient group [171].

o Dobutamine/dopamine

In a porcine model, Agusti et al. found that dobutamine, in contrast to dopamine, partly corrected cardiac output, systemic vascular resistance, and hepatic artery blood flow alterations during pneumoperitoneum, but neither drug restored total hepatic blood flow [172].

o Clonidine (α_2 adrenergic agonist)

Clonidine, when given intravenously or orally before CO_2 pneumoperitoneum, reduces catecholamine release and attenuates hemodynamic changes during laparoscopy [173, 174]. No data on its effect during CO_2 pneumoperitoneum in children were found.

ENO added to CO_2 insufflation gas

Ali et al. added ethyl nitrite (ENO, a nitric oxide donor) to insufflated CO_2 and were able to show that liver blood flow but not renal blood flow was better maintained [77].

- ***Modulation of the oxidative stress response***

Although "minimally invasive surgery" causes less surgical trauma, it certainly does not eliminate the surgical stress response. Oxidative stress is an integral part of this surgical stress response, which can be modulated both mechanically and pharmacologically [175].

Mechanical modulation

CO_2 pneumoperitoneum produces significant splanchnic organ ischemia, followed by reperfusion injury after desufflation [80, 176]. Ischemic pre-conditioning by a CO_2 pneumoperitoneum for five minutes at an IAP of 15 mm Hg reduced ischemia/reperfusion injury in rats [177].

Pharmacological manipulation

Erythromycin, melatonin, mesna, verapamil, pentoxiphylline, N-acetylcystein and zinc have been investigated in animal studies on their ability to reduce oxidative stress markers caused by CO_2 pneumoperitoneum. Contrasting data were obtained for pento-

xiphylline, but the other agents lowered oxidative stress markers [175]. Melatonin seems promising. It reduces oxidative damage related to surgical and ischemia/reperfusion injury. Moreover, it has proven to be a safe drug with very low toxicity [178]. Melatonin has been tested in neonates undergoing surgery. Here, it reduced cytokines and NOx levels and showed potent antioxidant properties [179]. Propofol and sevoflurane also have antioxidant effects [180, 181]. A systematic review concluded that pharmacological modulation of the stress response to MAS might be feasible, but that there was not enough evidence to permit valid conclusions or claim clinical benefits [175].

- ***Ventilation strategies***

Not only the pharmaca used during anesthesia play a role, but also the parameters of (mechanical) ventilation. Respiratory rate, PEEP and tidal volume/inspiratory pressure can be modulated.

Permissive hypercapnia

Hypercapnia by itself increases minute ventilation by as much as 60% to normalize $ETCO_2$ [107]. Hypercapnia can be managed by adjusting the artificial ventilation [107, 166]. $ETCO_2$ monitoring is important but may not accurately reflect arterial CO_2 tension ($PaCO_2$), especially in neonates with uncuffed endotracheal tubes [107, 164, 182]. Debate exists whether it is necessary to achieve normocapnia. Hypercapnia increases cardiac index by as much as 40% for each 10 mm Hg increment of arterial CO_2 tension [49, 50]. Moreover it causes a rightward shift of the oxyhemoglobin dissociation curve [183], decreases systemic vascular resistance, and increases oxygen availability to tissues [51, 55]. Accepting a $PaCO_2$ up to 50 mm Hg seems defendable. Up to an $ETCO_2$ of 70 mm Hg, hypercapnia does not cause tachycardia in sedated or anesthetized humans [51]. Neonate and preterm infant cerebral vessels are more sensitive to $PaCO_2$ elevation (vasodilatation) than to a decrease in $PaCO_2$ (vasoconstriction). Rapid elevation of $PaCO_2$ to 12.0–14.67 kPa (90–110 mm Hg) can induce consciousness alterations, cataphoria, and hyperspasmia [184]. Controlled permissive hypercapnia must be distinguished from accidental severe acute hypercapnia, which may lead to decreased myocardial contractility, changes in systemic vascular resistance, increased sympathetic activity, high cardiac output, and arrhythmias. Experiments have shown poor responses to resuscitation in hypercapnic animals. All these effects are reversible by correcting intra-cellular pH. With slower increases in $PaCO_2$, most patients can tolerate extremely high values of $PaCO_2$ and low values of pH with good recovery when returned to normocapnia [185, 186]. The optimal peri-operative $PaCO_2$ goal remains to be determined, but large variations in $PaCO_2$ should be avoided [57, 186]. Hypercapnia targeting $PaCO_2$ at 50-70 mm Hg was associated with increased cardiac output and increased central venous and arterial O_2 tension in a group of children with a mean age of 13 years undergoing video-assisted

thoracoscopic patent ductus arteriosus closure using single-lung ventilation, without any deleterious cardiopulmonary effects [187].

Very low birth weight infants seem to lose their cerebral auto-regulation control with hypercapnia [188]. Hypercapnia in these infants during the first 3 days of life is reported to be associated with severe intra-ventricular hemorrhage [189]. Therefore, one should be very careful with permissive hypercapnia in this group of patients [188, 189].

Artificial hypocapnia

Artificial hypocapnia before and during CO_2 insufflation attenuates the increases in blood pressure during laparoscopic cholecystectomy in adults [190]. Such policy is however not without danger [191, 192]. Hypocapnia is especially dangerous in preterm born children requiring mechanical ventilation [184].

Spontaneous versus mechanical ventilation

Williams et al. compared the effect of mechanical ventilation with spontaneous ventilation during laparoscopic gynecological procedures [193]. Mechanical ventilation in combination with neuromuscular blockade (NMB) resulted in improved CO_2 pneumoperitoneum, facilitating surgical access and lower IAP. The contribution of NMB to this effect is unclear.

Pressure- versus volume-controlled ventilation

Pressure-controlled ventilation (PCV) has theoretical advantages over volume-controlled ventilation (VCV) [194]. PCV results in a lower peak inspiratory pressure but higher mean airway pressure by means of its different flow pattern. Under conditions of passive respiration, mean airway pressure correlates with alveolar ventilation, arterial oxygenation, hemodynamic performance, and barotrauma. PCV is suggested to improve gas exchange in extreme conditions such as in patients with hypoxia in the intensive care unit, patients with adult respiratory distress syndrome, patients with morbid obesity undergoing bariatric surgery and patients undergoing thoracic surgery with single-lung ventilation [194-196]. Results regarding the superiority of PCV over VCV during laparoscopic surgery have been conflicting, both in obese [197, 198] and non-obese patients [199]. No superiority of PCV over VCV was found in a series of laparoscopic cholecystectomies [200]. In contrast, lower pulmonary compliance with PCV has been reported during laparoscopic procedures in the lower abdomen [195, 201, 202]. This may be position related, as the head-down tilt used in pelvic surgery also causes a decrease in lung compliance [131, 200].

High frequency ventilation

High-frequency jet ventilation (HFJV) is associated with much lower airway pressures, potentially facilitating venous return. Bickel et al. compared classic mechanical ventilation with HFJV during laparoscopic cholecystectomy [203]. In the group receiving classic mechanical ventilation, cardiac output decreased significantly during the initiation of head-up tilt with a reciprocal change in stroke volume. Such changes were not noticed under HFJV. Total peripheral vascular resistance was significantly increased, but heart rate was not affected in both groups. Arterial blood gas values of PaO_2, $PaCO_2$, and pH were similar during all phases of surgery and between the study groups. Good results have been reported with high frequency oscillating ventilation during thoracoscopic MAS in neonates [204].

Positive end expiratory pressure (PEEP)

The major effect of PEEP on the lungs is an increase in functional reserve capacity (FRC), preventing atelectasis and shunting [205]. A PEEP of 10 cm H_2O in laparoscopic cholecystectomy patients, after an initial recruitment maneuver, preserved homogeneous regional ventilation in most patients and improved oxygenation and respiratory compliance [206]. Kim et al. found a similar positive effect of 5 cm H_2O PEEP in pressure-controlled ventilated patients [205]. In obese patients undergoing laparoscopic gastric bypass high PEEP levels (up to 15 cm H_2O) are needed to maintain a normal FRC and to minimize shunting. Volume loading prevents the circulatory depression that normally occurs with high PEEP levels [207]. The hemodynamic effect of PEEP during CO_2 pneumoperitoneum has been found to vary from a minimal to a significant decrease in preload and cardiac output. PEEP of 10 cm H_2O in combination with an IAP of 15 mm Hg decreases preload and cardiac output [208]. Again volume loading is essential to counteract these effects. Elevated PEEP has no effect on gas embolism frequency or severity in experimental laparoscopic liver resection [209].

- ***Volatile drug anesthesia versus total intravenous anesthesia***

  Volatile anesthetic drugs

Desflurane, sevoflurane, halothane, and isoflurane can cause myocardial contractility depression with a negative inotropic effect [210]. Volatile anesthetic drugs can also have negative chronotropic effects by reducing sinoatrial node activity [211]. The mechanisms that initiate those various effects are complex and related to myocardial calcium transport abnormalities [212, 213].

Total intravenous anesthesia

Various combinations of anesthetic drugs are used for total intravenous anesthesia. Bickel et al. promote a technique where propofol (hypnotic) is combined with remifent-

anil (opiate), reporting only minor negative hemodynamic effects of CO_2 pneumoperitoneum using this regimen in their study [203]. Propofol combines quick anesthesia with smooth awakening. Its main hemodynamic side effect is hypotension. This is the combined result of direct myocardial depression, a reduction in systemic vascular resistance, and a reduction of muscle sympathetic activity [214, 215]. The negative cardiovascular effects of propofol can be decreased by careful drug titration, adequate fluid administration, and proper integration with short-acting opiates like remifentanil [203]. Puglisi et al. also showed that propofol assured better hemodynamic- and respiratory conditions during laparoscopy than did sevoflurane in a porcine model [216].

- ***Locoregional anesthesia***

Combined epidural and general anesthesia during laparoscopic surgery effectively blocks the sympathetic nerve system and reduces nitric oxide (NO) inactivation and oxidative stress [217]. Although modest hypoventilation is often effective in treating hypotension during general anesthesia, animal studies suggest that hypoventilation may be detrimental during the combination of epidural and general anesthesia [218, 219]. Epidural anesthesia may cause abdominal wall muscle relaxation. In clinical practice however, the level of motor blockade is not sharply defined with only limited relaxation [220].

Spinal anesthesia produces better muscle relaxation, which can be an advantage in MAS. In pediatric surgery, the practice of spinal anesthesia in pediatric patients requires skill and experience [221]. Failure rates of up to 28% and post-dural-puncture headache and transient neurological symptoms have been reported [222].

- ***Muscle tone***

Deep neuromuscular blockade (NMB) until the end of an operation may be beneficial during certain types of complex surgery, such as laparoscopic procedures, with the potential to improve surgical access and augment the surgical field [223-225]. However, clinical and experimental data do not demonstrate a significant reduction in pulmonary peak pressure or IAP [226-228]. Maracaja-Neto et al. confirmed these findings, showing that NMB did not cause any significant change in esophageal pressure, respiratory system pressure, pulmonary elastance and chest wall elastance [229]. The effect of NMB on working space dimensions has not been the subject of quantitative, experimental research. Almost all studies have used surgeons' subjective assessment of surgical conditions or duration of surgery as endpoint [193, 230]. Relaxation of the diaphragm caused by anesthesia in combination with increased IAP impairs movement of the diaphragm and leads to atelectasis of the dependent regions of the lungs [18, 231].

Propofol decreases muscle tone in the absence of neuromuscular blocking drugs [232]. Opioids stimulate active-phase expiratory muscle activity and can cause large increases

in abdominal pressure and severe chest wall rigidity [233-235]. Ketamine produces a cataleptic anesthetic state with an increase in muscle tone [236-237].

Section III Strategies to optimize laparoscopic working space

Several factors influence working space. Some of these factors cannot be modified, others can (table 4).

Table 4. Summary: How can working space in (pediatric) laparoscopic surgery be optimized?

Mechanical bowel preparation prior to laparoscopy may increase laparoscopic working space
CO_2 pneumoperitoneum – An initial CO_2 pneumoperitoneum at a higher pressure for a relatively short period, followed by desufflation and re-insufflation seems advisable as it causes ischemic pre-conditioning and allows for easier and safer trocar-placement – If possible, CO_2 pneumoperitoneum pressure should be low (5-7 mm Hg) – CO_2 humidification seems advisable – With expedient surgery, long duration of the CO_2 pneumoperitoneum should be avoided
Intravascular volume loading is indicated as it counteracts the CO_2 pneumoperitoneum effects on hemodynamics
Vasoactive medication – Clonidine intravenously may be of benefit in reducing catecholamine release and diminishing hemodynamic changes
Pharmacological manipulation of the stress response – Melatonin seems promising
Ventilation strategies – (Laryngeal) mask ventilation or endotracheal tube leaks should be avoided – Permissive hypercapnia can be used to avoid high PIP (CAVE very low birth weight infants and acute changes in $PaCO_2$) – PEEP of 5 cm H_2O is advisable – Pressure controlled ventilation may be superior to volume controlled – High Frequency (Jet) Ventilation may be useful in neonatal (thoracoscopic) MAS
Anesthesia – General anesthesia in combination with epidural anesthesia seems best for children – Total intravenous anesthesia with propofol and short acting opiates seems superior to anesthesia with volatile drugs in MAS – NMB is needed to prevent unintended patient movement but has no effect on laparoscopic working space

- ***Patient size***

Patient size or body mass are usually not amenable to intervention prior to surgery. In children, working space volume and dimensions are very much determined by their age. A child one-half as tall as an adult presents the surgeon with only one-eighth the working volume in the chest or abdomen [41]. In a full term neonate, laparoscopic working space volume is about 300 ml.

- ***Bowel content***

Preoperative mechanical bowel preparation could augment intra-abdominal working space at a given intra-abdominal pressure [238-240].

- ***CO_2 pneumoperitoneum pressure***

In the previous two sections, the focus was on the effects of CO_2 insufflation and the management of its adverse effects. Insufflation-pressure is the factor with the most obvious effect on working space but also the greatest negative effect on hemodynamics and pulmonary mechanics. The incremental effect of CO_2 pressure on pneumoperitoneum volume decreases with higher intra-abdominal pressures, making the gain in working space increasingly smaller and the physiologic burden larger [241]. Quantitative data of the relationship between IAP and laparoscopic workings space in humans are lacking. This may be related to the absence of a reliable clinical method for measuring working space. Most studies that have been done used surgeon's satisfaction, subjective assessment of surgical conditions, or duration of the intervention as surrogate primary outcomes.

- ***Patient positioning***

Positioning of the patient most likely does not affect total working space volume, but it undoubtedly affects effective working space dimensions [242-244]. The effect of different body positions on pathophysiology has been studied in detail, but not the effect on effective laparoscopic working space.

- ***Muscle tone***

The effect of muscle tone on working space is certainly important but has not been studied well either. Many factors are co-responsible for muscle tone e.g. depth of anesthesia, the use of neuromuscular blocking agents and loco-regional anesthesia. Unfortunately, an accurate method for assessing muscle tone is lacking. The benefit of adding muscle paralysis to deep anesthesia in order to increase working space seems limited, although solid data in literature on this subject are lacking [193, 227]. The now more and more common practice of deep NMB with antagonization/reversal at the end of endoscopic procedures adds to the cost of MAS and is not evidence-based [245].

- ***Mask ventilation and endotracheal tube leakage***

When (laryngeal) mask ventilation is used, gas often passes through the esophagus into the stomach and the rest of the gastrointestinal (GI) tract [246]. Endotracheal tube leakage may also result in inhalation gas traveling down the GI tract. The amount of gas entering the GI tract depends on several factors such as ventilation pressure, anesthetic gas flow and PEEP. Troublesome endotracheal intubation with periods with forced mask

ventilation may cause so much gastric and bowel distention that sufficient working space for MAS cannot be created. Upper GI endoscopy may have the same effect. Most of the time, gas insufflated into the stomach may be removed with a nasogastric tube but once past the pylorus, it is difficult to remove. Limiting the amount of anesthetic gas entering the stomach and rest of the GI tract by rapid sequence intubation and preventing tube-leaks with cuffed tubes improves laparoscopic working space and control over ventilation [182, 247, 248]. Especially when working pressures are limited by patient size/age and physiology, e.g. in neonates, this helps to achieve adequate exposure at lower IAPs.

- ***Nitrous oxide as inhalation gas***

Nitrous oxide (N_2O), used as an inhalation gas, will move into air-filled cavities in the body that normally contain nitrogen. However, as nitrous oxide is 34 times more soluble in blood than nitrogen, substantial quantities of nitrous oxide leave the blood and enter the bowel, but only a limited amount of nitrogen can be reabsorbed into the bloodstream. The result is that during exposure to nitrous oxide, bowel distention occurs. The amount of distention depends on the alveolar partial pressure of nitrous oxide, the intestinal blood flow, and the duration of nitrous oxide administration [249]. In the clinical study of Akca et al., patients given nitrous oxide as inhalation gas were more than twice as likely (23% vs. 9%) to have subjective moderate or severe distention. The debate in the literature about the use of N_2O as an inhalation gas during laparoscopy however has not settled [250, 251]. One of the problems is quantifying gastrointestinal distention. Most studies rely on the surgeon's evaluation. With ample working space, as in adult laparoscopic surgery, evaluation of the quality of the surgical field in relation to bowel distension is much less reliable than in children with limited working space and a more pronounced effect of bowel distention. An objective method for measuring working space is required to settle the matter on nitrous oxide.

- ***Size of the optical system and instruments, intra-abdominal trocar length***

The size of the optical system and instruments that are used defines the dimensions of the working space required for safe and efficient surgery (figure 1). We measured the length of the jaws of commonly used 5-mm laparoscopic instruments of three major companies and found them to be 2-3 cm, except for the monopolar hook, which always was shorter than 1 cm. The jaws of similar 3-mm instruments were 1-2 cm. Kalfa et al. found a maximum vertical working distance of 3 cm in a 3-kg neonate with an IAP of 7 mm Hg [72]. This endorses the need for further miniaturization, but the relatively small pediatric surgical market hampers this development. Only a few companies produce optics and instruments with a diameter less than 5 mm. Small diameter optics usually have a lower image quality and light output. For 3D imaging a 10-mm optic is still most

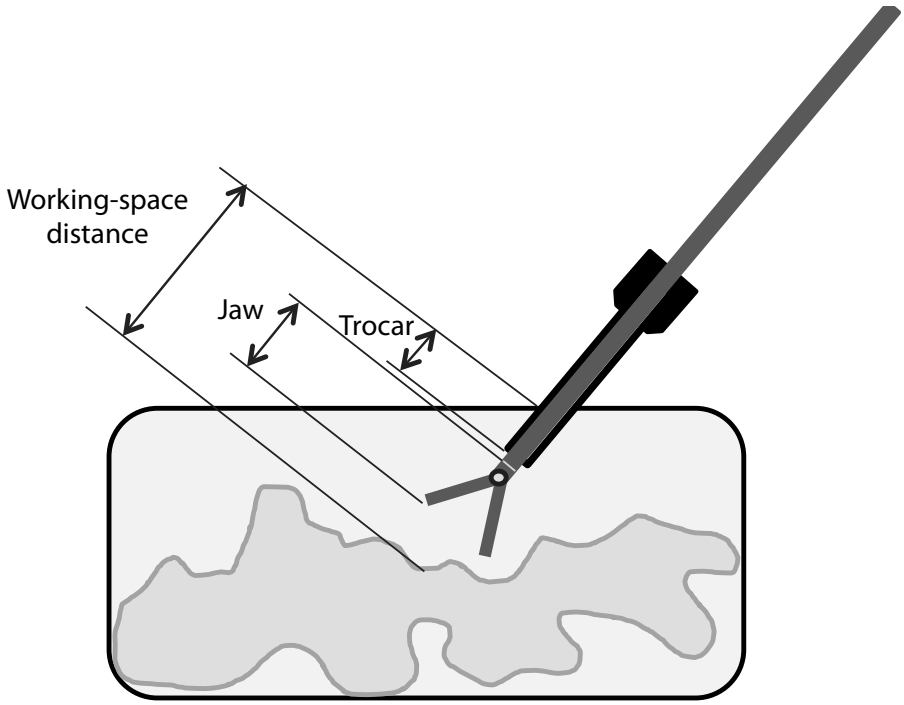

Figure 1.
Schematic drawing demonstrating limitation of usable working space by instrument size and intra-abdominal trocar length

commonly used. The diameter of most energy supplying systems e.g. ultrasonic scissors and bipolar sealing devices, is 5 mm or larger. Almost all stapling devices require 12-mm ports and need a substantial intra-corporeal length for their deployment. Small diameter optics and instruments are more fragile, requiring delicate use by their users with usually higher cost of maintenance.

The length of the intra-abdominal part of the trocar also has a substantial influence on working space in small children (figure 1). However, when too short an intra-abdominal segment is used, trocars will easily be pulled out, leading to gas leakage, poor visibility, possible hypothermia and a longer duration of the operation. To date, no usable technical solutions exist for 3 and 5-mm trocars to limit the intra-abdominal length of the trocar, yet provide firm fixation.

A major problem in studying working space is the method of its assessment. In clinical practice, the volume of CO_2 released by the insufflator is often used as an indication, but this method is prone to bias by leakage and absorption of CO_2 by the peritoneum and

effects of temperature and compressibility. Objective clinical measurement of working-space distances and volumes is not yet technically possible.

DISCUSSION

Working space is especially a concern in pediatric endoscopic surgery. Small gains in working space can enable more efficient and safer surgery and be of major benefit here. CO_2 pneumoperitoneum pressure is a major component in the determination of working space during laparoscopy. However, especially at higher IAPs, it causes important pathophysiologic changes, even more so in children than in adults [40, 70, 72, 164]. To counteract these consequences, corrective measures have to be undertaken. Table 4 summarizes which actions can be taken to minimize the negative side effects of CO_2 pneumoperitoneum whilst optimizing working space.

A major problem in studying laparoscopic working space is the method of its evaluation. Use of the volume of released CO_2 as displayed by the CO_2 insufflator is prone to errors by leaking and absorption of gas. Most clinical studies have used surgeon's satisfaction, subjective assessment of surgical conditions, or duration of the operation as surrogate primary outcomes. However, assessment of laparoscopic working space asks for a precise, quantitative method of evaluation. In experimental work this can be computed tomography [252]. This of course is not applicable in endoscopic surgery in humans. However, 3D camera technology may be able to provide similar distance and volume information in the near future.

CONCLUSIONS

Working space in laparoscopic surgery, although essential, has not been adequately studied. Most research has focused on the side effects of the CO_2 pneumoperitoneum and on strategies to avoid these, but not on working space itself. Working space is especially limited in small children. Here, small gains in working space could be of major benefit. A simple but accurate clinically usable method for measuring working space is needed in studying the effects of various interventions. In animal experiments this may be computed tomography. In the clinical setting, 3D optics could provide this information together with improved visualization.

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CHAPTER 2

Optimizing working space in porcine laparoscopy:
CT measurement of the effects of intra-abdominal pressure

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ABSTRACT

Background

Several factors may affect volume and dimensions of the working space in laparoscopic surgery. The precise impact of these factors has not been well studied. In a porcine model we used CT-scanning for measuring working space volume and distances. In a first series of experiments we studied the relationship between intra-abdominal pressure (IAP) and working space.

Methods

Eleven 20kg pigs were studied under standardized anesthesia and volume-controlled ventilation. Cardiorespiratory parameters were monitored continuously, and blood gas samples were taken at different IAP levels. Respiratory rate was increased when $ETCO_2$ exceeded 7 kPa. Breath-hold CT-scans were made at IAP levels of 0, 5, 10, and 15 mm Hg. Insufflator volumes were compared to CT-measured volumes. Maximum dimensions of pneumoperitoneum were measured on reconstructed CT-images.

Results

Respiratory rate had to be increased in three animals. Mild hypercapnia and acidosis occurred at 15mm Hg IAP. Peak inspiratory pressure (PIP) rose significantly at 10 and 15mm Hg. CT-measured volume increased relatively by 93% from 5 to 10 mm Hg IAP and by 19% from 10 to 15 mm Hg IAP. Comparing CT volumes to insufflator volumes gave a bias of 76 ml. The limits of agreement were -0.31 to +0.47, a range of 790 ml.

The internal antero-posterior (AP) diameter increased 18% by increasing IAP from 5 to 10 mm Hg and by 5% by increasing IAP from 10 to 15 mm Hg. At 15 mm Hg the total relative increase of the pubis-diaphragm distance was only 6%. Abdominal width did not increase.

Conclusions

CT allowed for precise calculation of the actual CO_2 pneumoperitoneum volume, whereas the volume of CO_2 released by the insufflator did not.

Increasing IAP up to 10mm Hg achieved most gain in volume and in internal AP diameter. At an IAP of 10mm Hg and higher, PIP was significantly elevated.

INTRODUCTION

Minimal Access Surgery (MAS) is used for a wide variety of surgical conditions in adults as well as in children [1, 2]. An essential pre-condition for this approach is sufficient working space providing good view and ease of instrument handling [3-5]. In laparoscopy this is mostly achieved by intra-peritoneal insufflation of CO_2 [6]. Within limits, the higher the pressure the more working space is generated. On the other hand, the CO_2 pneumoperitoneum has adverse effects. Absorption of CO_2 may cause acidosis, and the increased intra-abdominal pressure interferes with cardiorespiratory function and regional perfusion[6-14]. In pediatric MAS, the working space is inversely related to the patient's size and thus also to age. It is tempting to increase intra-peritoneal insufflation pressure, but the adverse consequences of CO_2 insufflation may be more evident in children [10, 15]. Therefore, a delicate balance between intra-abdominal CO_2 insufflation pressure and ventilatory settings is needed for patient safety on the one side and having a good working space on the other side[16-22]. As there are few experimental data in the literature addressing this delicate balance we decided to study this in a porcine model.

Working space in laparoscopy is determined by three types of factors: patient-related; pneumoperitoneum-related; and anesthesiology related (table 1).

In a first series of experiments, we addressed the relationship between one of the pneumoperitoneum-related factors – CO_2 insufflation pressure – and working space in a porcine model with volume-controlled ventilation. The effects of different CO_2 insuffla-

Table 1. Factors that determine laparoscopic working space

Factor	Description
Patient factors	Age/size
	Bowel content
	Body wall thickness e.g. obesity
	Organomegaly
	Space occupying lesions
	Muscular rigidity e.g. cerebral palsy
Pneumoperitoneum	Pressure
	Positioning of the patient
Anesthesiologic factors	Influencing muscle tone
	Direct effect of anesthetic drugs on muscle tone
	Depth of anesthesia
	Use of systemic neuromuscular blocking agents
	Loco-regional techniques
	Type of ventilation (volume- versus pressure controlled ventilation)
	Ventilator settings

tion pressures on pneumoperitoneum volume and intra-abdominal linear dimensions were investigated with computed tomography (CT).

MATERIALS AND METHODS

The institutional animal ethics committee granted approval for the experiments. Female pigs of approximately 20kg were used. The animals were not fasted. On the day of the experiment they were given an intramuscular injection of 1mg/kg midazolam and 30mg/kg ketamine. Spontaneous breathing was maintained. They were then transferred from the animal housing facility to the laboratory, where a cannula was placed in the auricular vein. A continuous intravenous infusion of 6-8 mg/kg/hr. propofol and 4 mcg/kg/hr. sufentanil was started. Next, tracheotomy was performed through a midline cervical incision and volume-controlled ventilation (EvitaXL®, Dräger, Lübeck, Germany) was started with an air-oxygen mixture (FiO_2 40%), I:E ratio at 1:2, a tidal volume of 10ml/kg and a rate of 40/minute. Positive end expiratory pressure (PEEP) was set at 5 cm H_2O. End tidal CO_2 ($ETCO_2$) was monitored on the ventilator. Tidal volume was kept constant; peak inspiratory pressures (PIP) were recorded during the experiment. Respiration rate was adjusted to maintain $ETCO_2$ within a range of 3.5 to 7 kPa.

A nasal temperature probe was placed and normothermia (38-40 degrees Celsius) was maintained with the use of an electric heating blanket (Inventum, Veenendaal, the Netherlands). Cardiac monitoring was initiated at this point using a 3-lead ECG. An intra-arterial line (Arrow® 20G, Reading, PA, USA) was placed in the right carotid artery for continuous blood pressure measurement and sampling of blood for hematocrit and blood gas analysis. A venous line (Arrow®, Percutaneous Sheath Introducer Set 8.5Fr.) was placed in the right internal jugular vein via a separate low-cervical incision.

A supra-umbilical midline abdominal trocar was placed after insufflation of the abdominal cavity with a Veress needle to 5mm Hg. Insufflation was by means of an electronic insufflator (Endoflator, Storz®, Tuttlingen, Germany). To prevent leakage of CO_2 and trocar-site bleeding a radially expanding trocar (VersaStep® 5mm, Covidien, Dublin, Ireland) was used [23, 24]. Correct intra-abdominal placement was verified by laparoscopy (Storz Telepack® and 5-mm 30° telescope). The abdomen was then desufflated by opening the CO_2 inlet of the trocar. A 30 minute infusion of 500 ml of colloid (Voluven®, Fresenius Kabi, Halden, Norway) was given, followed by continuous infusion of 10 ml/kg/hr. of isotonic saline. When hemodynamic and respiratory parameters were stable, the pig was transported to a CT-scanner (Definition Flash Dual Source®, Siemens, Erlangen, Germany). The electronic insufflator was attached to the abdominal trocar after the pig was installed on the scanning-tray. Thorax and abdomen were scanned at intra-abdominal pressures of 0, 5, 10 and 15 mm Hg. To minimize respiratory motion artefacts, scans were made during expiratory arrests whilst maintaining PEEP at 5 cm

H_2O. Scanning duration for a CT-run was approximately 5 seconds. At each new pressure-level, further scanning was paused until PIP and end-tidal CO_2 ($ETCO_2$) had stabilized, which always was within 5 minutes. Blood gas samples were taken directly after scanning before proceeding to the next pressure level and values of cardiorespiratory parameters were recorded at these points. Pigs were sacrificed after scanning.

Three different measures of working space were analyzed:

1. Linear dimensions as measured on CT (figures 1A and B):

a. in a sagittal midline plane
   - maximal internal abdominal AP diameter from the front of the vertebral column to the anterior peritoneal lining
   - maximal distance between the upper border of the pubic symphysis and the highest diaphragmatic peritoneal lining

b. in a transverse and coronal plane
   - maximal internal diameter of the abdomen between the lateral peritoneal linings

2. Volume of the free intra-abdominal CO_2 as measured on CT.

Intra-abdominal volumes were calculated with the Syngo 3D volume-module of a Siemens Navigator® workstation using a dataset of 5-mm slices. Free CO_2 in the abdomen on transverse slices was detected semi-automatically after appropriate thresholds were defined. Slices could be integrated to a total volume of free intra-abdominal air. All volumes were visually checked for inadvertent inclusion of intra-luminal air in the bowels.

3. Volume of insufflated CO_2 as given by the insufflator (Endoflator®, Storz)

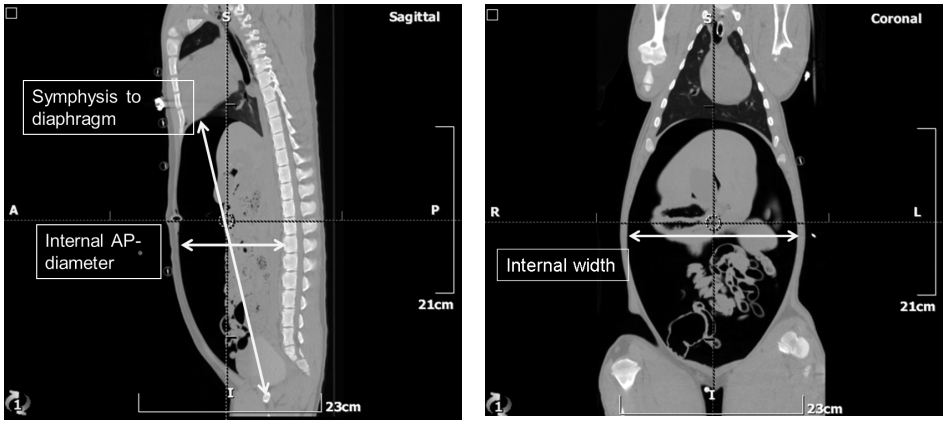

Figure 1A (left) and B (right)
Reconstructed CT-images at an IAP of 5 mm Hg.
A. Internal AP diameter and pubis-diaphragm diameter, sagittal view
B. Internal width, coronal view

All data were analyzed using SPSS for Windows version 16. The increase in linear dimensions of abdominal working space with increasing intra-abdominal pressure was measured on reconstructed CT-images. The volume indicated by the electronic insufflator was compared to the volume measured on CT. Agreement between these volume measurements was visualized in a Bland-Altman plot [25]. The significance of changes in cardiorespiratory measurements at the different intra-abdominal pressures was calculated with paired *t*-tests. A *p*-value of less than 0.05 was taken to signify a statistical difference.

RESULTS

Twelve pigs entered the study. Mean body weight was 22.8 kg (range 19.2 – 25.2 kg). However, one pig died during surgical preparation; data of 11 pigs were analyzed.

Cardiorespiratory monitoring data including blood gas analysis are presented in table 2. As described in the anesthesia protocol, respiratory rate was adjusted to compensate for hypercapnia during the experiments ($ETCO_2$ > 7 kPa). This was done in 3 pigs: in 2 with an increase of five breaths/minute; in 1 with a two-stepped increase to a total of ten breaths/minute. Table 2 shows that the peak inspiratory pressure significantly increased

Table 2. Cardiorespiratory monitoring data

Characteristic	**IAP**			
	0 mm Hg	**5 mm Hg**	**10 mm Hg**	**15 mm Hg**
Heart rate (beats/min)	84 (15)	81 (17)	83 (18)	88(16)
Respiratory rate (breaths/min)	30 (7)	30 (7)	30 (8)	31(7)
pH (n=7 pigs)	7.44 (0.07)	7.43 (0.02)	7.40 (0.07)	7.37(0.02) †
pCO_2 kPa (n=7)	5.45 (0.96)	5.66 (0.65)	5.99 (1.40)	6.62(0.27) †
$ETCO_2$ kPa	5.81 (1.08)	5.94 (1.18) †	6.27 (1.29) †	6.49(1.67)
PIP cm H_2O	19 (2)	19 (2)	22 (2) †	28(3) †
BP (mm Hg)				
Systolic	102 (12)	99 (15)	104 (18)	109(13)
Diastolic	70 (15)	69 (17)	67 (18)	74(17)

$ETCO_2$ End tidal CO_2 measured by capnography
pCO_2 Partial pressure of CO_2 measured by blood gas analysis
PIP Peak inspiratory pressure
BP Blood pressure measured by arterial cannula
IAP intra-abdominal pressure

Data are presented as mean (SD)
† Statistically significant change from value at IAP 0 mm Hg

to a maximum of 28 cm H_2O when IAP was raised to 15 mm Hg. Mild hypercapnia ($ETCO_2$ 6.49 kPa) occurred with this increased IAP.

Regarding the linear dimensions on CT (figure 2), the mean internal AP diameter increased by 3.2 cm (from 8.8 to 12 cm) when IAP was raised from 0 to 5 mm Hg; a relative increase of 36%. This diameter increased by another 2.2 cm (to 14.2 cm) when IAP was raised from 5 to 10 mm Hg; a relative increase of 18%. At the final step from 10 to 15 mm Hg, the mean AP diameter increased by 0.8 cm; a relative increase of 5%.

In contrast to the AP diameter, the transverse diameter did not significantly increase with increasing pressure. It even slightly, but non-significantly (p=0.154) decreased at the maximum IAP of 15 mm Hg.

The mean distance between the pubic symphysis and the highest point of the peritoneal lining of the diaphragm increased a total of 2.2 cm (6% relative increase) with increasing intra-abdominal pressure. This increase was statistically significant (p<0.01).

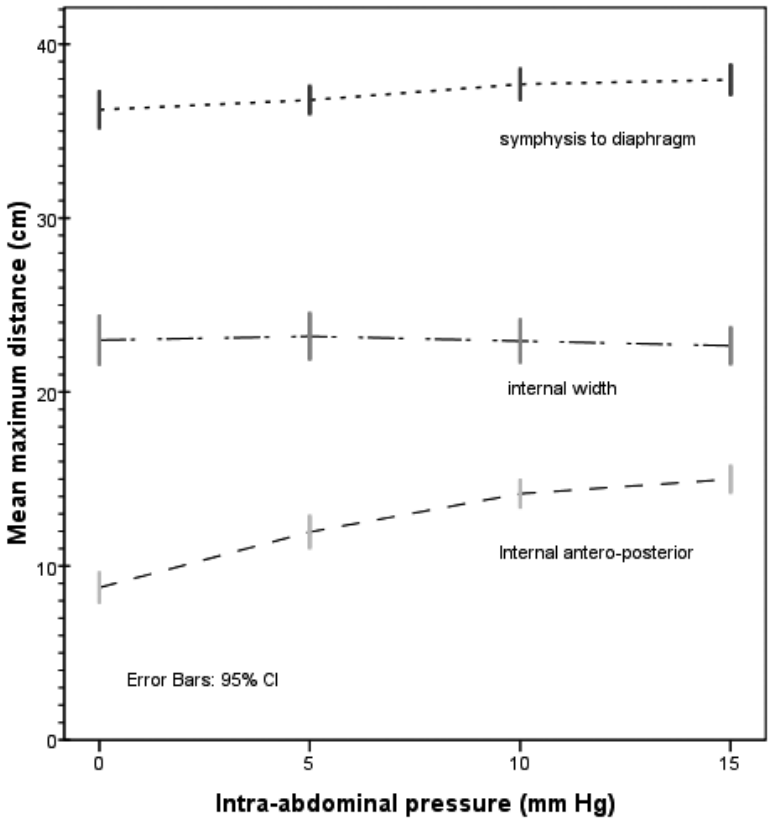

Figure 2.
Graph illustrating linear dimensions of the working space with increasing IAP

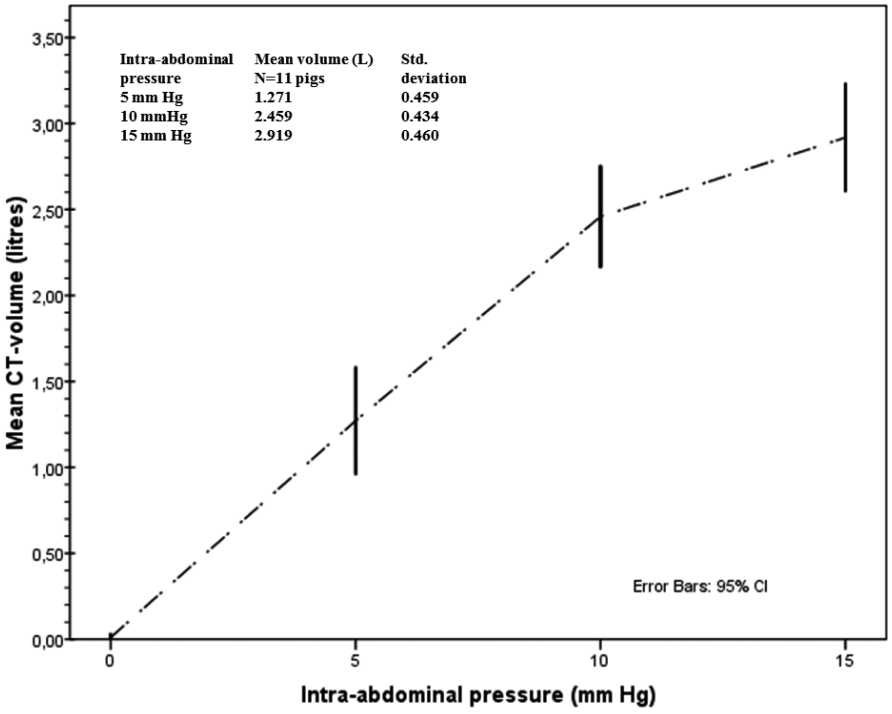

Figure 3.
Graph illustrating CT-volumes with increasing IAP

A combined pressure-volume curve for all 11 pigs is depicted in figure 3. It shows the CT-measured volumes of intra-abdominal CO_2 at the predefined intra-abdominal pressures. Mean volume of insufflated CO_2 at the lowest pressure of 5 mm Hg was 1.271 L. It increased to a mean of 2.459 L at 10mm Hg; a relative increase of 93%. At 15 mm Hg, it increased further to a mean of 2.919 L; a relative increase of 19%.

Figure 4 shows a Bland-Altman plot in which the volumes of intra-abdominal CO_2 measured on CT are plotted against the volumes as indicated on the electronic insufflator. The bias is 0.076 L, indicating that CT measures a somewhat larger volume than the insufflator. The limits of agreement are -0.31 to +0.47, a range of 0.79 L.

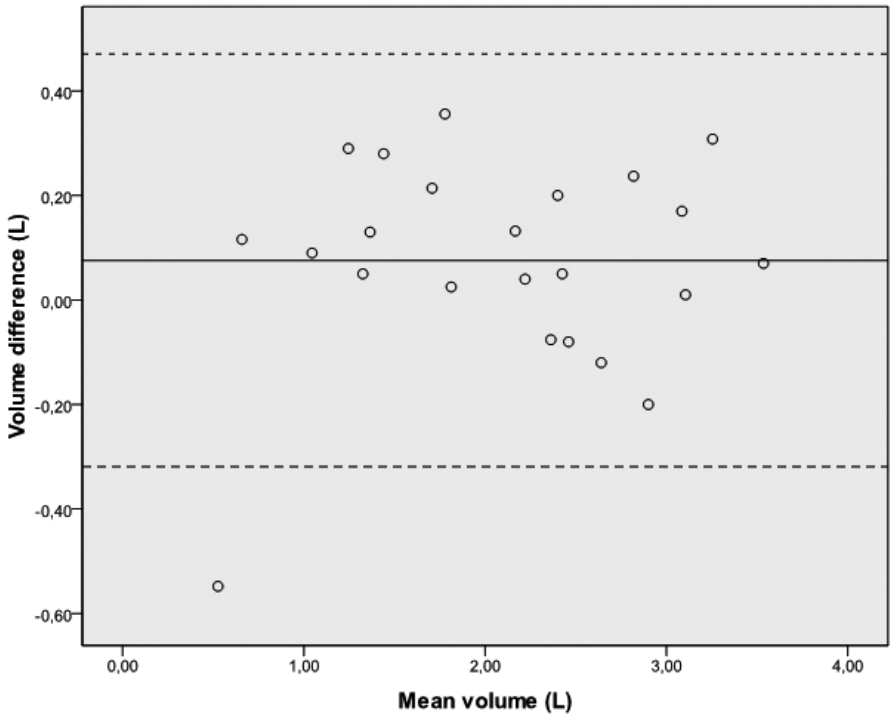

Figure 4
Bland-Altman plot
Ordinate: CT-volume minus insufflator volume (volume difference)
Abscissa: mean of volumes as measured by the 2 methods
Dashed lines represent limits of agreement

DISCUSSION

"The higher the pressure, the better the view" is a remark heard from surgeons involved in laparoscopic surgery [26]. This axiom is only true within limits. Pressure increments at higher pressures will cause less gain in working space than increments at lower IAP levels. This can be explained by the mechanical properties of the abdominal wall. The abdominal wall becomes progressively less compliant at higher levels of deformation (stretch)[27]. Song et al. described anisotropic mechanical properties of the abdominal wall based on the orientation of stiff connective tissue fibres [28, 29]. As explained in physiology textbooks, muscle-containing tissues have active and passive states where muscle tone greatly influences mechanical properties [30]. The stretching of muscles also influences the maximum force their sarcomeres can generate [31]. This makes the

abdominal wall a non-linear, anisotropic, dynamic and highly difficult to describe mechanical entity.

Moreover, increasing IAP negatively affects cardiorespiratory function and tissue oxygenation, and may result in more postoperative pain [6-14].

With this study we aimed to gain a more precise insight into the effects of increasing intra-abdominal pressure on working space distances and volume against the background of cardiorespiratory function. We created a quite stable porcine model using an anesthesia protocol that allowed for an $ETCO_2$ limit of 7 kPa (permissive hypercapnia). Levels of $ETCO_2$ rose with increasing IAP. Ventilator rate needed to be adjusted in three animals only in order to keep $ETCO_2$ within the desired limit. A statistically significant rise in PIP occurred when the insufflation pressure was raised to 10 and 15 mm Hg. Such high pressures may damage the lungs [32, 33]. A pneumoperitoneum pressure of 15 mm Hg is considered high for a juvenile 20 kg pig [34] and is considered to be the upper limit in laparoscopy in adult humans as well [6, 19].

CT showed a non-linear increase of the abdominal volume with increasing pressure (figure 3). The pressure rise to 10 mm Hg achieved the most gain in working space; the next step to 15 mm Hg achieved much smaller gain.

We found a marginal, but statistically significant cranial displacement of the diaphragm with increasing intra-abdominal pressure. The limited displacement is due to the volume-controlled ventilation with PEEP. The pneumoperitoneum transverse diameter did not change significantly. Therefore, the internal AP diameter was the only dimension substantially influenced by the intra-abdominal pressure created by CO_2 insufflation. For the best result this should be taken into account when positioning the patient and presenting the area of surgical interest [35, 36].

Use of the volume of CO_2 released by the insufflator as the only indicator of the amount of CO_2 that is in the abdomen results in errors due to gas-leakage, absorption of gas and effects of temperature and compressibility. In contrast, multi-planar CT-analysis of the working space is a reliable way to measure CO_2 peritoneum and its linear dimensions as it clearly depicts the boundaries of the actual working space (figures 1A and B) [37].

As shown in figure 3, the limits of agreement between the volumes measured on CT and the volumes indicated by the insufflator span a large range of 0.79 L. This inaccuracy is comparable to the size of the effect of interventions aimed at increasing working space.

Determining an optimal relationship between working space and homeostasis during laparoscopic procedures is not easy [16-22]. In contrast to our experiments, complex MAS in humans can take several hours, adding to the negative effects of the CO_2 pneumoperitoneum. Avoiding high insufflation pressure will counteract the negative influences of CO_2 insufflation [6, 14, 19, 26].

Exact measurement of the working space against the background of cardiorespiratory monitoring is imperative when studying how certain factors can influence the working space. CT-scanning allows for such an exact measurement. Pressure of pneumoperitoneum was the first factor we investigated. Experiments on the effects of other factors mentioned in table 1 are in preparation. The findings can help improve surgical and anesthesiological management in MAS.

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DISCLOSURES

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René Wijnen	No conflict of interest or financial ties to disclose
Robert Jan Stolker	No conflict of interest or financial ties to disclose
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CHAPTER 3

Bowel preparation prior to laparoscopic colorectal resection: What is the current practice?

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ABSTRACT

Background

Much has been published on the role of mechanical bowel preparation (MBP) in open colorectal resection; however current literature shows little evidence on the use of MBP prior to laparoscopic colorectal resections. In contrast to open procedures, MBP could influence the diameter of the bowel and thus the exposure of the surgical field in laparoscopy. This study aimed to assess the current practice of Dutch laparoscopic surgeons regarding MBP prior to colorectal resections.

Methods

In January 2010, members of the Dutch Association for Endoscopic Surgery were invited to fill out an online questionnaire investigating whether MBP is prescribed prior to laparoscopic colorectal surgery, and which considerations are taken into account when choosing or omitting MBP.

Results

The 82 (49%) returned questionnaires showed that 20% of respondents prescribe MBP prior to colonic resections, while 63% prescribe MBP prior to rectal resections. The most common reasons for giving MBP were the construction of a protective ileostoma (22%), improvement of the surgical field exposure (16%), and 'other reasons' specified by free text (21%). The three most common reasons for conversion were inadequate surgical field exposure (88%), locally advanced tumour (68%), and adhesions (29%). Concerning the question which stages of the operation are influenced by MBP 29% of respondents believed the diameter of the small bowel was influenced by MBP, 29% indicated that the exposure of the surgical field was influenced by MBP, and 52% did not believe that any of the stages of the operation were influenced by MBP.

Conclusion

The results of this questionnaire indicate that the implementation of MBP in laparoscopic colorectal surgery is based on individual preferences in the Netherlands. This emphasizes the need for new studies investigating the role of MBP on surgical field exposure in colorectal laparoscopic surgery.

INTRODUCTION

The introduction of laparoscopic procedures has led to an important progress in colorectal surgery. Not only does this technique achieve similar long-term results as the conventional open procedure, short-term results have been shown to be superior [1-4]. These include less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay. In case of colorectal cancer, which is the third most common cancer in the developed world, colorectal resection is the only curative treatment and short-term advantages obtained by laparoscopy represent an important difference for the operated patient. Long-term results, defined as disease-free survival, do not differ between patients operated through laparotomy or laparoscopy [2, 3].

Thorough mechanical cleansing of the bowel has long been considered essential prior to colorectal operations [5-7]. One believed an empty bowel would diminish the risk of anastomotic leakage and septic complications. However, during the last decade several studies have been conducted investigating the use of mechanical bowel preparation (MBP). Most recent randomized controlled trials and meta-analyses uniformly conclude that there is no advantage of MBP prior to colorectal resections, finding equal or lower rates of anastomotic leakage and septic complications in patients without MBP compared to patients with pre-operative MBP [8-17]. However, these studies have not included patients operated by means of minimally invasive techniques, and therefore this conclusion cannot be extrapolated to laparoscopic surgery. Logically, one does not expect the effect of MBP on anastomotic leakage and other septic complications to be different between patients with a laparoscopic or open approach. However, the effect of bowel preparation on the volume of the bowel, and thus on exposure, could play an important role in the course of the laparoscopic intervention itself. Contradictory opinions are found in literature concerning this subject [12, 16, 18], and very few studies have investigated the role of MBP prior to laparoscopic interventions [19, 20]. To evaluate the current practice among Dutch laparoscopic gastrointestinal surgeons we performed a questionnaire survey. The aim of this questionnaire was to investigate whether MBP is prescribed prior to laparoscopic colorectal surgery, and which considerations are taken into account when choosing or omitting MBP.

METHODS

The Dutch Society for Endoscopic Surgery (NVEC, Nederlandse Vereniging Endoscopische Chirurgie) was contacted and asked to participate in the study by sharing their members' contact information. In January 2010, members from the NVEC were invited by e-mail to fill out an online questionnaire on MBP prior to laparoscopic procedures.

Table 1. Summarized version of the questionnaire.

What is your surgical field of interest?
How many laparoscopic colonic- or rectal resections do you perform per month?
Do you prescribe MBP to your patient prior to laparoscopic colonic resections?
If yes: What MBP do you prescribe?
Do you prescribe MBP to your patient prior to laparoscopic rectal resections?
If yes: What MBP do you prescribe?
Why do you use MBP? (more than 1) - this is according to the guideline of the department - to improve exposure of the surgical field - to diminish postoperative septic complications - I do not use MBP - other:
How many degrees Trendelenburg do you position your patient?
What are your 3 major reasons for conversion? - adhesions - locally advanced tumour - inadequate surgical field exposure - difficult localization of the tumour - intra-abdominal haemorrhage or injury to organs - technical difficulties - patient obesity - other:
Do you feel MBP can influence: (more than 1) - the diameter of the small bowel - the ease of mobilizing the small bowel - operation time - exposure of the surgical field - risk of conversion - none of mentioned above - other:

The target group of this study comprised surgeons performing laparoscopic colorectal surgery. The answers were automatically submitted online at the end of the questionnaire. After two weeks the questionnaire was again sent to the members who had not yet responded.

The questionnaire consisted of 10 questions; 4 open and 6 multiple-choice questions. Of these 6 multiple-choice questions, 4 could be answered with "other" and specified with free text. Answers specified by free text were reviewed for validity (i.e. not just one letter or incoherent text).

Surgeons were asked whether they use MBP for laparoscopic procedures, what type of MBP they use, for what reason they use it, and what aspects of the procedure could be influenced by MBP. Because of the interest of this study in surgical field exposure, major reasons for conversion were asked, as well as the degree of Trendelenburg-positioning of the patient.

RESULTS

The NVEC has 247 members. Fifty-three surgeons not performing general surgery or gastro-intestinal surgery were not contacted (mostly gynaecologists, urologists, and thoracic surgeons). The online survey was sent to the remaining 194 members.

Thirty-five members did not receive it due to incorrect e-mail addresses (defined as e-mails that could not be delivered due to errors in the address or non-existing addresses), or responded that they did not perform gastro-intestinal surgery. Of the 169 laparoscopic surgeons that received the online survey, 82 responded (49%). In 84.1% of respondents lower gastro-intestinal surgery was included in their field of interest, 15.9% indicated that their field of interest was upper gastro-intestinal surgery. The median quantity of colorectal resections performed per month was 5 (3-7).

Twenty percent of respondents declared to give MBP prior to laparoscopic colorectal resections, while 63% of respondents declared to give MBP prior to laparoscopic rectal resections. The distribution of the different types of MBP can be found in figures 1 and 2. The median percentage Trendelenburg positioning of the patient was 30° (26.5° - 42.5°).

Of the 63% of respondents giving MBP, most common reasons for giving MBP are shown in figure 3. The construction of a protective ileostoma, not intending to leave a 'filled' colon, was the most frequent answer (22%), followed by 'other reasons' and free text (21%), and improvement of the surgical field exposure (16%). The two most frequent text when choosing 'other reasons' was (1) better handling of the bowel when it is empty and (2) easier introduction of the stapler. The three most common reasons for conversion were inadequate surgical field exposure (88%), locally advanced tumour (68%), and adhesions (29%) (figure 4). Concerning the question which stages of the operation are influenced by MBP, 52% of respondents believed that MBP does not influence any stage of the operation. Twenty-nine per cent of respondents thought that the diameter of the small bowel was influenced by MBP, and 29% indicated that the exposure of the surgical field was influenced by MBP (figure 5).

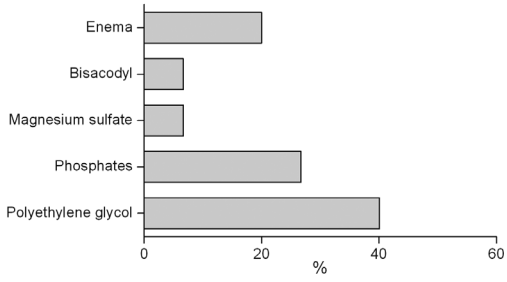

Figure 1.
Mechanical bowel preparation (MBP) used prior to colonic resection

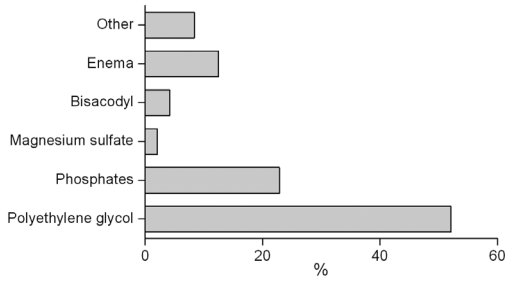

Figure 2.
MBP used prior to rectal resection

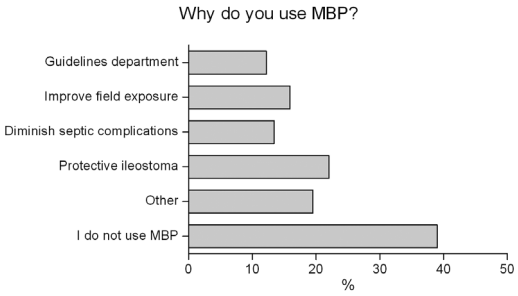

Figure 3.
Reasons for giving MBP

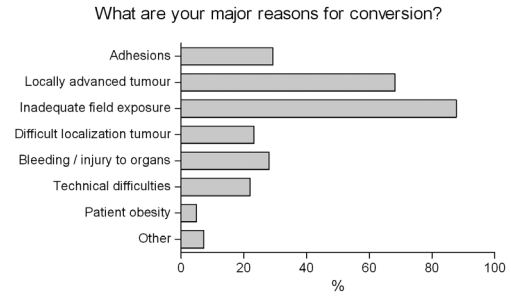

Figure 4.
Reasons for conversion from laparoscopic to open approach

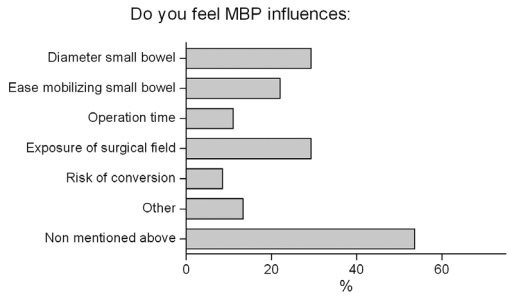

Figure 5.
Influence of MBP on different stages of the operation

DISCUSSION

Due to strong evidence that MBP does not lower the risk of anastomotic leakage and other septic complications in elective colorectal surgery [8-17], its standardized use has been abandoned in many centres. However, no studies regarding MBP have yet been conducted focusing on patients operated by means of minimally invasive techniques. In the Netherlands a significant part of colorectal resections is performed through laparoscopy nowadays, and the improved short-term results (less postoperative pain, earlier recovery of bowel function, less blood loss, shorter hospital stay) and similar disease-free survival rates have resulted in the important increase of laparoscopic procedures [1-4].

In our opinion, the results of studies on MBP and infectious complications can also be applied to laparoscopic surgery; however the effect of MBP on the volume of the bowel and its competition with the insufflated CO_2 influencing exposure could play an important role in the course of the laparoscopic intervention itself. Evidence-based guidelines concerning this issue are lacking, and contradictory opinions are found in literature concerning this subject. Guenaga and coworkers mention in their Cochrane review that it has been argued that it is easier to perform laparoscopic surgery if the bowel contains solid matter in order to use gravity to obtain better overview [12]. Slim and coworkers state in a meta-analysis that MBP usually results in dilated bowel which could hamper laparoscopic vision and make mobilization of the intestines more difficult [16]. Cheung and co-workers have described their results of a questionnaire on the technique of laparoscopic total mesorectal excision [18]. They find that most surgeons apply MBP routinely for different reasons, and that reduction of intestinal volume to facilitate laparoscopic exposure appears to be a specific incentive.

Two studies in literature evaluated the effect of MBP on exposure in gynaecologic laparoscopy. In the first study, performed by Muzii et al., patients were randomized between pre-operative MBP (90ml sodium phosphate) and no MBP; the endpoint was

the appropriateness of the surgical field as judged by the surgeon on a scale going from poor to excellent in five steps. No advantage of MBP on the evaluation of the surgical field could be demonstrated [19]. Another randomized trial, performed by Yang et al., divided patients in two groups. The first group received MBP through oral sodium phosphate solution; the second group received only a sodium phosphate enema. Assessment of the quality of the surgical field and bowel characteristics was performed using a surgeon questionnaire with Likert and visual analog scales. No significant differences were observed between the 2 groups in evaluation of the surgical field, bowel handling, degree of bowel preparation, or surgical difficulty [21].

The results of this questionnaire show that bowel preparation is still frequently used in laparoscopic colorectal procedures in the Netherlands, mostly in rectal resection. Sixteen percent of respondents prescribe MBP prior to surgery in order to improve surgical field exposure; on the other hand, inadequate surgical field exposure was by far the most common reason for conversion (88%). Almost a third of the respondents felt MBP might influence the diameter of the small bowel and the exposure; this can be placed in either a positive or a negative perspective since some feel MBP results in an emptied bowel and some in a bowel filled with liquid or gas bowel contents [22].

The most important limitation of this questionnaire is the response rate of 49%. A low response rate to questionnaires is a well-known problem, and to make the chances of response as high a possible we sent an online questionnaire by e-mail, made it as short as possible (10 questions), and with automatic sending of the results at the end of the questionnaire. Another limitation is the fact that ideally all Dutch surgeons performing laparoscopic gastro-intestinal procedures should have been contacted, however from a practical point of view that is not feasible. We have chosen to send this questionnaire through the Dutch Association of Endoscopic Surgery since that provided us an e-mail list of Dutch surgeons with particular interest for laparoscopic surgery.

A different questionnaire was performed by Wells et al., amongst 110 members of the Society of Gynecologic Oncologists of Canada to assess the practice pattern and beliefs on MBP [23]. The results show that half of the respondents routinely use MBP for gynaecologic oncologic surgery (laparotomy and laparoscopy). The most common reasons for using MBP were to decrease risk of anastomotic leak and to improve visualization.

To present, no evidence exists on the role of MBP on the diameter of the bowel and exposure in colorectal laparoscopy. To achieve optimal exposure in laparoscopic colorectal surgery, the small bowel has to be mobilized cranially. Several aspects can influence the ease of mobilizing the small bowel: the degree of muscle relaxation and Trendelenburg-position, the thickness of the omentum and mesocolon of the small bowel (related to Body Mass Index), and the diameter of the small bowel. The first aspect is in the hands of both surgeon and anaesthetist; the second aspect is patient-dependent and cannot be influenced. Concerning the diameter and contents of the small bowel and the ease

in which it can be mobilized only little is known. Whether a completely emptied bowel is preferable over normal stool contents in order to use gravity remains an unanswered question until now. Furthermore, it is questionable whether MBP can achieve a complete emptied bowel at all, or whether it will result in a more voluminous small bowel due to inadequate bowel cleansing and liquid or gas bowel contents [22]. The latter could also be influenced by the type of MBP being administrated and patient compliance.

The scarce quantity of studies regarding the subject of MBP in laparoscopy indicates the following: (1) Questionnaires regarding MBP indicate a number of laparoscopic surgeons use MBP with the aim to improve surgical field exposure (this study, [23]). (2) Randomized studies on MBP in gynaecologic laparoscopy seem to conclude that there is no amelioration of surgical field exposure with MBP. The difficulty in these studies is the outcome measure, which is the evaluation of the surgical field using a surgeon questionnaire [19, 21].

In conclusion, the results of this questionnaire show that the indication for MBP in laparoscopic colorectal surgery is undefined in the Netherlands. A review of literature shows the influence of MBP on diameter of the bowel and thus laparoscopic vision is not clear. Studies investigating the role of MBP on intestinal volume and surgical field exposure in colorectal laparoscopic surgery are necessary.

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CHAPTER 4

Optimizing working space in laparoscopy:
measuring the effect of mechanical bowel preparation in a porcine model

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ABSTRACT

Background

Adequate working space is a prerequisite for safe and efficient minimal access surgery. No objective data exist in literature about the effect of mechanical bowel preparation (MBP) on working space in laparoscopic surgery. We objectively measured this effect with computed tomography (CT) in a porcine laparoscopy model

Methods

Using standardized anesthesia, twelve 20kg pigs without MBP and eight 20 kg pigs with MBP were studied with computed tomography at intra-abdominal pressure (IAP) levels of 0, 5, 10 and 15 mm Hg. Volumes and dimensions of the pneumoperitoneum were measured on reconstructed CT-images and compared between the pigs with and those without MBP.

Results

A reproducible and statistically significant increase of around 500 ml in pneumoperitoneum volume was found in the MBP group at all levels of IAP. This represents a 43% relative increase at a pneumoperitoneum pressure of 5 mm Hg, 21% at IAP 10 mm Hg and 18% at IAP 15 mm Hg. Peak inspiratory pressure was lower at IAP 0 and 5 mm Hg in the MBP group. Antero-posterior diameter in the group with MBP was lower at 0 mm Hg, but abdominal dimensions were similar in both groups at all other IAPs. This shows the gain in working space is due to a diminished volume of the intra-abdominal content and not to compression or displacement of the bowel.

Conclusions

MBP increases working space by reducing bowel content. Especially at low intra-abdominal working pressures the increase in working space associated with MBP could represent an important benefit in challenging laparoscopic surgery.

INTRODUCTION

The introduction of laparoscopic procedures has led to important progress in colorectal surgery. Short-term results have been shown to be superior, including less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay [1-4]. Long-term results, defined as disease-free survival, do not differ between patients operated by means of laparotomy or laparoscopy [1, 3]. However, despite the short-term advantages, laparoscopy also has negative aspects. It has a longer learning curve [5] , increases operating-times and costs [2, 3] and it has the disadvantages of a CO_2 pneumoperitoneum [6-18]. Various solutions have been proposed to overcome the consequences of CO_2 pneumoperitoneum [19-23, 24]. Nevertheless, obtaining enough working space is essential for good view and handling of instruments [25-27].

Several factors influence working space, e.g. age and size of the patient, obesity, bowel content, pneumoperitoneum-pressure, positioning of the patient, use of systemic neuromuscular blocking agents and ventilation settings [28]. Whether preoperative mechanical bowel preparation (MBP) influences working space has not been established [29, 30]. However, several randomized controlled trials and meta-analyses have been conducted on MBP prior to colorectal operations, investigating its influence on anastomotic leakage and septic complications. The vast majority of studies conclude there is no advantage of MBP prior to colorectal resections regarding the aforementioned complications [31-38].

The aim of this study was to investigate in a porcine model whether MBP has a positive influence on working space during laparoscopy.

METHODS

Animals

Twenty female Landrace pigs, weighing approximately 20 kg, were studied: eight pigs received MBP while 12 pigs did not. The study was approved by the institutional animal ethics committee.

Mechanical Bowel Preparation

In the MBP group food was withheld and replaced by water ad libitum and sweetened water at 30 hours before the experiment. Animals were placed in cages without floor-coverage. At 24 hours and 8 hours before surgery, 20 ml of sodium phosphate was administered orally, followed by 100 ml of water. Pigs in the non MBP group were fed ad libitum until premedication.

Anaesthesia

All pigs were subjected to the same anesthesia protocol as described earlier by the authors [28]. After premedication with midazolam and ketamine in the animal housing facility, animals were brought to the laboratory and intubated. Maintenance anaesthesia consisted of sufentanil and propofol. No neuromuscular blocking agents were used for these experiments. Artificial ventilation was volume-controlled(10 ml/kg), with a positive end expiratory pressure (PEEP) set at 5 cm H_2O. Only the respirator frequency was adjusted when End-Tidal CO_2 ($ETCO_2$) rose above 7 kPa. Arterial and venous access was established. Heart rate, blood pressure, respiratory rate, peak inspiratory pressure (PIP) and $ETCO_2$ were measured continuously. A 5-mm radially expanding trocar (Versastep®, Covidien, Dublin, Ireland) was placed in the supra-umbilical midline. Its correct intra-abdominal position was verified endoscopically (Storz Telepack®, Tuttlingen, Germany, 5-mm 30° telescope).

Study protocol

With stable cardiorespiratory parameters, the pig was transported to the CT-scanner (Somatom Definition Flash Dual Source®, Siemens Healthcare, Erlangen, Germany). After installation of the pig on the scanning-tray, an electronic CO_2 insufflator (Endoflator®, Storz) was attached to the abdominal trocar. Breath-hold end-expiratory Computed Tomography (CT) of thorax and abdomen, lasting ca. 5 seconds, was performed at intra-abdominal pressures (IAP) of 0, 5, 10 and 15 mm Hg. At each pressure-level, a stabilization period of 5 minutes was taken into account and cardiorespiratory parameters were documented. After finishing the scans, the pig was euthanized.

Outcome measurements

Body weight as well as the total length of the first 5 lumbar vertebral bodies in a sagittal CT midline plane was measured. This CT length was measured to get an objective measure for the size of the pig, not dependent on food-status like the weight [39]. All pigs had 6 lumbar vertebrae, but the physiologic lordosis made measuring of the length of the first 5 lumbar vertebrae easiest and most reproducible.

Intra-abdominal volume of pneumoperitoneum was calculated with the Syngo 3D volume-module of a Siemens Navigator® workstation using a dataset of 5-mm slices. With the definition of appropriate thresholds, semi-automatic detection of CO_2 in the abdomen was done on transverse slices [40]. These could be integrated to a total volume of pneumoperitoneum. All volumes were visually checked for inadvertent inclusion of air in the bowel (figures 1A and B).

In a sagittal midline plane maximal external antero-posterior diameter of the abdomen and maximal distance between the upper border of the pubic symphysis and the highest diaphragmatic peritoneal lining was measured on CT-images at all levels of IAP. In a coronal plane the maximal external transverse diameter was measured (figure 1A and B).

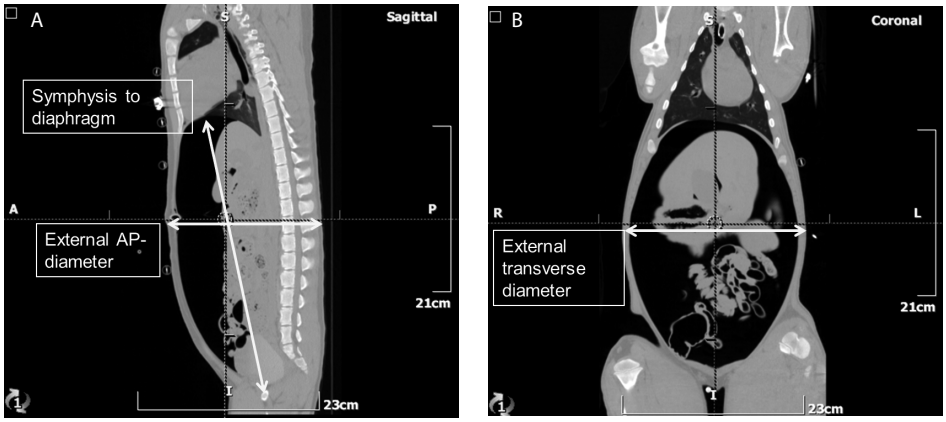

Figure 1A (left)
Reconstructed sagittal CT-image at an intra-abdominal pressure of 5 mm Hg. Measured are the maximal abdominal external antero-posterior (AP) diameter in a sagittal midline plane and the maximal distance between the upper border of the pubic symphysis and the highest diaphragmatic peritoneal lining

Figure 1B (right)
Reconstructed coronal CT-image at an intra-abdominal pressure of 5 mm Hg. Measured is the maximal abdominal external transverse diameter in a transverse and coronal plane

Statistics

Normality of the data was confirmed by means of visual assessment and Kolmogorov Smirnov testing. Data are presented as means with standard errors of the mean. Differences between groups were assessed using an independent samples *t*- test. A *p*-value lower than 0.05 was considered significant.

RESULTS

One pig in the non MBP group died during surgical preparation leaving the data of 19 pigs eligible for analysis. There was no statistically significant difference in body weight

Table 1. Body weight and length of first five lumbar vertebrae

	Non MBP Mean(SEM)	MBP Mean(SEM)	*p* value
Weight (kg)	22.7 (0.65)	21.5 (0.47)	0.15
Length vertebrae (cm)	11.77 (0.10)	11.87 (0.09)	0.50

MBP mechanical bowel preparation
SEM standard error of the mean

or in length of the first five lumbar vertebrae between the non-MBP and the MBP group but mean body weight was 1.2 kg lower in the MBP group (table 1). Cardiorespiratory parameters are shown in table 2. Changes in respiratory rate to compensate for hypercapnia were made in 3 pigs in the non-MBP group (average increase 10 breaths/min) and 5 pigs in the MBP group (average increase 14 breaths/min). PIP was significantly lower in the MBP group at IAP of 0 and 5 mm Hg. This reduction in PIP disappeared at IAPs of 10 and 15 mm Hg.

Table 2. Cardiorespiratory parameters (mean values)

IAP	0 mm Hg		5 mm Hg		10 mm Hg		15 mm Hg	
	MBP-	MBP+	MBP-	MBP+	MBP-	MBP+	MBP-	MBP+
MAP	80.3	94.4	79.2	96.3	79.7	91.4	85.5	88.9
HR	83.7	88.1	81.1	76.0	83.3	78.0	88.4	81.4
RR	29.6	28.8	29.6	28.8	30.5	28.8	31.4	32.5
PIP	19.2	16.8*	19.0	16.8*	22.3	21.1	28.1	27.4
$ETCO_2$	5.8	5.8	5.9	6.2	6.3	6.6	6.5	6.6

A significant difference exists in PIP between non-MBP and MBP pigs at 0 mm Hg (*p* value 0.02) and 5 mm Hg (*p* value 0.03).
* Significant, unpaired *t* test

IAP intra-abdominal pressure
MBP mechanical bowel preparation
MAP mean arterial blood pressure (mm Hg)
HR heart rate (beats/min)
RR respiratory rate (breaths/min)
PIP peak inspiratory pressure (cmH_2O)
$ETCO_2$ End-tidal CO_2 (kPa)

Table 3. Volumes of pneumoperitoneum (ml)

IAP	Non MBP	MBP	Difference (% increase)	*p*-value
	Mean (SEM)	Mean (SEM)	Mean	
0 mm Hg	11 (7)	21 (2)	9	0.27
5 mm Hg	1271 (138)	1823 (130)	551 (43.4%)	0.01*
10 mm Hg	2459 (131)	2968 (165)	509 (20.7%)	0.03*
15 mm Hg	2919 (140)	3438 (167)	519 (17.8%)	0.03*

* $p < 0{,}05$

IAP intra-abdominal pressure
MBP mechanical bowel preparation
SEM standard error of the mean

When comparing the CT pneumoperitoneum volumes at different IAPs between groups, pigs in the MBP group had a significantly higher pneumoperitoneum volume, gaining approximately 500 ml at each IAP level (table 3). The relative increase associated with MBP was 43% at IAP 5mm Hg, 21% at 10 mm Hg, and 18% at 15 mm Hg. The pneumoperitoneum volume attained at IAP 10 mm Hg with MBP was similar to the volume at IAP 15 mm Hg without MBP.

The dimensions of the abdomen are presented in table 4. As can be seen, a difference in antero-posterior diameter of the abdomen exists between the non-MBP and MBP group only in the non-insufflated state. There were no significant differences in transverse diameter or symphysis-to-diaphragm distance of the abdomen between the non-MBP and MBP group.

Table 4. Dimensions of the abdomen in centimeters (see also Figures 1A and B).

	IAP (mm Hg)	Non MBP Mean (SEM)	MBP Mean (SEM)	*p* value
External AP diameter	0	15.4 (0.37)	13.5 (0.30)	0.02
	5	18.5 (0.36)	17.9 (0.42)	NS
	10	20.6 (0.29)	19.8 (0.43)	NS
	15	21.4 (0.29)	20.7 (0.41)	NS
External transverse diameter	0	25.4 (0.53)	24.4 (0.24)	NS
	5	25.4 (0.51)	24.3 (0.28)	NS
	10	25.0 (0.46)	24.3 (0.31)	NS
	15	24.9 (0.45)	24.3 (0.26)	NS
Symphysis to diaphragm distance	0	36.2 (0.47)	36.3 (0.43)	NS
	5	36.8 (0.36)	37.2 (0.48)	NS
	10	37.7 (0.40)	38.1 (0.55)	NS
	15	38.0 (0.39)	38.4 (0.45)	NS

IAP intra-abdominal pressure
AP antero-posterior
MBP mechanical bowel preparation

DISCUSSION

The standard use of MBP has been largely abandoned, since studies have proven its use does not diminish the risk of anastomotic leakage or wound infections [31-38]. However, the relationship between MBP and working space in laparoscopic surgery is still matter of debate. The two level 1A studies on MBP in open colorectal surgery have contradictory discussions on the theoretical influence of MBP in laparoscopy. It has been argued that it is easier to perform laparoscopic surgery if the bowel contains solid matter in order to use gravity to obtain better overview [35], or that MBP results in dilated bowel

which could hamper laparoscopic vision and make mobilization of the intestines more difficult [37].

Only a few studies have evaluated the effect of MBP on exposure in gynaecologic laparoscopy. In the first study, performed by Muzii et al., patients were randomized between pre-operative MBP (sodium phosphate) and no MBP; the endpoint was the appropriateness of the surgical field as judged by the surgeon on a scale going from poor to excellent in five steps [29]. No advantage of MBP on the evaluation of the surgical field could be demonstrated. Another randomized trial, performed by Yang et al., divided patients undergoing gynaecologic laparoscopy in two groups [30]. The first group received MBP through oral sodium phosphate solution; the second group received only a sodium phosphate enema. Assessment of the quality of the surgical field and bowel characteristics was performed using a surgeon questionnaire with Likert and visual analog scales. No significant differences were observed between the 2 groups in evaluation of the surgical field, bowel handling, degree of bowel preparation, or surgical difficulty.

Two additional surveys (laparoscopic colon and rectum surgery, and laparoscopic gynaecology) show MBP is still used for different reasons in these fields of laparoscopy [41, 42]. One of these reasons is the possible influence MBP could have on surgical field exposure.

All these studies reflect individual preferences rather than evidence based practice. Moreover, the surgeon's evaluation of the working space may be too subjective to detect significant differences in outcome.

For this reason we conducted this animal study, aiming to investigate whether MBP has an influence on laparoscopic working space. The results show a significant increase in pneumoperitoneum volume in the group receiving MBP pre-operatively. This gain in pneumoperitoneum volume of 500 ml CO_2 is independent of the pressure of pneumoperitoneum, and represents a relative increase of 43% at 5 mm Hg and 21% at 10 mm Hg and 18% at 15 mm Hg. Consequently, with pre-operative MBP, the same volume of pneumoperitoneum can be obtained at lower IAPs (table 3).

Concordantly, mechanical ventilation is easier in MBP pigs at low pneumoperitoneum pressures (diminished peak inspiratory pressure at 0 and 5 mm Hg in the MBP group, table 2). Antero-posterior diameter in the group with MBP was lower at 0 mm Hg, but abdominal dimensions were similar in both groups at all other IAPs. This shows the gain in working space is due to a diminished volume of the intra-abdominal content and not to compression or displacement of the bowel (table 4).

In this animal study our choice for MBP was sodium phosphate. The most commonly prescribed preparations for bowel cleaning in humans are sodium phosphate (90 ml), poly-ethylene glycol (PEG, 4 L), and magnesium citrate (300 mL). Literature shows sodium phosphate has the highest patient compliance, and least residual stool [43-45] In animals orogastric intubation is required to administer large volumes of lavage solution

over several minutes, leading to discomfort, struggling, and apparent increased stress [46]. Sodium phosphate is a low-volume, hyperosmolar, buffered saline laxative that osmotically draws water into the gastrointestinal tract lumen. It relies on osmotic action to draw plasma water into the colon to soften and flush faecal material out of the colon [44, 45]. Its use for mechanical bowel preparation in pigs prior to colonoscopy is shown by Pfeffer et al. [47] .

A difference between the two groups of pigs, except for MBP, is the duration of fasting. Food was withheld from pigs receiving MBP beginning the day before the experiment. Whether this also influences the volume of intra-abdominal content or might have caused the 1.2 kg difference in mean body weight has not been investigated in this study. This raises the question of the necessity of MBP. In a blinded, randomized controlled trial in gynaecologic laparoscopic surgery for benign disease, a 7-day low fiber diet gave as good exposure as PEG (scored by the surgeon) but was far better tolerated [48].

In conclusion, MBP prior to laparoscopy in pigs results in an increased volume of CO_2 pneumoperitoneum, irrespective of IAP. This could represent an important benefit in technically challenging intestinal and non-intestinal laparoscopic surgery. The relative gain in volume of CO_2 pneumoperitoneum by MBP is highest at lower insufflation pressures, which can be helpful in low-pressure laparoscopic surgery, as is custom in pediatric surgery.

Further studies are necessary to investigate whether a similar effect could be obtained with more patient-friendly bowel preparations such as low-fiber diet.

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John Vlot	No conflict of interest or financial ties to disclose
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René Wijnen	No conflict of interest or financial ties to disclose
Johan Lange	No conflict of interest or financial ties to disclose
Klaas Bax	No conflict of interest or financial ties to disclose

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CHAPTER 5

Optimizing working space in laparoscopy:
CT measurement of the effect of pre-stretching of the abdominal wall in a porcine model

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ABSTRACT

Background

Determinants of working space in minimal access surgery have not been well studied. Using computed tomography (CT) to measure volumes and linear dimensions, we are studying the effect of a number of determinants of CO_2 working space in a porcine laparoscopy model. Here we report the effects of pre-stretching of the abdominal wall.

Methods

Earlier we had noted an increase in CO_2 pneumoperitoneum volume at repeat insufflation with an intra-abdominal pressure (IAP) of 5 mm Hg after previous stepwise insufflation up to an IAP of 15 mm Hg. We reviewed the data of this serendipity group. Data of 16 pigs were available. In a new group of 8 pigs, we explored this effect also at repeat IAPs of 10 and 15 mm Hg. Volumes and linear dimensions of the CO_2 pneumoperitoneum were measured on reconstructed CT-images and compared between the initial and repeat insufflation runs.

Results

Previous stepwise insufflation of the abdomen with CO_2 up to 15 mm Hg significantly ($p < .01$) increased subsequent working space volume at repeat 5 mm Hg by 21%, 7% at repeat 10 mm Hg and 3% at repeat 15 mm Hg. The external antero-posterior diameter significantly ($p < .01$) increased by 0.5 cm (14%) at repeat 5 mm Hg. Other linear dimensions showed a much smaller change. There was no statistically significant correlation between the duration of the insufflation-run and the volume-increase after pre-stretching at all IAP levels.

Conclusions

Pre-stretching of the abdominal wall allows for the same surgical-field exposure at lower IAPs, reducing the negative effects of prolonged high-pressure CO_2 pneumoperitoneum on the cardiorespiratory system and microcirculation. Pre-stretching has important scientific consequences in studies addressing ways of increasing working space in that its effect may confound the possible effects of other interventions aimed at increasing working space.

INTRODUCTION

Minimal access surgery (MAS) has gained acceptance in all major surgical specialties [1, 2]. It has clear benefits for patients in that it brings faster recovery and better cosmetic and functional outcome [3-8]. It does however require a different set of motor-skills from the surgeon, is more difficult and more costly [6, 9, 10]. Furthermore, sufficient working space is required for safety and efficiency of the procedure [11-13]. This is usually created by means of CO_2 insufflation [14]. Little basic scientific research has focused on the determinants of the dimensions of this CO_2 created working space [15]. Only some of the determinants e.g. IAP can be influenced to increase the working space [16]. We have studied a number of these factors in a porcine laparoscopy model [16, 17]. In experiments with mechanical bowel preparation (MBP) and neuromuscular blockade (NMB) we serendipitously found that previous stepwise insufflation up to an intra-abdominal pressure (IAP) of 15 mm Hg had a positive effect on CO_2 pneumoperitoneum volume at repeat insufflation with an IAP of 5 mm Hg. This pre-stretching effect hampered interpretation of the effect of neuromuscular blockade. We therefore decided to first further study and quantify it. In a new series of experiments using the same porcine laparoscopy model we studied whether pre-stretching of the abdominal wall would increase working space not only at a repeat IAP of 5 mm Hg, but also at repeat IAPs of 10 and 15 mm Hg. Pre-stretching of the abdominal wall could be used as a method to increase the working space at a given IAP, on the premise that a high IAP can be tolerated for small periods of time. The larger working space would allow for the same surgical-field exposure at lower IAPs, reducing the negative effects of prolonged high-pressure CO_2 pneumoperitoneum on the cardiorespiratory system and microcirculation [18-22]. In this manuscript we examine the effect of pre-stretching on CO_2 pneumoperitoneum volume and linear dimensions.

METHODS

Animals

Female Landrace pigs weighing approximately 20 kg were studied. All experiments were approved by the institutional animal ethics committee. From earlier experiments we had usable scan data of 16 pigs, 9 without MBP and 7 with MBP, at a repeat IAP of 5 mm Hg (serendipity group). In all animals working space dimensions were assessed at 0, 5, 10 and 15 mm Hg. Working space was re-assessed in a second run of insufflation up to 5 mm Hg, before NMB. In an additional 8 animals (new study group) we specifically looked into the effect of pre-stretching of the abdominal wall. Again IAP was stepwise increased. Working space was re-assessed during a second run of abdominal insufflation, now not

only at an IAP of 5 mm Hg, but also at 10 and 15 mm Hg. Pigs were euthanized after the experiments.

Anesthesia and instrumentation

A standardized anesthesia protocol was used as in earlier experiments [16, 17]. In short: after premedication with intramuscular midazolam and ketamine animals were intubated and venous as well as arterial vascular access was attained. Anesthesia was maintained with sufentanil and propofol. Artificial ventilation was volume-controlled (tidal volume 10 ml/kg). Respirator frequency was adjusted when end-tidal CO_2 ($ETCO_2$) rose above 7 kPa. A 5-mm trocar was placed in the supra-umbilical midline.

Study protocol

An electronic CO_2 insufflator (Endoflator®, Storz, Tuttlingen, Germany) was used for abdominal insufflation. IAP was set at 0, 5, 10 and 15 mm Hg and maintained constant for 5 minutes at each level. At each pressure, computed tomography (CT) (Somatom Definition Flash Dual Source®, Siemens Healthcare, Erlangen, Germany) of the abdomen was performed during breath-hold at a positive end expiratory pressure (PEEP) of 5 cm H_2O. Table 1 summarizes the experimental setup.

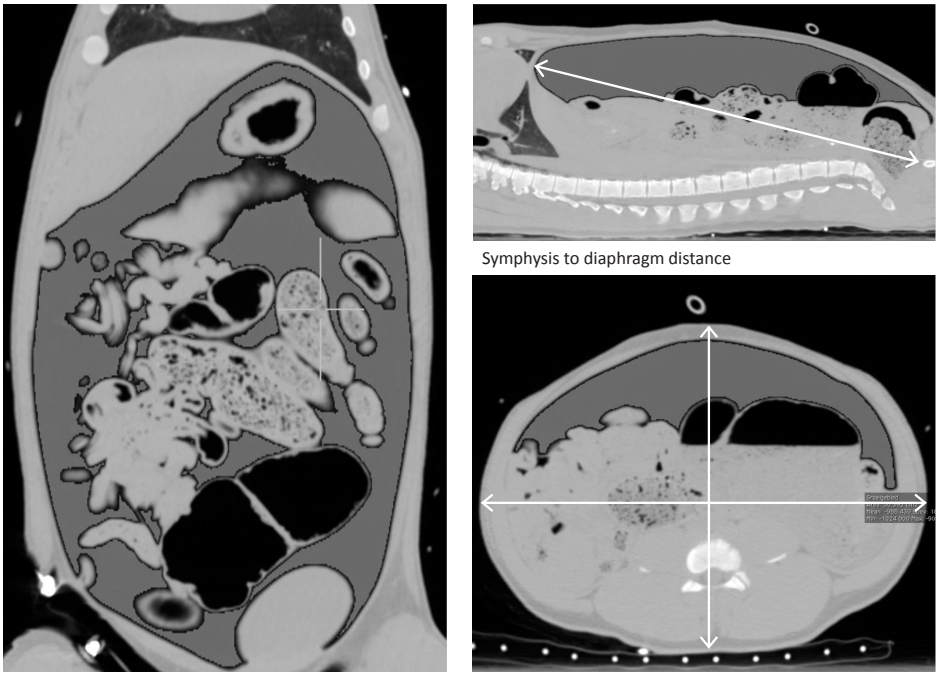
Table 1. Study design. CT-scans were made at all IAP levels after a 5 minute stabilization period

	Serendipity group		**New study group**
	No-MBP n=9	**MBP n=7**	**n=8**
Weight (kg) (SEM)	22.5 (0.77)	21.3 (0.49)	22.7 (0.56)
L_{1-5} (cm) (SEM)	11.7 (0.10)	11.8 (0.09)	11.8 (0.11)
IAP (first run)	0	0	0
	5	5	5
	10	10	10
	15	15	15
		Desufflation of the abdomen	
IAP (second run)	0	0	0
	5	5	5
			10
			15

MBP mechanical bowel preparation
SEM standard error of the mean
L_{1-5} length of first 5 lumbar vertebrae
IAP intra-abdominal pressure

Outcome measurements

Body weight and total length of the first five lumbar vertebrae were measured [23]. Heart rate, blood pressure, respiratory rate, peak inspiratory pressure (PIP) and $ETCO_2$ were recorded. Volumes of CO_2 pneumoperitoneum and abdominal linear dimensions were measured using a dataset of 1-mm slices in Osirix® [16, 17] (figure 1).



Calculated volume of pneumoperitoneum (dark grey area)

Symphysis to diaphragm distance

External AP and transverse diameter

Figure 1.
Reconstructed CT-images showing the dimensions of CO_2 pneumoperitoneum and working distances
AP Antero posterior

Statistics

Normality of the data was confirmed by visual assessment and Kolmogorov Smirnov testing. Data are presented as mean with standard errors of the mean (SEM). Differences between groups were assessed with an independent samples *t* test. Differences within the same animal were assessed with a paired-samples *t* test. A Pearson product-moment correlation coefficient with 2-tailed significance was computed to assess the relationship between the duration of the insufflation-run and the volume-increase after pre-stretching. A p value of $< .05$ was considered significant.

RESULTS

Weight and lumbar length did not differ significantly between all study groups. One pig in the new study group developed a cardiac effusion due to a perforation from the introducer of the venous catheter (Arrow®, percutaneous sheath introducer set 8.5Fr). This was quickly diagnosed and could be managed by CT-guided pericardiocentesis without lasting hemodynamic consequences.

Breath-hold during each scan never lasted longer than 20 seconds. Median total duration of the first insufflation run was 20 minutes (range 18-35 min). Variation in the duration of the insufflation-run was the result of a variety of issues, including technical problems with the CT-scanner and IV pumps, requiring our attention during the experiments. As described earlier [16, 17], cardiorespiratory data showed a significant increase in PIP with IAP upwards of 10 mm Hg whilst $ETCO_2$ was maintained below 7 kPa by minor increments of respiratory rate (data not shown here).

Mean CO_2 pneumoperitoneum volume in the pigs from the serendipity group that did not receive MBP increased from 1245 ml (SEM 167) during the first insufflation run at an IAP of 5 mm Hg to 1575 ml (SEM 162) at the second insufflation run at 5 mm Hg. This 330 ml increase (27%) was statistically significant ($p < .01$). Pigs from the serendipity study group that received MBP had a larger mean CO_2 pneumoperitoneum volume of 1845 ml (SEM 148) during the first insufflation run at an IAP of 5 mm Hg. It increased to 2137 ml (SEM 137) at the second insufflation run. This 292 ml increase (16%) was statistically significant ($p < .01$).

The rise in volume at the second insufflation run was not significantly different between pigs without and those with MBP ($p = .732$, unpaired *t*-test).

In the new study group volume rose from 1403 ml (SEM 183) to 1691 ml (SEM 220) at the second insufflation run to 5 mm Hg. This increase of 288 ml (21%) was statistically significant ($p < .01$). Combining the data of all 24 pigs from the serendipity and new study group at an IAP of 5 mm Hg resulted in an increase from 1472 ml (SEM 107) to 1777 ml (SEM 110). This 305 ml (21%) increase was statistically significant ($p< .01$).

In the new study group, at repeat IAP of 10 mm Hg, volume had increased from 2628 ml (SEM 235) to 2819 ml (SEM 263). This increase of 191 ml (7%) was significant ($p < .01$). At repeat IAP of 15 mm Hg, volume had increased from 3189 ml (SEM 262) to 3290 ml (SEM 271). This 101 ml increase (3%) was significant ($p < .01$).

Results are summarized in table 2.

Of the linear dimensions (figure 1), external antero-posterior (AP) diameter rose by 0.5 cm (14%) at repeat IAP of 5 mm Hg ($p < .01$). Some increases in other linear dimensions

Table 2. Volumes of CO_2 pneumoperitoneum before and after pre-stretching

	n	IAP	1st run Mean (SEM)	2nd run Mean (SEM)	Mean difference (% increase)	*p* value
Serendipity group	9 (no-MBP)	5	1245 (167)	1575 (162)	330 (27%)	0.005[a]
	7 (MBP)	5	1845 (148)	2137 (137)	292 (16%)	0.001[a]
New study group	8	5	1403 (183)	1691 (220)	288 (21%)	0.001[a]
Combining all groups at IAP 5 mm Hg	24	5	1472 (107)	1777 (110)	305 (21%)	0.000[a]
New study group	8	10	2628 (235)	2819 (263)	191 (7%)	0.002[a]
	8	15	3189 (262)	3290 (271)	101 (3%)	0.000[a]

[a] significant, paired *t* test

MBP mechanical bowel preparation
IAP intra-abdominal pressure
SEM standard error of the mean

were significant as well, maximum increase however did not exceed 0.2 cm. Working space linear dimensions at first and second insufflation run are shown in figure 2.

There was no statistically significant correlation between the duration of the insufflation-run and the volume-increase after pre-stretching at all IAP levels.

DISCUSSION

Pre-stretching of the abdominal wall by a previous stepwise insufflation with CO_2 up to 15 mm Hg significantly increased subsequent working space volume by 21% at repeat 5 mm Hg, 7% at repeat 10 mm Hg and 3% at repeat 15 mm Hg. All working space linear dimensions increased after pre-stretching. Although several of these increases are statistically significant, most will probably have little clinical impact. An exception can be made for the 0.5 cm increase in external AP diameter at repeat IAP of 5 mm Hg. Here, the actual intra-abdominal working distance in the AP-direction at an IAP of 5 mm Hg is 3.6 cm (18.1 cm at IAP=5 mm Hg minus 14.5 cm at 0 mm Hg). Consequently, the 0.5 cm increase adds 14% in working distance.

Pre-stretching seems especially effective at lower IAPs. Small gains in AP working space distance may be important when working space is very limited and high IAPs are not tolerated e.g. in laparoscopic surgery in small children. To illustrate this, working space volume in the full term neonate is only 300 ml.

Figure 2.
Linear working space dimensions during first and second run of abdominal insufflation (combined data of serendipity and new study group)

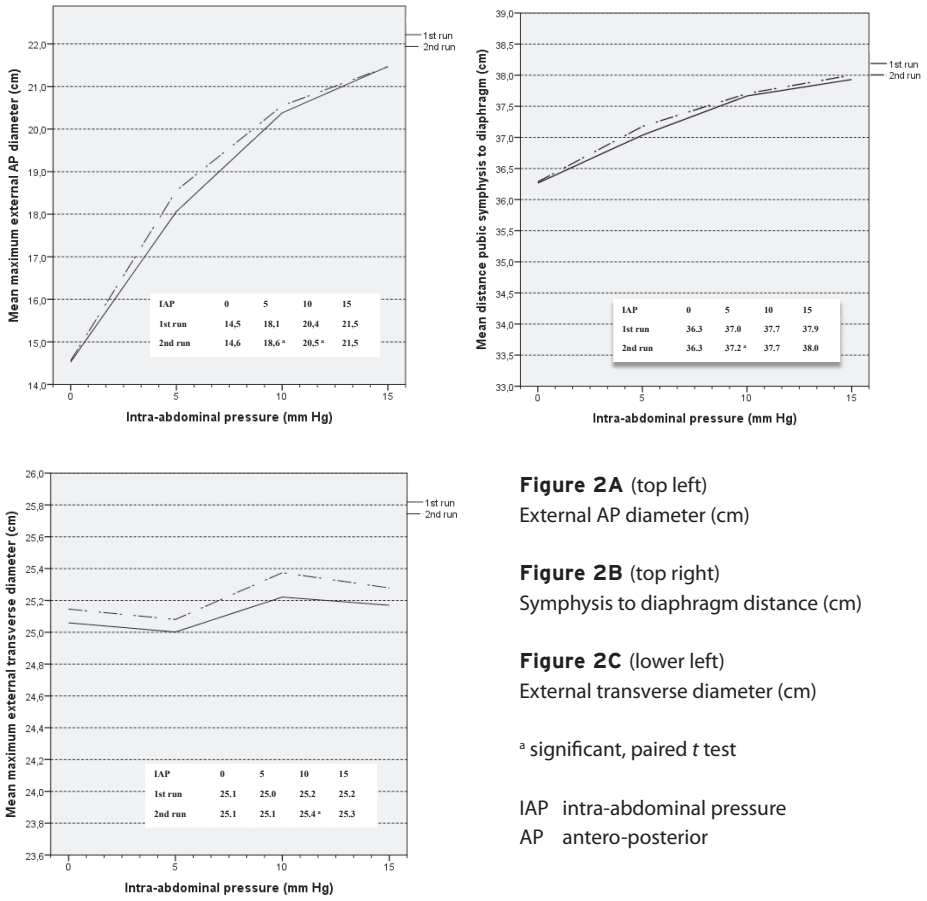


Figure 2A (top left)
External AP diameter (cm)

Figure 2B (top right)
Symphysis to diaphragm distance (cm)

Figure 2C (lower left)
External transverse diameter (cm)

[a] significant, paired *t* test

IAP intra-abdominal pressure
AP antero-posterior

In the serendipity group, working space volume at an IAP of 5 mm Hg in animals with MBP was higher than that in animals without MBP. In earlier experiments in these animals we found that MBP resulted in a significant increase (500 ml) in working space volume at all IAPs [17]. The higher volume in the first run explains the relatively smaller effect of pre-stretching in this group. The absolute increase of around 300 ml in CO_2 pneumoperitoneum volume at an IAP of 5 mm Hg did not significantly differ between all groups.

Apart from effects on working space dimensions, pre-stretching may provide a form of ischemic preconditioning. Increased IAP has adverse effects on splanchnic circulation and desufflation may result in ischemia/reperfusion injury [24]. In a rat model, less

ischemia/reperfusion injury was noted after increasing IAP in a stepwise fashion as well as after short single insufflation up to 15 mm Hg followed by re-insufflation [25, 26]. In one of the cited studies, duration of the pre-conditioning period (5 or 10 minutes) did not influence the beneficial effect [25]. These and other studies on oxidative stress focus on biochemical markers of ischemia/reperfusion injury resulting from CO_2 pneumoperitoneum, but do not address clinical impact.

The median total stepwise pre-stretching period (duration of the first insufflation run) was 20 minutes. From the present data we cannot deduce what the minimum period at relatively high IAP has to be to increase abdominal compliance. Neither can we deduce whether pre-stretching is best done in a stepwise fashion or not. Future studies should also shed a light on how long the effect of pre-stretching will last. A consequence of a stepwise pre-stretching policy is that operation time is prolonged by the period of pre-stretching. The expected advantage of pre-stretching has to outweigh this disadvantage. The clinical impact of pre-stretching has yet to be determined. In research dealing with working space however, the effect of pre-stretching has to be taken into account as it may confound the possible effects of other interventions aimed at increasing working space.

CONCLUSIONS

Results from this experimental animal study show that pre-stretching of the abdominal wall results in a significant increase in abdominal working space. The increase is relatively higher at lower insufflation pressures. The best way and optimal duration of pre-stretching deserve further study.

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DISCLOSURES

John Vlot	No conflict of interest or financial ties to disclose
René Wijnen	No conflict of interest or financial ties to disclose
Robert Jan Stolker	No conflict of interest or financial ties to disclose
Klaas Bax	No conflict of interest or financial ties to disclose

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CHAPTER 6

Optimizing working space in laparoscopy:
CT measurement of the effect of neuromuscular blockade and its reversal in a porcine model

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MINIABSTRACT

Using computed tomography, the effect of neuromuscular blockade on laparoscopic working-space dimensions was investigated in a standardized porcine laparoscopy model. No statistically significant effect of neuromuscular blockade on abdominal dimensions or CO_2 pneumoperitoneum volume was found.

ABSTRACT

Objective

To determine the effect of neuromuscular blockade (NMB) on working space in a porcine laparoscopy model

Background

Conflicting results on the effect of NMB on laparoscopic working space are found in literature. All studies are limited by lack of objective assessment of working space or use surrogate outcomes.

Methods

In a standardized porcine laparoscopy model, laparoscopic working-space dimensions with and without NMB were investigated in 16 animals using computed tomography at intra-abdominal pressures of 0, 5, 10 and 15 mm Hg during multiple runs of abdominal insufflation.

Results

No statistically significant effect of NMB on abdominal dimensions and laparoscopic working-space volume was found. In contrast, the effect of pre-stretching of the abdominal wall by a previous abdominal insufflation was found to be significant.

Conclusions

This experimental study confirms the results from several clinical studies that NMB does not influence laparoscopic working space. Studies dealing with working space during laparoscopy should take note of pre-stretching bias.

INTRODUCTION

Optimizing working space is essential for safe and efficient minimal access surgery (MAS) [1-4]. It seems logical to assume that decreasing muscle tone by neuromuscular blockade (NMB) will have a positive effect on working space during laparoscopic surgery. However, the available literature on this subject is scarce and does not support this assumption, neither experimentally [5], nor clinically [6-8]. Almost all clinical studies used surgeon's subjective assessment of working space [6-10] or the duration of surgery [7-11] as endpoints. In addition, the level of neuromuscular block was not well documented in some of the studies [7, 8]. As working space in laparoscopic surgery is strongly related to the age/size of the patient, it becomes more critical in small children [12]. Even a small gain in working space can markedly improve surgical conditions in this patient group. To measure the effect of various interventions on laparoscopic working space we have previously developed a porcine model with standardized anesthesiologic and surgical techniques [13]. Computed tomography (CT) was used to accurately measure laparoscopic working-space dimensions. The present study evaluates the effect of NMB and its reversal on laparoscopic working-space dimensions in this animal model.

METHODS

Animals

Sixteen juvenile female Landrace pigs, weighing approximately 20 kg were studied. Approval was obtained from the institutional animal ethics committee.

Anesthesia

Pigs were subjected to a similar anesthesiologic protocol as used in prior experiments [13]. In short: Premedication consisted of intra-muscular midazolam (1 mg/kg) and ketamine (30 mg/kg). Tracheotomy was performed after cannulation of an auricular vein and induction of anesthesia with propofol (1.5 mg/kg) and sufentanil (5 mcg/kg). Anesthesia was maintained with intravenous sufentanil (4 mcg/kg/h) and propofol (8 mg/kg/h). Mechanical ventilation was volume-controlled (10 ml/kg) with a positive end expiratory pressure (PEEP) of 5 cm H_2O. Tidal volumes were kept constant, respiratory rate was adjusted to maintain end-tidal CO_2 ($ETCO_2$) between 4.5 and 7.0 kPa. Arterial (carotid artery) and central venous access (jugular vein) was established. Regular sampling of blood for hematocrit and blood gas analysis was done. Core temperature, heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RR), peak inspiratory airway pressure (PIP), and $ETCO_2$ were measured continuously. Normothermia was maintained during the experiments using an electric heating blanket.

CO_2 pneumoperitoneum and CT-scanning

Here also, a technique similar to the one used in prior experiments was used [13]. In short: A radially expanding trocar (VersaStep™, Covidien, Dublin, Ireland) was placed in the midline a few centimeter above the umbilicus. The correct intra-abdominal position was verified endoscopically. When hemodynamic and respiratory parameters were stable, pigs were transported from the laboratory facility to the CT-scanner. An electronic CO_2 insufflator was attached to the abdominal trocar after the pig was installed on the scanning tray. Abdominal CO_2 insufflation with a stepwise increase of IAP from 0 to 5, 10 and 15 mm Hg was performed (insufflation-run). At each level of intra-abdominal pressure (IAP), a 5-minute waiting period was taken into account for stabilization of blood pressure, PIP and $ETCO_2$. Thorax and abdomen were then scanned. To minimize respiratory motion artifacts, scans were made during an expiratory-hold maneuver whilst maintaining PEEP at 5 cm H_2O. Scanning at each IAP level took approximately 5 seconds. Pigs were sacrificed after completion of all scans.

Neuromuscular Blockade

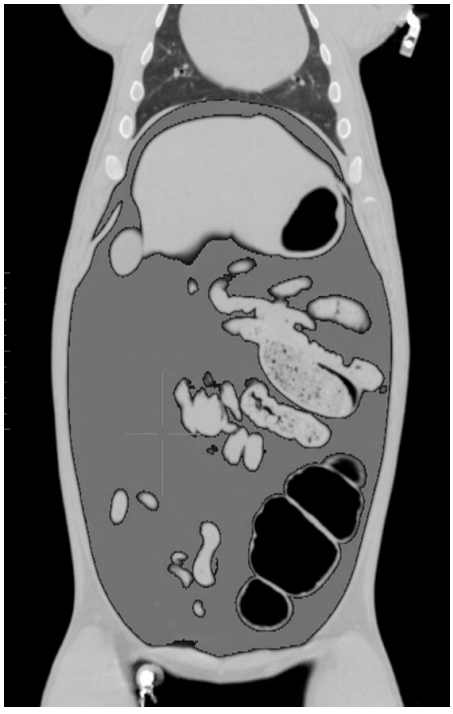
In all animals neuromuscular function was monitored continuously by acceleromyography at the quadriceps femoris muscle using the TOF Guard (Organon Teknika NV, Turnhout, Belgium). The femoral nerve was stimulated using surface pediatric electrodes. After stabilization and calibration of the Train of Four (TOF) signal, repetitive TOF stimulation was performed every 15 seconds, using supra-maximal stimuli of 0.2 milliseconds. The TOF ratio is the height of the fourth twitch, compared to the first twitch height (T4/T1). During deep NMB there is no response to TOF stimulation. When all four responses to TOF stimulation are present and the TOF ratio is > 90%, NMB is considered to be fully recovered [14]. Rocuronium was used for muscle paralysis. A bolus of 1.4 mg/kg (2 x ED_{90} i.e. twice the effective dose at which 90% of subjects in the pig population is paralyzed) was followed by continuous administration of rocuronium 4 mg/kg/hour under TOF guidance. When T1 reappeared, another bolus of rocuronium ED_{90} was administered. For reversal of NMB, sugammadex (4 mg/kg) was used, its effect on neuromuscular function also monitored with the TOF-Guard.

Half of the animals (group A) received no NMB during the first and second run of stepwise abdominal insufflation up to an IAP of 15 mm Hg. In this way, the effect of pre-stretching of the abdominal wall on working-space dimensions could be measured. After NMB, a third insufflation-run was performed and, after reversal of NMB, a fourth one. This was done to measure the additional effect of NMB and its reversal on working-space dimensions.

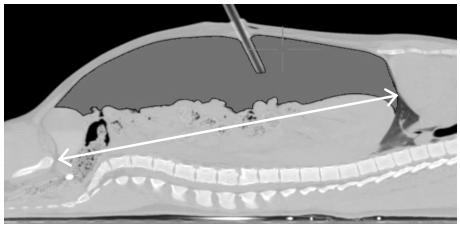
In the other 8 animals (group B), NMB was attained prior to the first insufflation-run and maintained during the second one. A third insufflation-run was performed after reversal of NMB.

Outcome measures

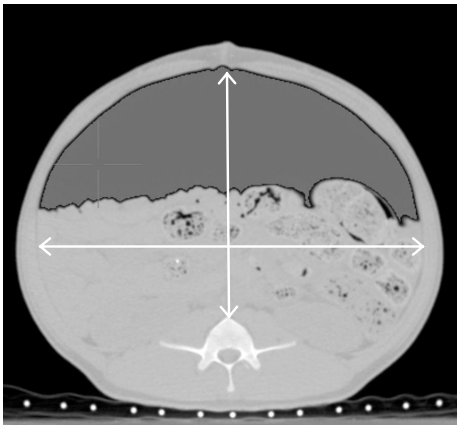
To establish homogeneity of the animals, body weight and total length of the first five lumbar vertebrae were measured [15]. Core temperature, HR, MAP, RR, PIP, $ETCO_2$ and TOF were recorded at each level of IAP. Pneumoperitoneum volumes and working-space linear dimensions (figure 1) were measured in Osirix® using a dataset of 1-mm slices [16]. With the definition of appropriate thresholds, semiautomatic detection of CO_2 in the abdomen could be done on transverse slices, which could be integrated to a total volume of CO_2 pneumoperitoneum [17]. All volumes were visually checked for inadvertent inclusion of air in the bowel. For the linear dimensions, maximal internal antero-posterior diameter of the abdomen (anterior peritoneal lining to the anterior vertebral column) and maximal internal transverse diameter were measured in a transverse plane at the level of the umbilicus. The maximal distance between the upper border of the pubic symphysis and the highest diaphragmatic peritoneal lining was measured in a mid-sagittal plane (figure 1).



CO_2 pneumoperitoneum (dark grey area)



Symphysis to diaphragm



Internal AP and transverse diameter

Figure 1.
Reconstructed CT-images showing working-space dimensions
AP antero-posterior (anterior peritoneal lining to the anterior vertebral column)

Statistics

Normality of the data was confirmed by Kolmogorov Smirnov testing. Data are presented as means with standard errors of the mean (SEM). Differences between groups were assessed with an independent samples *t*-test. Differences within the same animal were assessed with a paired samples *t*-test. A *p* value of < .05 (two-tailed analysis) was considered significant.

RESULTS

Homogeneity of the pigs

Mean body weight for all pigs was 23.0 kg (SEM 0.31). Mean length of the first five lumbar vertebrae was 11.8 cm (SEM 0.06). No statistically significant differences in body weight and lumbar length existed between the animals in group A and B.

Cardiorespiratory parameters

A statistically significant increase in PIP and $ETCO_2$ from baseline (IAP=0 mm Hg) occurred during the first insufflation-run at an IAP of 10 and 15 mm Hg. A minor increase in respiratory rate (p= .197) was necessary at the end of the first insufflation-run to maintain $ETCO_2$ below 7 kPa in group A at an IAP of 15 mm Hg. During the first insufflation-run, blood pressure increased in both groups when compared to baseline. In group A the increase was not statistically significant. In group B however, MAP showed a statistically significant increase

Table 1. Cardiorespiratory parameters during the first insufflation-run (mean values)

IAP	0			5		10		15	
	NMB	-	+	-	+	-	+	-	+
MAP		72	77	75	90	76[a]	97[a]	76[b]	95[b]
HR		83	88	78	85	81	81	80	83
RR		26	24	26	24	26	24	28	24
PIP		20	20	20	20	24	24	30	29
$ETCO_2$		5.3	5.7	5.5	6	5.9	6.4	5.9	6.6

[a] p= .038

[b] p< .01 (independent samples *t*-test)

IAP intra-abdominal pressure (mm Hg)
NMB neuromuscular blockade
MAP mean arterial blood pressure (mm Hg)
HR heart rate (beats/min)
RR respiratory rate (breaths/min)
PIP peak inspiratory airway pressure (cm H_2O)
$ETCO_2$ end-tidal CO_2 (kPa)

during the first insufflation-run. When comparing the effect of IAP on MAP between both groups, statistically significant differences existed during the first insufflation-run at an IAP of 10 and 15 mm Hg. Values for all cardiorespiratory parameters during the first insufflation-run are shown in table 1. The effects found during the second insufflation-run were similar (data not shown). No statistically significant other changes were found.

Neuromuscular blockade

In group A, TOF ratio was always above 91% before NMB, below 4% with NMB and above 99% after reversal of NMB. In animals in group B, TOF ratio was always below 5% with NMB and above 92% after its reversal.

CO_2 pneumoperitoneum (working-space dimensions)

When comparing the CO_2 pneumoperitoneum volumes during the first insufflation-run between group A (no-NMB) and B (NMB), no statistically significant differences were found (table 2). A second insufflation-run without changing the paralysis-state was performed in both groups.

Table 2. Mean volumes of CO_2 pneumoperitoneum in milliliters (SEM)

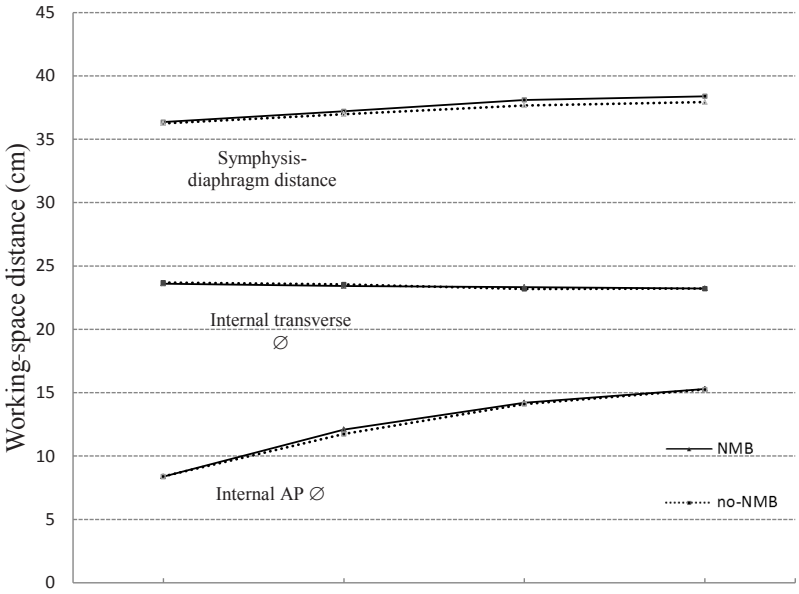
Group A		**insufflation-run →**			
		1st	**2nd**	**3rd**	**4th**
n=8	IAP (mm Hg)	**no-NMB**	**no-NMB**	**NMB**	**Reversal**
	0	0	0	0	0
	5	1403 (183)[a]	1691 (220)	1808 (210)	1774 (235)
	10	2628 (235)[b]	2819 (263)	2930 (266)	2979 (282)
	15	3189 (262)[c]	3290 (271)	3369 (281)	3459 (284)
Group B		**insufflation-run →**			
		1st	**2nd**		**3rd**
n=8	IAP (mm Hg)	**NMB**	**NMB**		**Reversal**
	0	0	0		0
	5	1572 (155)[a]	1870 (155)		1912 (151)
	10	2812 (161)[b]	3042 (152)		3174 (148)
	15	3386 (145)[c]	3516 (125)		3660 136)

[a] p= .493
[b] p= .529
[c] p= .523 (independent samples *t*-test)

n	number of animals
SEM	standard error of the mean
IAP	intra-abdominal pressure
NMB	neuromuscular blockade
mmHg	millimeters of mercury

In group A, this pre-stretching resulted in an increase in CO_2 pneumoperitoneum volume of 21% at a repeat IAP of 5 mm Hg ($p < .01$), 7% at a repeat IAP of 10 mm Hg ($p < .01$) and 3% at a repeat IAP of 15 mm Hg ($p < .01$). The third insufflation-run with NMB resulted in an additional increase of 7% at an IAP of 5 mm Hg ($p < .01$), 4% at an IAP of 10 mm Hg ($p = .01$) and 2% at an IAP of 15 mm Hg ($p = .02$).

In group B, mean CO_2 pneumoperitoneum volume showed an increase during the second insufflation-run of 19% at a repeat IAP of 5 mm Hg ($p < .01$), 8% at a repeat IAP of 10 mm Hg ($p < .01$) and 4% at a repeat IAP of 15 mm Hg ($p < .01$). We found no statistically significant differences in the pre-stretching effect between group A and B at all levels of IAP ($p = .887$ at 5 mm Hg, $p = .455$ at 10 mm Hg and $p = .315$ at 15 mm Hg).



IAP (mmHg)	0		5		10		15	
NMB	–	+	–	+	–	+	–	+
Internal AP ∅	8,4	8,4	11,7	12,1	14,1	14,2	15,3	15,3
Internal transverse ∅	23,7	23,6	23,5	23,4	23,2	23,3	23,2	23,2
Symphysis-diaphragm	36,3	36,4	37,0	37,2	37,7	38,1	37,9	38,4

Figure 2.
Working-space linear dimensions (cm) during the first insufflation-run (mean values)
No statistically significant differences exist between group A (no-NMB) and group B (NMB)

IAP intra-abdominal pressure
NMB neuromuscular blockade
AP antero-posterior

Reversal of NMB and a subsequent insufflation-run mostly showed a small further increase in mean CO_2 pneumoperitoneum volume with a small decrease only at an IAP of 5 mm Hg in group A (table 2).

Mean internal working-space distances at all IAP levels during the first insufflation run are shown in figure 2. None of the linear dimensions showed a statistically significant difference between group A (no-NMB) and group B (NMB) in the first or second insufflation-run (data not shown).

DISCUSSION

It seems logical to assume that neuromuscular blockade increases working space during laparoscopy. This assumption however has not been endorsed by literature. In a study in pigs, Chassard et al. did not find a positive effect of muscle paralysis on working space [5]. Also in a clinical study in young, non-obese gynecologic patients, Chassard et al. could not demonstrate a positive effect [6]. In the guidelines on pneumoperitoneum of the European Association for Endoscopic Surgery, nothing is written about neuromuscular blockade [18]. The subject of neuromuscular blockade during laparoscopic surgery has re-emerged in recent studies. Staehr-Rye et al. plan to investigate the correlation between the level of muscle paralysis and the surgeon's interpretation of working space [10]. This and most other studies use postoperative surgeon's questionnaires on adequacy of exposure as an endpoint [6, 9, 10]. The robustness of such subjective evaluations can be questioned. Lindekaer et al. used the distance from the trocar entrance to the promontory as a more objective measure of working-space dimensions [19]. However, measuring the trocar distance before and after NMB implies two measurements, inevitably introducing a confounding effect of pre-stretching of the abdominal wall [20]. Although no quantitative data on this pre-stretching effect are available in human laparoscopy, we believe that it should be taken into consideration when interpreting the results of studies dealing with laparoscopic working space.

Our porcine laparoscopy model, as used in prior experiments to investigate the effect of IAP, mechanical bowel preparation and pre-stretching of the abdominal wall, abided by strict anesthesiologic and surgical protocols [13, 20, 21]. In this way, the effect of NMB per se could be investigated. Moreover we used objective measurements from CT-scanning for the determination of working-space dimensions.

As in prior experiments, PIP was shown to increase with an IAP of 10 mm Hg and higher. All other parameters did not show statistically significant differences, with the exception

of a significant increase in MAP in group B (1st run NMB) only. As also seen in table 1, rocuronium itself did not affect heart rate and blood pressure at baseline [22]. A possible explanation for the increase in MAP with abdominal CO_2 insufflation in group B could be the interference of NMB with the reactions of the autonomic nervous system [23, 24].

No statistically significant effect of NMB on laparoscopic working-space dimensions was found in our porcine laparoscopy model. In contrast there was an important effect of pre-stretching of the abdominal wall, irrespective of NMB. The gain in CO_2 pneumoperitoneum volume by NMB in the third insufflation-run, after two insufflation-runs without NMB, could have also been caused by an extra insufflation run and possible additional pre-stretching. The existence of such an additive effect could also explain the ever-increasing volumes with consecutive insufflation-runs, irrespective of paralysis-state or reversal of NMB, found in this study. Pre-stretching was not facilitated by NMB, also negating its use for this purpose.

Most of the recent clinical studies [25] use deep neuromuscular block with a post-tetanic count of 1-2 responses, as opposed to the standard NMB with a TOF count of 1-2 responses (e.g. BLISS study [26], CURES study [27]). Also, patient populations can be morbidly obese patients undergoing bariatric surgery [27]. In our study with non-obese pigs we used standard NMB with a TOF of 0-1 responses. We feel this still reflects a policy used in the majority of laparoscopic procedures in humans nowadays. Depth of anesthesia and anesthetic drugs influence muscle tone [28]. A profound level of anesthesia could also have influenced the effect of neuromuscular blockade on working space in our experiments. This correlation between depth of anesthesia and working space needs to be investigated further.

Although we could not demonstrate a positive effect of NMB on working-space dimensions, this does not negate the role of NMB in the anesthesiologic management of laparoscopic surgery. It is very effective in preventing inadvertent, sudden patient movement, which is dangerous, especially when working space is very limited as in small children.

We realize that our study is a study in animals and not in humans. Physiologic reactions to CO_2 pneumoperitoneum in pigs may differ from humans [29]. Also, the anatomy of the pig's abdominal wall and pelvis differs from humans [30]. There are however enough similarities [31] to take note of the absence of a significant positive effect of NMB on laparoscopic working-space dimensions found in this experimental and several clinical studies [6-8].

CONCLUSION

We found no evidence that neuromuscular blockade increases laparoscopic working space in the porcine laparoscopy model as described. Studies dealing with working space during laparoscopy should take note of pre-stretching bias.

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CHAPTER 7

Optimizing working space in laparoscopy:
CT measurement of the influence of small body size in a porcine model

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ABSTRACT

Introduction

In our continuing research into the determinants of laparoscopic working space, the influence of small body size was investigated.

Methods

In eight 6-kg pigs, the effects of intra-abdominal CO_2 pneumoperitoneum pressure (IAP), pre-stretching of the abdominal wall, and neuromuscular blockade (NMB) on laparoscopic working-space volume and distances were studied. Computed tomography was used to measure working space during two stepwise abdominal insufflation-runs up to an IAP of 15 mm Hg. Results were compared with data from earlier experiments in 20-kg pigs.

Results

Cardiorespiratory parameters were stable up to an IAP of 8-10 mm Hg.
Working-space volume, anteroposterior (AP) diameter and symphysis-diaphragm distance increased linearly up to an IAP of 8 mm Hg. Above 8 mm Hg, compliance decreased. Eighty percent of the total volume (618 ml) and of AP diameter (3 cm) at 15 mm Hg had been achieved at an IAP of 10 mm Hg. Pre-stretching by a first insufflation resulted in a statistically significant increase in working space volume and in AP diameter during the second insufflation. This effect was significantly larger than in 20-kg pigs. Neuromuscular blockade did not have a significant effect on working space.

Conclusions

Working space in growing individuals is very limited. In 6-kg pigs it was five times smaller than in 20-kg pigs. Eighty percent of the working space created by an IAP of 15 mm Hg was already achieved at 10 mm Hg, while cardiorespiratory side effects at an IAP of 8-10 mm Hg seem acceptable. Pre-stretching of the abdominal wall significantly increased working space, even more so than in 20-kg pigs. As in 20-kg pigs, NMB had no significant effect on laparoscopic working space. Pre-stretching of the abdominal wall is a promising cheap, safe and easy strategy to increase laparoscopic working space, lessening the need for prolonged high-pressure pneumoperitoneum.

Key words

Laparoscopy, working space, animal model, body size, pre-stretching, neuromuscular blockade

INTRODUCTION

Exposure of the surgical field during laparoscopic surgery is usually accomplished by creating a carbon dioxide (CO_2) pneumoperitoneum [1]. The factors determining the dimensions of this working space are poorly understood and scarcely studied. Research has mainly focused on the anesthesiologic management of the pathophysiologic consequences of CO_2 pneumoperitoneum, rather than on working space itself [1-3]. The age/body size of growing individuals is a key factor in laparoscopic working space. Intra-abdominal volumes have been suggested to vary with subject size to the power of three [4]. A high intra-abdominal pressure (IAP) has a negative effect on hemodynamic and respiratory parameters, even more so in smaller patients [1, 3, 5, 6]. Increasing IAP to achieve better exposure is therefore not the most obvious strategy in (pediatric) minimal access surgery (MAS). In the past we have studied the effects of IAP, mechanical bowel preparation, pre-stretching of the abdominal wall and neuromuscular blockade (NMB) in 20 kg pigs, using standardized anesthesiologic and surgical techniques. Computed tomography (CT) was used to measure working-space dimensions accurately and objectively. In these experiments, we found that distensibility of the abdominal cavity decreased with increasing IAP [7]. Moreover we found that pre-stretching of the abdominal wall led to a significant increase in working space at re-insufflation [8]. In contrast, neuromuscular blockade did not increase laparoscopic working space [9]. To introduce evidence in choosing the best strategy to create sufficient working space in pediatric laparoscopy, we subsequently studied 3 week old, 6 kg pigs using the aforementioned methodology. In this paper we report on the pressure-volume relationship and on the effects of pre-stretching of the abdominal wall and NMB on working-space dimensions in these small pigs. Effects found were compared to similar data from earlier experiments in 9-10 week old, 20 kg pigs to determine the influence of age/body size [7-10].

METHODS

Animals

Eight female Landrace pigs approximately 3 weeks old and weighing circa 6 kg were studied. All experiments were approved by the institutional animal ethics committee.

Anesthesia and instrumentation

A standardized anesthesia protocol was used as in earlier experiments [7-10], only now using endotracheal instead of tracheotomy intubation. After premedication with intramuscular midazolam (20 mg/kg) and ketamine (0.7 mg/kg) anesthesia was induced with propofol (1.5 mg/kg) and sufentanil (5 mcg/kg) through a cannula in an auricular

vein. Animals were then endotracheally intubated with a cuffed tube. The lungs were ventilated with a mixture of 40% oxygen and air. Venous as well as arterial vascular access was attained. Anesthesia was maintained with intravenous sufentanil (4 mcg/kg/h) and propofol (6 mg/kg/h). Artificial ventilation was volume-controlled (tidal volume 10 ml/kg), with a positive end-expiratory pressure (PEEP) set at 5 cm H_2O. Initial respiratory rate (RR) was 35 breaths/minute, which was adjusted to maintain end-tidal CO_2 ($ETCO_2$) between 4.5 and 7.0 kPa. Core temperature, heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RR), peak inspiratory airway pressure (PIP) and $ETCO_2$ were measured continuously. Normothermia was maintained during the experiments using an electric heating blanket.

CO_2 pneumoperitoneum and CT-scanning

A 3-mm trocar (VersaPort ™ bladeless 2/3mm, Covidien, Dublin, Ireland) was placed in the midline just above the umbilicus. The correct intra-abdominal position was verified endoscopically (Storz Telepack, Tuttlingen, Germany, 2-mm 0° telescope). When hemodynamic and respiratory parameters were stable, the pig was transported from the laboratory facility to the CT-scanner (Definition Flash Dual Source; Siemens, Erlangen, Germany). An electronic CO_2 insufflator (Endoflator®, Storz, Tuttlingen, Germany) was used for abdominal insufflation. IAP was set at 0, 3, 5, 6, 8, 10 and 15 mm Hg and maintained constant for 5 minutes at each IAP level for stabilization of blood pressure, PIP and $ETCO_2$. After this stabilization period, CT-scans of chest and abdomen were made during a ventilatory arrest in the end-expiratory phase whilst maintaining PEEP. More IAP levels in these smaller pigs as compared to our previous experiments in larger pigs were investigated to better define the pressure-volume relationship and to more accurately observe the effect of IAP on cardiorespiratory parameters. The entire cycle of stepwise insufflation (insufflation-run) was performed twice in all animals. Additional scans were made at an IAP of 30 mm Hg in five animals after completing the second insufflation-run. This final insufflation was performed during respiratory arrest with scanning immediately after stabilization of IAP at 30 mm Hg to avoid extreme airway pressures by the volume-controlled ventilation. After completion of all scans, pigs were sacrificed.

Neuromuscular Blockade

In all animals neuromuscular function was monitored continuously by accelero-myography at the quadriceps femoris muscle using the TOF Guard (Organon Teknika NV, Turnhout, Belgium). The femoral nerve was stimulated using surface pediatric electrodes. After stabilization and calibration of the Train of Four (TOF) signal, repetitive TOF stimulation was performed every 15 seconds, using supra-maximal stimuli of 0.2 milliseconds. The TOF ratio is the height of the fourth twitch, compared to the first

twitch height (T_4/T_1). During deep NMB there is no response to TOF stimulation. When all four responses to TOF stimulation are present and the TOF ratio is > 90%, NMB has fully recovered [11].

According to predetermined randomization, half of the animals (n=4) received no NMB during the first and second run of stepwise abdominal insufflation (no-NMB group). Thus, in the second insufflation-run the effect of pre-stretching of the abdominal wall could be determined.

In the other animals (NMB group, n=4), deep NMB was attained prior to the first insufflation-run and maintained during the second insufflation-run, also to determine the effect of pre-stretching. In this group, rocuronium was used for muscle paralysis, administered as an intravenous bolus dose of 1.4 mg/kg (2 x ED_{90} , i.e. twice the effective dose at which 90% of subjects is paralyzed in the pig population), followed by continuous administration of 4 mg/kg/hour under TOF guidance. When T1 reappeared, another bolus dose of rocuronium ED_{90} was administered.

Outcome measurements

Body weight and total length of the first five lumbar vertebrae were measured [12]. Core temperature, HR, MAP, RR, PIP and $ETCO_2$ were recorded. Volumes of CO_2 pneumoperitoneum and abdominal linear dimensions were measured in Osirix® using a dataset of 1 mm slices [13]. With the definition of appropriate thresholds, semiautomatic detection of CO_2 in the abdomen was done on transverse slices, which could be integrated to a total volume of CO_2 pneumoperitoneum [14]. All volumes were visually checked for inadvertent inclusion of air in the bowel. For the linear dimensions, maximal internal antero-posterior (AP) diameter of the abdomen (measured from the anterior peritoneal lining to the anterior vertebral column) and maximal internal transverse diameter were measured in a transverse plane at the level of the umbilicus. The maximal distance between the upper border of the pubic symphysis and the highest diaphragmatic peritoneal lining was measured in a mid-sagittal plane. For comparison, published data from previously studied animals weighing approximately 20 kg were used [7-9].

Statistics

Normality of the data was confirmed by Kolmogorov Smirnov testing. Data are presented as mean with standard errors of the mean (SEM). Differences between groups were assessed with an independent samples *t* test. Differences within the same animal were assessed with a paired-samples *t* test. A Spearman's rho correlation with 2-tailed significance was computed to assess the relationship between the duration of the insufflation-run and the volume-increase after pre-stretching. A p value of $< .05$ was considered significant.

RESULTS

Homogeneity of the groups

Mean body weight and length of the first five lumbar vertebrae (L_{1-5}) for the no-NMB group was 6.33 kg (SEM 0.33) and 6.83 cm (SEM 0.26) respectively. For animals in the NMB group this was 6.83 kg (SEM 0.15) and 7.08 cm (SEM 0.11). No statistically significant differences in body weight and L_{1-5} existed between both groups.

Duration of the insufflation-run

Median total duration of the first insufflation run was 42 minutes in the no-NMB group and 47 minutes in the NMB group (p= .326). There was no statistically significant correlation between the duration of the insufflation-run and the volume-increase after pre-stretching at all IAP levels.

Neuromuscular blockade

In animals of the no-NMB group, the TOF ratio was always above 87% (median 100). In animals of the NMB-group, the TOF ratio was always below 4% (median 0) during the procedure.

Cardiorespiratory parameters

A statistically significant increase in PIP and $ETCO_2$ from baseline (IAP=0 mm Hg) occurred with increasing IAP in both the no-NMB and NMB group, albeit at slightly different IAP levels (table 1). Animals in the NMB group had a higher HR and MAP as compared

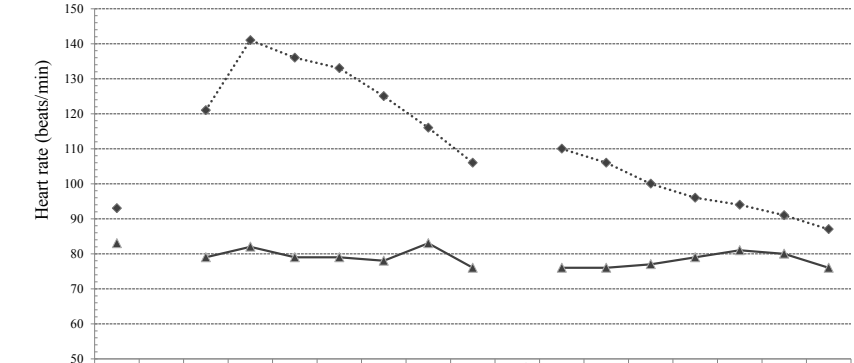
Table 1. Cardiorespiratory parameters during the first insufflation-run (mean values)

IAP	0		3		5		6		8		10		15	
NMB	-	+	-	+	-	+	-	+	-	+	-	+	-	+
MAP	61	77	63	73	62	67*	63	68*	64	67*	65	67	66	70
HR	79	121	82	141	79	136	79	133	78	125	83	116	76	106
RR	36	35	36	35	36	35	36	35	38	35	38	36	39	36
PIP	16	17	16	18	17	18	17	19	18*	20	20*	21*	22*	23*
$ETCO_2$	5.2	5.1	5.1	5.3	5.5	5.6*	6.0*	6.0*	6.1*	6.2*	6.2*	6.3*	6.6*	6.4*

* Statistically significant change from value at IAP 0 mmHg

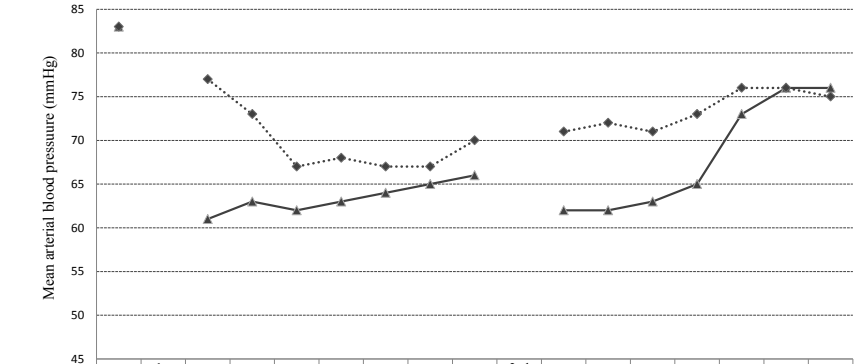
IAP intra-abdominal pressure (mm Hg)
NMB neuromuscular blockade
MAP mean arterial blood pressure (mm Hg)
HR heart rate (beats/min)
RR respiratory rate (breaths/min)
PIP peak inspiratory pressure (cm H_2O)
$ETCO_2$ end-tidal CO_2 (kPa)

to the animals in the no-NMB group during the entire first and second run of abdominal insufflation (statistical significance for MAP at initial IAP of 0 mm Hg only, for HR up to IAP 8 mm Hg during the first run only). With initial CO_2 insufflation, a further increase in HR was accompanied by a decrease in MAP in the NMB group. Heart rate in the no-NMB group was stable, whilst in the NMB group, after the initial rise with insufflation, HR gradually decreased during the second insufflation-run (figure 1A). During the course of the first and second insufflation-run, MAP in the no-NMB group gradually increased to match MAP of the NMB group (figure 1B). No statistically significant other changes were



	after induction	1st insufflation-run	IAP mmHg 0	3	5	6	8	10	15	2nd insufflation-run	IAP mmHg 0	3	5	6	8	10	15
no-NMB	83		79	82	79	79	78	83	76		76	76	77	79	81	80	76
NMB	93		121	141	136	133	125	116	106		110	106	100	96	94	91	87

Figure 1A
Heart rate during the first and second run of abdominal CO_2 insufflation



	after induction	1st insufflation-run	IAP mmHg 0	3	5	6	8	10	15	2nd insufflation-run	IAP mmHg 0	3	5	6	8	10	15
no-NMB	83		61	63	62	63	64	65	66		62	62	63	65	73	76	76
NMB	83		77	73	67	68	67	67	70		71	72	71	73	76	76	75

Figure 1B
Mean arterial blood pressure during the first and second run of abdominal CO_2 insufflation

found. In the five animals in which IAP was raised to 30 mm Hg, hemodynamic instability at this level of IAP was obvious.

Effect of IAP on working-space volume and linear working-space dimensions

When looking at the volumes of the four animals in the no-NMB group, the volume attained at an IAP of 5 mm Hg comprised 42% of the "maximal" volume attained at 15 mm Hg. At an IAP of 10 mm Hg this was 82%. For comparison, these values were 43% and 84% respectively in the 20 kg pigs [7]). Figure 2 visualizes the incremental effect of IAP up to 30 mm Hg on CO_2 pneumoperitoneum volume. It uses the combined mean CT volumes during the second insufflation-run of all 8 animals up to an IAP of 15 mm Hg and of five animals up to an IAP of 30 mm Hg. The pressure-volume curve is linear up to an IAP of 8 mm Hg. Above 8 mm Hg, the curve changes into a nonlinear configuration.

Regarding the linear working-space dimensions, the mean internal AP diameter increased by 1.4 cm (from 5.9 to 7.3 cm) when IAP was raised from 0 to 5 mm Hg; a relative increase of 24%. This diameter increased by another 1.0 cm (to 8.3 cm) when IAP was raised from 5 to 10 mm Hg; a relative increase of 14%. The step from 10 to 15mm Hg increased the mean AP diameter by 0.6 cm (to 8.9 cm); a relative increase of 7%. The transverse diameter did not significantly change with increasing IAP. The mean

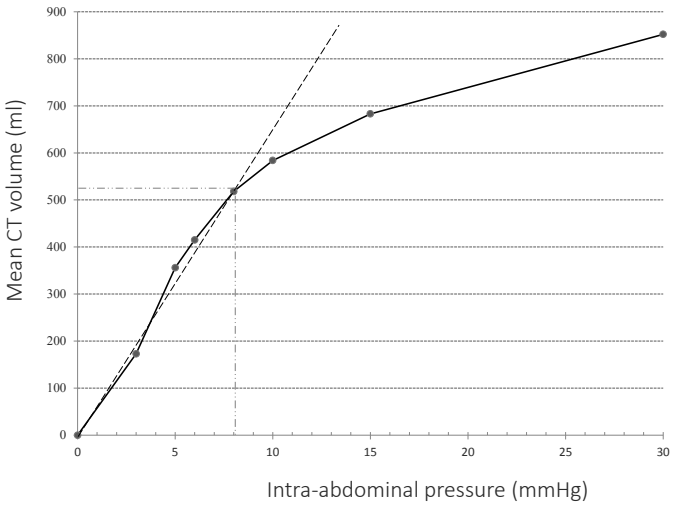
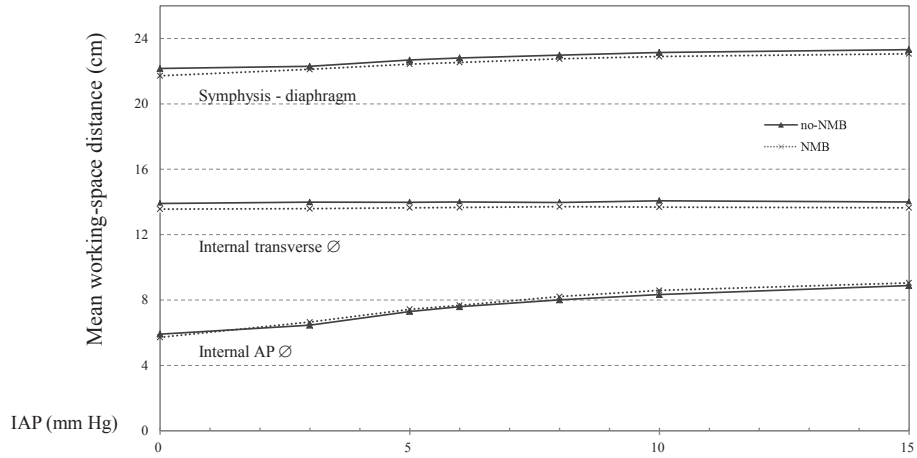


Figure 2

Effect of IAP on CO_2 pneumoperitoneum volume

Combined mean CT-volume during the second insufflation-run showing all eight animals up to an IAP of 15 mm Hg and five animals up to 30 mm Hg. The single-dotted line shows the compliance of the linear section of the pressure-volume curve

distance between the pubic symphysis and the highest point of the peritoneal lining of the diaphragm increased a total of 1.1 cm when IAP was increased to 15 mm Hg (from 22.2 to 23.3 cm, a 5% relative increase). This increase was statistically significant (p= .01). The linear working-space dimensions for all 8 pigs (no-NMB and NMB) during the first insufflation-run are shown in figure 3.



no-NMB (n=4)	0 mm Hg	3 mm Hg	5 mm Hg	6 mm Hg	8 mm Hg	10 mm Hg	15 mm Hg
Internal AP ∅	5.9	6.5	7.3	7.6	8.0	8.3	8.9
Internal transverse ∅	13.9	14.0	14.0	14.0	14.0	14.1	14.0
Symphysis-diaphragm	22.2	22.3	22.7	22.8	23.0	23.1	23.3

Figure 3.
Linear working-space dimensions during the first insufflation-run (cm)
AP antero-posterior
NMB neuromuscular blockade
mmHg millimeters of mercury

Effect of pre-stretching of the abdominal wall

The second insufflation-run always resulted in a statistically significant increase in CO_2 pneumoperitoneum volume at all IAPs and a significant increase in mean internal AP diameter above an IAP of 3 mm Hg. No statistically significant differences were found in this pre-stretching effect between the no-NMB and NMB group (data not shown). The relative increase (%) in CO_2 pneumoperitoneum volume after pre-stretching for all eight animals in both groups combined is shown in table 2.

Effect of NMB

When comparing the volumes of CO_2 pneumoperitoneum between the no-NMB and the NMB group, no statistically significant differences were found during the first or the second insufflation-run (table 3). Figure 4 shows the pressure-volume curves for both

Table 2. Pre-stretching effect. CO_2 pneumoperitoneum volumes during the first and second insufflation-run. Data from similar experiments in 20 kg pigs.

	6 kg pigs (n=8)				**20 kg pigs** [8]
	1st run	**2nd run**			
IAP (mm Hg)	Volume (ml) mean (SEM)	Volume (ml) mean (SEM)	*p* value	% increase	% increase
3	107 (22)	173 (36)	.011*	62	
5	263 (44)	356 (50)	.000*	35a	21a
6	330 (48)	415 (56)	.000*	26	
8	435 (52)	518 (61)	.001*	19	
10	511 (54)	584 (63)	.002*	14a	7a
15	618 (59)	683 (68)	.003*	11a	3a

* 1st vs. 2nd run: significant (paired samples *t* test)

a 6 kg vs. 20 kg pigs: significant (independent samples *t* test)

IAP intra-abdominal pressure
mmHg millimeters of mercury
SEM standard error of the mean

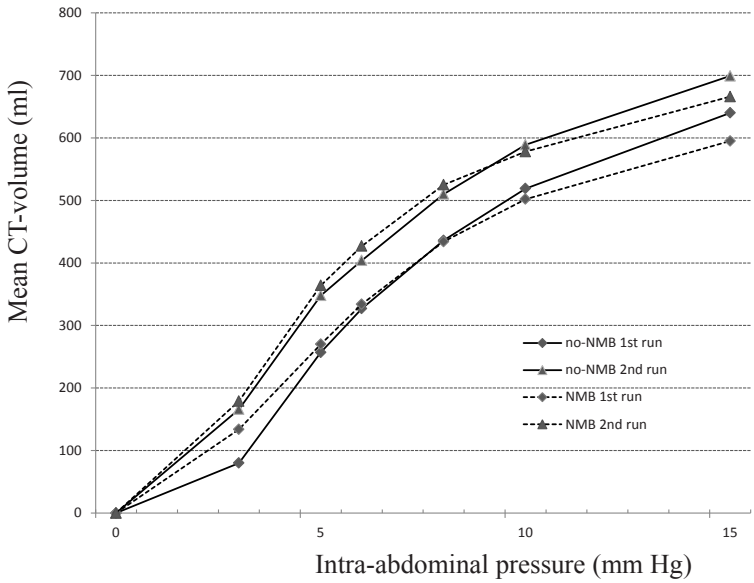


Figure 4
Pressure-volume curves during a first and second insufflation-run
Effects of IAP, pre-stretching and NMB
IAP intra-abdominal pressure
NMB neuromuscular blockade
mmHg millimeters of mercury

Table 3. CO_2 pneumoperitoneum volume (ml): mean (SEM)

IAP (mm Hg)	No-NMB Group	NMB Group	
First insufflation-run	**n=4**	**n=4**	***p* value***
0	1 (1)	2 (2)	.658
3	80 (24)	134 (36)	.256
5	257 (63)	270 (70)	.895
6	327 (70)	334 (76)	.942
8	436 (79)	434 (81)	.990
10	519 (82)	502 (82)	.889
15	640 (88)	595 (90)	.734
Second insufflation-run	**n=4**	**n=4**	
0	12 (7)	28 (7)	.180
3	166 (44)	179 (63)	.874
5	348 (63)	364 (87)	.885
6	404 (69)	427 (99)	.849
8	510 (74)	525 (108)	.915
10	589 (79)	578 (112)	.940
15	699 (86)	666 (119)	.830
Extra insufflation**	**n=2**	**n=3**	
30	892 (173)	825 (162)	.803

* independent samples *t* test comparing no-NMB to NMB group
** further insufflation up to 30 mm Hg after completion of the second insufflation-run

IAP intra-abdominal pressure
NMB neuromuscular blockade
mmHg millimeters of mercury
SEM standard error of the mean

groups during both insufflation-runs. The pre-stretching effect can clearly be seen for animals in both the no-NMB and NMB group. The maximal internal AP diameter, transverse diameter and symphysis-diaphragm distance did not show a statistically significant difference between the no-NMB and NMB group (data not shown).

DISCUSSION

After investigating the effect of IAP, pre-stretching of the abdominal wall and NMB on laparoscopic working space in 9-10 week old, 20 kg pigs, we wanted to find out what the effects of these interventions were in much younger/smaller pigs. The smallest pigs available to us were approximately three weeks old, weighed circa 6 kg and tolerated solid food. Cardiorespiratory responses to CO_2 pneumoperitoneum in these smaller pigs

were different from those in the larger 20 kg animals used in earlier studies. Rocuronium now resulted in an increase in HR that was enhanced by the CO_2 pneumoperitoneum. In other studies, rocuronium has been shown to have a slight vagolytic effect [15]. Decreased vagal tone could explain the initially higher HR and MAP in the NMB group. The further changes in HR and MAP could be explained by mild hypercapnia that occurred with the CO_2 pneumoperitoneum [16, 17]. Respiratory rate in the 6 kg pigs was higher (mean 36 breaths/min) than in the 20 kg pigs from earlier studies (mean 25 breaths/min). This can be explained by the fact that tidal volume scales isometrically (about 7 to 8 mL/kg/breath), whereas CO_2 production scales allometrically [4].

When taking an IAP of 15 mm Hg as the maximal physiologically tolerable pressure, 82% of the CO_2 pneumoperitoneum volume was already achieved at an IAP of 10 mm Hg. Abdominal wall compliance progressively decreased above an IAP of 8 mm Hg in this study. This suggests that in 6 kg pigs, an optimal balance between working space and cardiorespiratory side-effects of CO_2 insufflation is found around an IAP of 8 mm Hg. In our earlier experiments in 20 kg pigs, we observed a similar pressure-volume relationship. There, we only measured working-space dimensions at three IAP levels, so we do not exactly know where the linear section of the pressure-volume curve ended [7].

The pressure-volume curve strongly resembles the stress-strain curve of ductile materials [18]. Non-elastic internal deformation of connective tissue or changes in sarcomere length by sliding of the myosin filaments could both explain the apparent decrease in compliance that occurs beyond an IAP of 8 mm Hg [19-21].

Of the linear working-space dimensions, both the AP-diameter and the symphysis-diaphragm distance were significantly influenced by IAP. With an IAP of 15 mm Hg, the total increase in internal AP-diameter was 3 cm (51%). The small absolute increase in AP diameter endorses the need for miniaturization of laparoscopic equipment and instruments to make optimal use of the limited working space. The cranial displacement of the diaphragm was statistically significant and comparable to the displacement in the 20 kg pigs (7% and 6% respectively). The limited increase is most probably caused by the volume-controlled ventilation and PEEP.

As in the 20 kg animals, a second insufflation run in the 6 kg animals significantly increased working space at all IAPs. The effect of pre-stretching of the abdominal wall was significantly greater in the 6 kg pigs than in the 20 kg pigs from earlier studies (table 2). When patients get smaller, working space disproportionately gets even smaller while the pathophysiologic consequences of CO_2 pneumoperitoneum are more pronounced [3, 5, 6]. This makes the clinical potential for pre-stretching in smaller patients promising. Additionally, pre-stretching functions as a means of ischemic preconditioning, which has been experimentally shown to reduce the oxidative stress induced by CO_2 pneumoperitoneum [22-24]. Finally, introduction of the trocars at an higher initial IAP is easier and safer [25].

Neuromuscular blockade in 6 kg pigs, as in 20 kg pigs, did not have a statistically significant effect on laparoscopic working space. It also did not have an added effect to the already significant effect of pre-stretching of the abdominal wall. This is an important experimental finding that contradicts the results of the recently published study by Lindekaer et al. [26]. In this clinical study, laparoscopic working space, defined as the distance from the promontory to the skin, was first measured without muscle relaxation (TOF > 90%). This was followed by a second measurement, in the same patient, after profound neuromuscular block (Post Tetanic Count < 2). In the study of Lindekaer et al, NMB was at a more profound level than in our animal study, which might explain the different results. However, the independent effect of pre-stretching of the abdominal wall has not been taken into consideration. In the only other clinical studies which investigated the effect of NMB on laparoscopic conditions, surgical view was similar [27-29]. Experimentally, Chassard et al. showed no influence of NMB on abdominal elastic properties in a pig model [30]. All this does not negate the role of NMB in the anesthesiologic management of laparoscopic surgery. It is very effective in preventing inadvertent, sudden patient movement, which is dangerous, especially when working space is very limited as in small children.

CONCLUSIONS

The effects of IAP, pre-stretching and NMB were studied in 3 week old, 6 kg pigs. The relative effect of IAP on working-space volume and linear dimensions in the 6 kg animals studied was similar to what was found earlier in 20 kg pigs. However, the absolute volumes of CO_2 pneumoperitoneum were five times smaller in the 6 kg pigs. With increasing IAP, the AP diameter increased significantly, as did the symphysis-diaphragm distance albeit with a much smaller absolute value for the latter. The gain in working-space volume by increasing IAP showed a decline above an IAP of 8 mm Hg.

Pre-stretching of the abdominal wall significantly increased working-space dimensions, the effect being even more pronounced than in 20 kg pigs. As in 20 kg pigs, NMB had no statistically significant effect on laparoscopic working space.

Limited working space makes endoscopic surgery in small children more difficult. Even a small gain in working space can markedly improve surgical conditions in this patient group. Pre-stretching of the abdominal wall is a promising cheap, safe and easy strategy to increase working space, lessening the need for prolonged high-pressure pneumoperitoneum.

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John Vlot	No conflict of interest or financial ties to disclose
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René Wijnen	No conflict of interest or financial ties to disclose
Robert Jan Stolker	No conflict of interest or financial ties to disclose
Klaas Bax	No conflict of interest or financial ties to disclose

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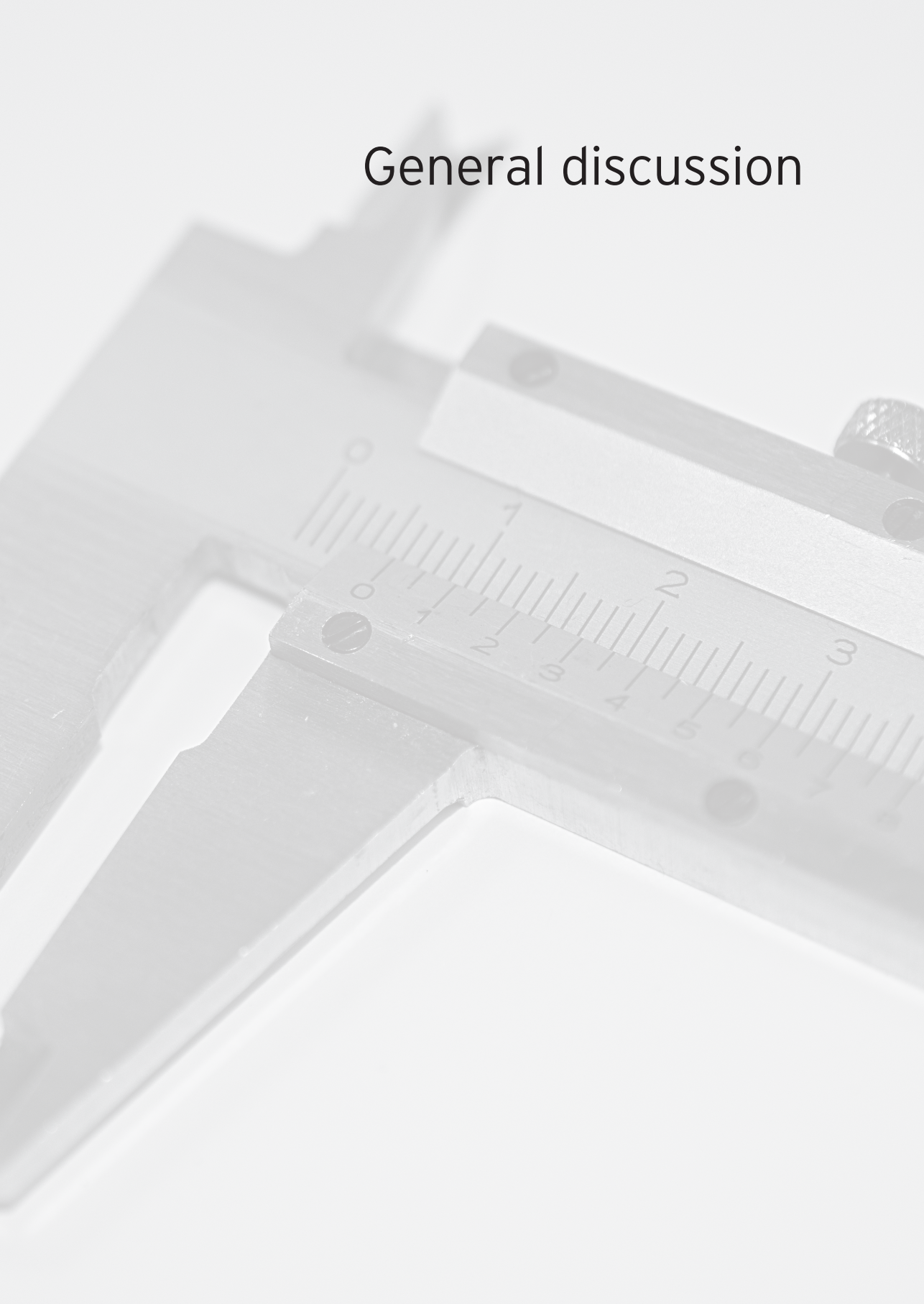
CHAPTER 8

General discussion



The traditional Hippocratic ethos provides the background for the idea that the less invasive a procedure, the better it is. It is morally preferable to avoid invading a patient's body whenever possible [1]. One of the obvious advantages of minimal access surgery is the minimization of scars. Patients would be willing to pay extra to have smaller scars or to accept an overall increase in risk of 10 % as a trade-off for total absence of scarring [2-4].

Bergmeijer, looking at the long-term results after Nissen fundoplication in childhood, found that 37.5% of the patients were not happy with the upper laparotomy scar [5]. Also, parents dislike scars being inflicted on their children – and each scar on a child is a scar on the parents' soul. Scars do grow with the child over time. Moreover, scars in infants often adhere to the underlying fascia because of a lack of subcutaneous fat. This results in retraction of the scar. It is not surprising therefore, that more and more grown-up children have their childhood scars corrected [6]. This emphasizes the importance of the cosmetic result of surgery. However, "primum non nocere" also implies that less mutilating treatment modalities have to be at least as safe and effective as the conventional ones they are meant to replace. In adult general surgery, equal efficacy and safety of minimal access approaches have been reported for several decades now [7-9]. In the early days of laparoscopic surgery, instruments tended to be long (30-35 cm) and bulky (10 mm diameter). Moreover, CO_2 insufflators were relatively unsophisticated with crude pressure control [10, 11]. This hindered the usability in smaller children. New and more refined instruments and equipment have become available since then, allowing for complex endoscopic procedures in even the smallest children [6, 11-13]. Today, most children are offered "basic" minimal access procedures such as laparoscopic appendectomy, but more advanced endoscopic procedures are still not commonly used by pediatric surgeons [7, 14]. There are several explanations for this. Except for appendicitis and inguinal hernia, commonly occurring pathologies with an indication for endoscopic surgery in children are rare. This, as well as the substantial learning curve of the procedure, prevents pediatric surgeons from developing a sufficient laparoscopic skill level for complex pathologies such as duodenal atresia [15-17]. Also, pathophysiological consequences of CO_2 pneumoperitoneum with unknown long-term morbidity can deter surgeons and anesthesiologists from minimal access surgery in neonates and larger children with complex pathology and/or comorbidity [18-20].

Working space for endoscopic surgery is limited. This holds especially true in children, because the size of the abdomen or chest is related to the child's size in a non-linear fashion. A child one-half as tall as an adult presents the surgeon with one-eighth the working volume in the chest or abdomen [10]. Such a tiny volume demands much finer movements, and limits tolerance for slips [10]. It undoubtedly increases the learning curve.

Optimizing geometric conditions for endoscopic tasks has been proven to increase efficiency and knot quality [21-23]. Increasing laparoscopic working space therefore would be indicated to optimize minimal access surgery. Intra-abdominal pressure (IAP) is a major determinant of working space during laparoscopy. However, high IAP negatively affects circulatory and respiratory parameters, especially in smaller patients [Chapter 1]. Consequently, increasing IAP to achieve better exposure would not seem to be the most obvious strategy in (pediatric) minimal access surgery. Research so far has mainly focused on the management of the pathophysiological consequences of CO_2 pneumoperitoneum [24-26], rather than on working space itself.

The feasibility and benefits of using lower IAPs for laparoscopic surgery have been well documented [25, 27-29]. Nevertheless, how IAP quantitatively affects working space volume has not yet been objectively investigated. One of the major problems in studying working space is the methodology of its assessment. The volume of CO_2 released by the insufflator is an indication of the pneumoperitoneum volume, but is prone to be biased by leakage of CO_2 from the abdomen and by CO_2 absorption through the peritoneum with elimination mainly by the lungs. Quantifying these biases is very complex. Almost all clinical studies on laparoscopic working space used surgeons' subjective assessment of working space [30-33] or the duration of surgery [30-34] as endpoints. However, the value of subjective evaluations can be questioned and duration of surgery does probably not accurately reflect working space.

We therefore decided to study laparoscopic working space in an animal model. We opted for pigs, as porcine anatomy is generally similar to human [35]. Also, pigs have already been extensively used in laparoscopic research and training, as demonstrated by well over 1.000 publications in PubMed (MeSH index terms [laparoscopy] and [swine]). Working space was quantified with computed tomography (CT). Although we were primarily interested in working space in (small) children, we started our studies in 20 kg juvenile pigs (9-10 weeks old). In a first series of experiments we studied the relationship between IAP and working space. From the results, we concluded that most gain in working space (83%) had been achieved at an IAP of 10 mm Hg, while cardiorespiratory parameters were mostly unaffected at this pressure. Comparing CT volumetry with the volumes released by the insufflator showed a bias of 76 ml with limits of agreement spanning 790 ml. This inaccuracy is comparable to the size of the effect of interventions aimed at increasing working space, which led us to conclude that insufflator volume of released CO_2 is inadequate for measuring the effect of interventions aimed at increasing working space [Chapter 2].

The bowel, when distended, can limit working space during laparoscopy. Emptying the bowel before surgery will logically increase working space. However, there is no conclusive clinical evidence on the effect of preoperative mechanical bowel preparation on laparoscopic working space [36, 37]. We evaluated the current practice of Dutch

laparoscopic surgeons regarding preoperative bowel preparation prior to colorectal resection. We concluded that the current practice is based on individual preferences, and that new clinical studies investigating the role of mechanical bowel preparation on surgical field exposure are needed [Chapter 3].

The use of standardized anesthesiologic and surgical techniques as well as CT-scanning to measure working space in 20 kg pigs proved helpful to study the effect of mechanical bowel preparation. We learned that preoperative mechanical bowel preparation resulted in a reproducible, statistically significant increase of laparoscopic working space by about 500 ml at all IAP levels. The relative increase was highest at lower IAP levels (43% at an IAP of 5 mm Hg, and around 20% at 10 and 15 mm Hg). This gain in working space is especially important when lower IAPs are used as e.g. in laparoscopic surgery in children [Chapter 4].

While emptying the bowel preoperatively was shown to increase laparoscopic working space, filling the bowel with gas evidently decreases working space. It is therefore paramount that ventilation techniques are used which prevent gas from entering into the gastrointestinal tract [38, 39]. Once past the pylorus, gas can hardly be removed with a nasogastric tube. The use of nitrous oxide as an inhalation gas also causes dilatation of the gastrointestinal tract [40].

Only few studies have investigated the effect of neuromuscular blockade on working space in a clinical setting [30, 33, 41]. In these studies, using the surgeon's subjective evaluation of working space, no effect of neuromuscular blockade was found. Experimentally, no changes in abdominal or chest wall elastic properties after neuromuscular blockade were found either [42, 43]. Several recent clinical trials, however, suggest a positive effect of neuromuscular blockade on laparoscopic working space [31, 32, 44]. This controversy prompted us to investigate the effect of neuromuscular blockade on laparoscopic working-space dimensions in our porcine model. In a series of experiments, a first stepwise insufflation-run up to an IAP of 15 mm Hg without neuromuscular blockade was followed by a second run with neuromuscular blockade. We serendipitously noted in a first series of experiments that working space was already increased during the second insufflation-run, even without neuromuscular blockade at a repeat IAP of 5 mm Hg. This discovery prompted us to investigate the "pre-stretching effect" in more detail. In a separate series of experiments we found a significant effect of pre-stretching of the abdominal wall, not only at an IAP of 5 mm Hg, but also at 10 and 15 mm Hg. The effect was most pronounced at lower IAPs, which again will be especially advantageous in (small) children [Chapter 5].

From previous experiments we concluded that the effect of pre-stretching biases the assessment of the effect of neuromuscular blockade. In a subsequent series of experiments in the same porcine model, we investigated the effects of both pre-stretching and neuromuscular blockade. We found a significant pre-stretching effect of the first

insufflation-run on subsequent working space in the second insufflation-run. No additional effect of neuromuscular blockade was detected [Chapter 6].

The absence of a positive effect of neuromuscular blockade on laparoscopic working space does not entirely negate its use during laparoscopic surgery. Inadvertent patient movement is dangerous and has to be effectively prevented – especially when working space is very limited as in small children. The correlation between depth of anesthesia and working space needs to be investigated further. A profound level of anesthesia during our experiments could have influenced the effect of neuromuscular blockade on working space.

As pediatric endoscopic surgeons, we were highly interested in the influence of body size/age on working space, more particularly in the effect of IAP, pre-stretching and neuromuscular blockade in much smaller pigs. The smallest pigs available to us were three-week-old, 6 kg pigs that tolerated solid food. In a final series of experiments, we used anesthesiologic and surgical techniques very similar to the ones used earlier in the 20 kg pigs in these 6 kg pigs. The 20 kg pigs were ventilated through a tracheotomy, while the 6 kg pigs were intubated endotracheally. Mean respiratory rate in the 20 kg pigs was 25 breaths/ minute, but in the 6 kg pigs it was 36 breaths/minute (allometric scaling effect [10]). In the 6 kg pigs, CT-scans were not only performed at 0, 5, 10, and 15 mm Hg but also at 3, 6 and 8 mm Hg to better define the pressure-volume relationship. Also, in five of the pigs, IAP was increased from 15 to 30 mm Hg at the end of the second insufflation-run. Neuromuscular blockade was given to half of the pigs to investigate its effect on working space. In these smaller 6 kg pigs, as in the 20 kg pigs, no statistically significant effect of neuromuscular blockade on working space was found. The pre-stretching effect, however, was more pronounced [Chapter 7].

Reliable assessment of working space is not easy when patients' underlying pathology, comorbidities and disease-state interfere with the standardization of anesthesiologic management [25, 26]. Our goal was to gain insight into the basic mechanisms involved in the determination of the CO_2 pneumoperitoneum volume and linear dimensions. To obtain reliable and reproducible results we would need:

- Healthy animals
- Standardized anesthesiologic and surgical techniques
- An objective method for evaluating working space (volume and linear dimensions)

We decided that (computed) tomography was the most reliable method for quantitative evaluation of working-space dimensions. Unfortunately, for ethical and practical reasons, CT-scanning or magnetic resonance imaging cannot be used clinically to quantify working space during laparoscopic surgery. It can be used in an appropriate animal model though, in which standardization of anesthesiologic and surgical techniques is also more easily achieved.

RECOMMENDATIONS

Based on the review of literature and on results of our experimental research, we feel entitled to make the following recommendations regarding CO_2 pneumoperitoneum and working space in laparoscopic surgery:

- (Laryngeal) mask ventilation or endotracheal tube leaks should be avoided to prevent inadvertent distension of the bowel, thereby limiting working space
- Permissive hypercapnia can be used to avoid high pressures of mechanical ventilation or to attenuate changes in blood pressure that result from CO_2 pneumoperitoneum
  - acute changes in arterial carbon dioxide pressure should be avoided
  - in very low birth weight infants this strategy is not advisable because of an increased risk of severe intraventricular hemorrhage
- Humidification of CO_2 is advisable
- Maximal effort should be made to prevent leakage of CO_2 from the abdominal cavity during laparoscopic surgery to prevent hypothermia and peritoneal damage
- Appropriately sized instruments should be used to prevent unnecessary trauma to the abdominal wall and to make optimal use of available working space
- Mechanical bowel preparation can be used to substantially increase laparoscopic working space, especially at low intra-abdominal pressures
- An initial high CO_2 pneumoperitoneum pressure of short duration
  - facilitates the introduction of trocars
  - provides ischemic pre-conditioning, thereby lowering oxidative stress
  - results in an increase in laparoscopic working space, especially when working at low intra-abdominal pressures
- Neuromuscular blockade does not augment laparoscopic working space but is important to prevent inadvertent patient movement during surgery
- Long duration of the CO_2 pneumoperitoneum should be avoided, which demands expedient surgery

FUTURE PERSPECTIVES

The findings presented in this thesis have provided insight into the effectiveness of a number of interventions aimed at increasing laparoscopic working space, both in 20 kg and 6 kg pigs.

We are in the process of investigating the effects of CO_2 pressure, pre-stretching, neuromuscular blockade, mode of ventilation and patient positioning on *thoracoscopic* working space dimensions in 20 kg and 6 kg pigs.

In collaboration with the Vision Robotics department of the Technical University Delft, we have recently performed internal optical distance measurement in a 6 kg pig using a 3D endoscopic camera. This has not yet provided clinically usable results, but this optical technology may in the near future enable us to measure working space objectively and non-invasively in real-time during minimal access surgery procedures in patients. Research into the optimization of laparoscopic- and thoracoscopic working space using objective distance and volume data will then be possible not only in the lab, but also in clinical practice.

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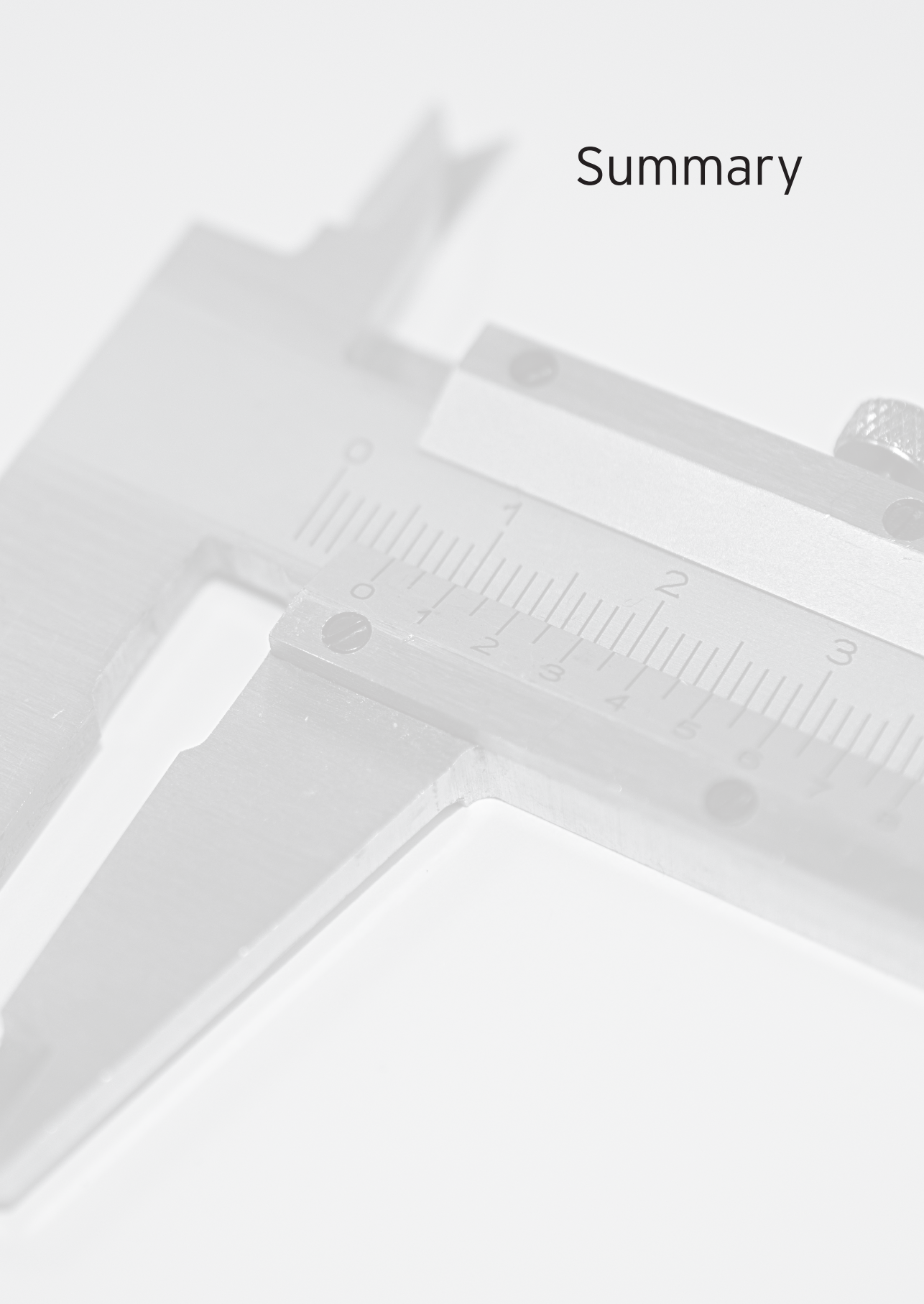
CHAPTER 9

Summary



This thesis addresses the issue of working space in laparoscopic (minimal access) surgery. As working space in laparoscopic surgery is strongly related to the age/size of the patient, even a small gain in working space can markedly improve surgical conditions in smaller children. The aim of this thesis was to investigate the effect of interventions aimed at increasing laparoscopic working space.

Chapter 1 reviews the problems encountered in (pediatric) minimal access surgery (MAS). It reviews literature on the side effects of CO_2 pneumoperitoneum and on strategies to minimize these side effects and to optimize laparoscopic working space. This involves modulation of intra-abdominal pressure (IAP), muscle tone and (oxidative) stress response. A major problem encountered in studies investigating laparoscopic working space is the subjective or indirect method of its evaluation. Assessment of (changes in) working space asks for a precise, quantitative method of evaluation. In animal experiments this may be computed tomography. In a clinical setting, 3D optics could provide distance and volume information.

Chapter 2 presents the results of a study looking into the effect of IAP on working space in a standardized laparoscopy model using 20 kg pigs and computed tomography for measuring. Volume of CO_2 released and displayed by the CO_2 insufflator was shown to be too inaccurate to measure the effect of interventions aimed at increasing working space. Pressure increments at higher intra-abdominal pressures were found to cause less gain in working space than increments at lower pressures. Also, the antero-posterior diameter was found to be the only abdominal dimension substantially influenced by intra-abdominal pressure.

In **chapter 3,** the results of a questionnaire sent to Dutch laparoscopic surgeons to investigate the current practice in- and motivation for the use of mechanical bowel preparation (MBP) prior to colorectal surgery are presented. The returned questionnaires showed that 20% of respondents prescribed MBP prior to colonic resections, while 63% prescribed MBP prior to rectal resections. The most common reasons for giving MBP were the construction of a protective ileostomy (22%) and improvement of surgical field exposure (16%). The most common reported reason for conversion was inadequate surgical field exposure (88%). Of the respondents, 29% believed that the diameter of the small bowel was influenced by MBP, 29% indicated that the exposure of the surgical field was influenced by MBP but 52% did not believe that any of the stages of the operation were influenced by MBP. It was concluded that the role of MBP on intestinal volume is unclear and that indications for MBP in laparoscopic colorectal surgery are not well defined in the Netherlands.

In **chapter 4**, the effect of using MBP in our porcine laparoscopy model is presented. A significant increase in CO_2 pneumoperitoneum volume with MBP was shown. The absolute gain in volume was independent of the pressure of the CO_2 pneumoperitoneum, but the relative gain was greater at a lower IAP. The increase with MBP was 43% at an IAP of 5 mm Hg, 21% at 10 mm Hg and 18% at 15 mm Hg. This was considered an important benefit especially in technically challenging MAS and in the pediatric age group in which lower IAPs are custom.

In **chapter 5,** a previously unrecognized positive effect on working space of pre-stretching of the abdominal wall in our porcine laparoscopy model is presented. Previous stepwise insufflation of the abdomen with CO_2 up to an IAP of 15 mm Hg significantly increased subsequent working-space volume by 21%, 7% and 3% at repeat IAPs of 5, 10 and 15 mm Hg respectively. The antero-posterior diameter significantly increased by 0.5 cm (14%) at repeat 5 mm Hg. It was concluded that although the clinical impact of pre-stretching is still unclear, it may play a substantial role in the outcomes of experimental and clinical studies investigating laparoscopic working space.

In **chapter 6**, the effect of neuromuscular blockade (NMB) on working space is investigated using our porcine laparoscopy model. No statistically significant effect of NMB was found. In contrast, the effect of pre-stretching of the abdominal wall was found to be significant. This confirmed the results of several clinical studies that NMB does not influence laparoscopic working space. It was postulated that studies dealing with working space during laparoscopy should take note of pre-stretching bias.

In **chapter 7,** the results of experiments regarding the effect of IAP, pre-stretching the abdominal wall and NMB on working space in 3 week old, 6 kg pigs are presented. As in the 20 kg pigs, most gain in working space occurred at and IAP of 5 and 10 mm Hg. The absolute CO_2 pneumoperitoneum volume was roughly 5 times smaller in the 6 kg pigs. Pre-stretching resulted in a significant increase in CO_2 pneumoperitoneum volume of up to 60% at an intra-abdominal pressure of 3 mm Hg and 35% at an intra-abdominal pressure of 5 mm Hg. The effect was significantly higher than in 20 kg pigs. The elastic (linear) section of the pressure-volume curve ended at 8 mm Hg, after which plastic deformation with a decrease in compliance occurred. Pre-stretching was deemed a cheap, safe and easy way to increase laparoscopic working space with the added benefit of ischemic preconditioning, resulting in less oxidative stress. No statistically significant effect of NMB on laparoscopic working space was found.

Chapter 8 reflects on the role of MAS in current pediatric surgical practice and discusses how the results of the studies presented in this thesis could be translated into clinically

usable strategies to optimize laparoscopic working space. Recommendations regarding CO_2 pneumoperitoneum and working space in laparoscopic surgery are presented.

NEDERLANDSE SAMENVATTING

Dit proefschrift belicht aspecten die van invloed kunnen zijn op de werkruimte voor de chirurg tijdens laparoscopische (kijk-) operaties. Voor een niet onaanzienlijk deel is deze bepaald door de grootte van de patiënt. Bij kleine kinderen is de werkruimte zeer beperkt, en kan zelfs een kleine toename erg belangrijk zijn voor de chirurg. Dit proefschrift beschrijft onderzoek naar manieren om de werkruimte te vergroten.

Hoofdstuk 1 geeft een overzicht van mogelijke problemen rond kijkoperaties. De bijwerkingen van het gebruik van koolzuurgas om de buik op te blazen worden systematisch beschreven. Door de koolzuurgas-druk in de buik te veranderen, spierverslappers toe te dienen en de stressreacties van het lichaam te beïnvloeden kan de optimale balans worden gevonden tussen werkruimte voor de chirurg en bijwerkingen voor de patiënt. In dierexperimenten kan de werkruimte nauwkeurig worden gemeten met CT-scans. In de kliniek is dit echter niet mogelijk. Mogelijk kan daar in de toekomst door het gebruik van moderne 3D operatiecamera's bruikbare informatie over de afmetingen van de werkruimte worden verkregen.

Hoofdstuk 2 beschrijft het effect van het verhogen van de koolzuurgas-druk in de buik in een gestandaardiseerd diermodel met varkens met een lichaamsgewicht van 20 kg. De werkruimte werd gemeten met CT-scans. De voor-achterwaartse diameter van de buik nam toe naarmate de druk hoger werd; in de andere twee richtingen trad nauwelijks verandering op. Echter, naarmate de druk in de buik hoger werd, werd de toename van de werkruimte steeds kleiner. Helaas bleek het ingeblazen volume gas niet nauwkeurig genoeg te worden weergegeven op het apparaat dat werd gebruikt om het koolzuurgas in te blazen. CT-scans blijven daarom aangewezen voor nauwkeurige metingen.

Hoofdstuk 3 beschrijft de resultaten van een enquête onder Nederlandse laparoscopisch chirurgen over het gebruik van preoperatieve darmvoorbereiding (het leegmaken van de darm). Twintig procent van de 82 respondenten gaf aan dit toe te passen voorafgaand aan laparoscopische dikke darmoperaties, 63% voorafgaand aan kijkoperaties aan de endeldarm. De twee meest genoemde redenen waren het leeg willen hebben van de gehele dikke darm, omdat deze tijdens de operatie werd uitgeschakeld met een stoma (22%), en het verbeteren van de werkruimte tijdens de operatie (16%). Wanneer tijdens een kijkoperatie moest worden overgegaan tot een klassieke open operatie was dit meestal (88%) het gevolg van onvoldoende werkruimte. Over de invloed van darmvoorbereiding op de diameter van de dunne darm en de werkruimte rapporteerde 29% een effect te verwachten; 52% gaf aan geen effect op het verloop van de gehele operatie te verwachten. Concluderend werd gesteld dat de invloed van darmvoorbereiding op

de werkruimte onduidelijk is en dat in Nederland de indicatie voor darmvoorbereiding voorafgaand aan kijkoperaties aan de dikke darm niet eenduidig is.

In **Hoofdstuk 4** wordt in het eerder gebruikte varkensmodel het effect van darmvoorbereiding op de werkruimte gemeten met CT-scans. Er werd een toename van de werkruimte door darmvoorbereiding gevonden van ongeveer 500 ml, onafhankelijk van de gebruikte koolzuurgas-druk in de buik. De relatieve toename was bij een lage druk van 5 mm Hg het grootst, namelijk 43%. Bij hogere drukken was de toename minder, respectievelijk 21% bij 10 mm Hg en 18% bij 15 mm Hg. Dit betekent dat darmvoorbereiding zeer bruikbaar kan zijn om werkruimte te vergroten, met name voor technisch lastige kijkoperaties of voor kijkoperaties bij kinderen. Bij kinderen wordt namelijk vaak met lage drukken in de buik geopereerd, waardoor met darmvoorbereiding relatief veel winst in werkruimte wordt verkregen.

Hoofdstuk 5 beschrijft een tot nu toe onbekend positief effect op de werkruimte van het oprekken van de buikwand. In het gestandaardiseerde varkensmodel werd de werkruimte gemeten met CT-scans tijdens een eerste en tweede keer insuffleren van de buik met 5, 10 en 15 mm Hg koolzuurgas-druk. Tijdens de tweede insufflatie bleek de werkruimte significant groter bij eenzelfde druk, namelijk 21% bij 5 mm Hg, 7% bij 10 mm Hg en 3% bij 15 mm Hg. De voor-achterwaartse diameter van de buik nam 14% (0,5 cm) toe bij een druk van 5 mm Hg. Concluderend werd gesteld dat de klinische impact van dit oprek-fenomeen nog onduidelijk is, maar dat het een belangrijke factor is in de beoordeling van de resultaten van experimentele en klinische studies naar werkruimte tijdens kijkoperaties.

In **Hoofdstuk 6** wordt het effect van spierverslapping onderzocht in het gestandaardiseerde varkensmodel voor kijkoperaties. Er werd geen statistisch significant effect van spierverslapping op de werkruimte gevonden. Deze experimentele bevinding bevestigt eerdere klinische studies die eveneens geen effect van spierverslapping op de laparoscopische werkruimte vonden. Zoals reeds beschreven in hoofdstuk 5, bleek ook bij deze experimenten het oprek-fenomeen van de buikwand zeer significant. Wederom werd gesteld dat het oprek-fenomeen de laparoscopische werkruimte zeer sterk kan beïnvloeden, en zodoende de resultaten van studies naar werkruimte kan vertekenen.

Hoofdstuk 7 beschrijft de resultaten van experimenten naar het effect op de werkruimte van koolzuurgas-druk, oprekken van de buikwand en spierverslapping in een diermodel met kleinere varkens met een lichaamsgewicht van 6 kg. Ook bij deze kleinere dieren werd de meeste werkruimte gewonnen bij drukken van 8-10 mm Hg. De absolute ruimte was ongeveer 5 maal kleiner dan bij de varkens met een lichaamsgewicht van 20 kg.

Het oprekken van de buik levert een significante toename op van de werkruimte van tot 60% bij een druk van 3 mm Hg, en 35% bij 5 mm Hg. Het oprek-effect was significant groter in de kleinere (6 kg) varkens vergeleken met de grotere (20 kg) varkens. Tot een koolzuurgas-druk van 8 mm Hg nam het volume in de buik evenredig toe met de druk. Boven deze druk werd de toename van het volume met het toenemen van de druk steeds kleiner. Ook in deze experimenten werd geen toename van de werkruimte door spierverslapping gevonden.

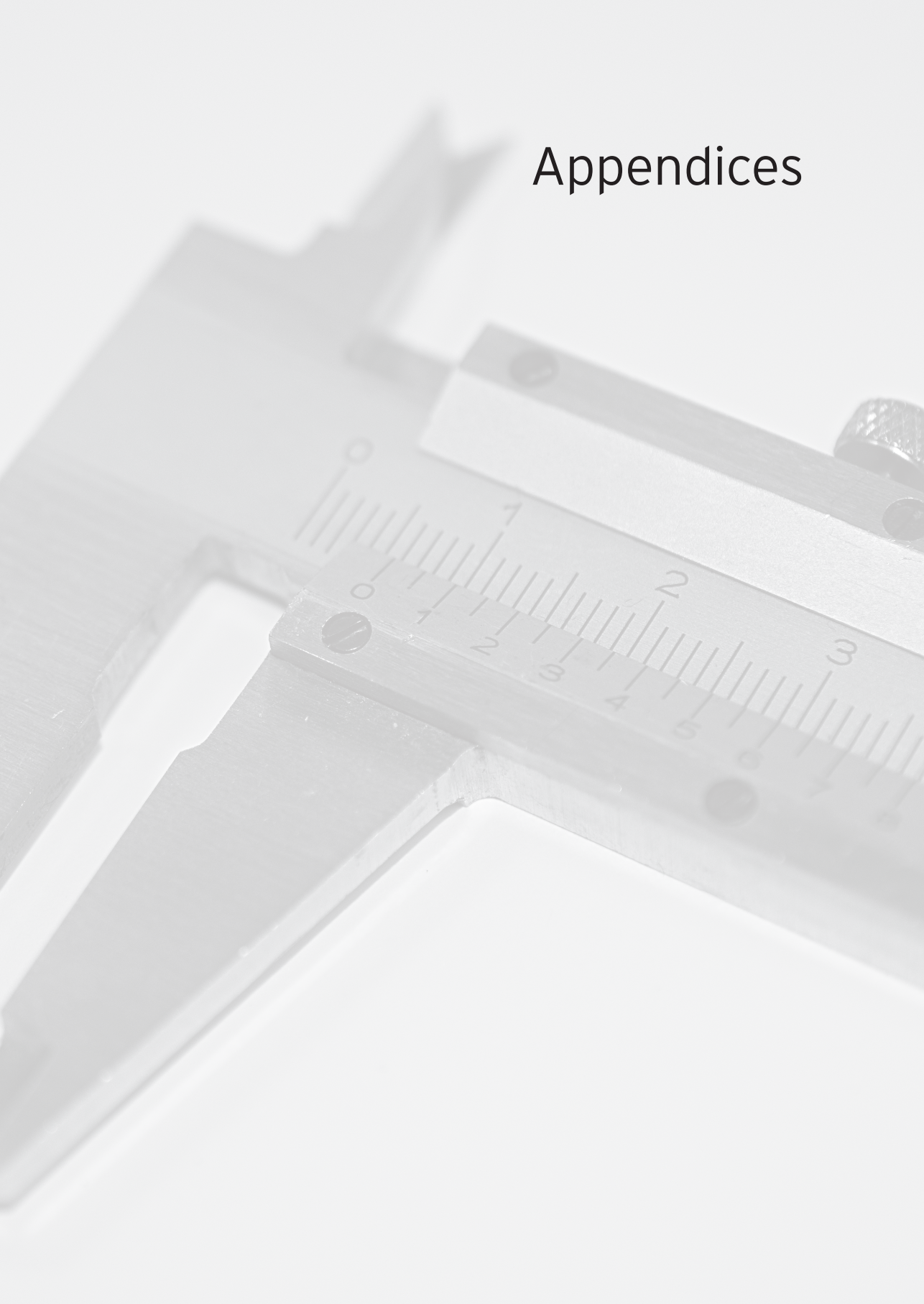
Het oprekken van de buik lijkt een goedkope, veilige en gemakkelijk toepasbare methode om de werkruimte in de buik tijdens kijkoperaties te vergroten. Een bijkomend voordeel is dat bij herhaald insuffleren en desuffleren minder schadelijke afvalstoffen als een gevolg van verminderde weefseldoorbloeding vrijkomen.

Hoofdstuk 8 geeft een overzicht van de rol van kijkoperaties in de huidige kinderchirurgische praktijk. Er wordt besproken hoe de resultaten van de experimenten in dit proefschrift kunnen worden vertaald naar in de kliniek bruikbare werkmethoden, en welke verdere onderzoeken nog nodig zijn. Aanbevelingen worden gedaan voor het optimaliseren van de laparoscopische werkruimte.

Now this is not the end.
It is not even the beginning of the end.
But it is, perhaps, the end of the beginning

Winston Churchill

Appendices



DANKWOORD

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LIST OF PUBLICATIONS

Vlot J, Wijnen R, Stolker RJ, Bax NMA. How can working space in laparoscopic surgery be optimized? A review of literature
Submitted for publication

Vlot J, Staals LME, Wijnen R, Stolker RJ, Bax NMA. Optimizing working space in laparoscopy: CT-measurement of the influence of small body size in a porcine model.
Submitted for publication

Vlot J, Specht PAC, Wijnen R, Mik EG, Bax NMA. Optimizing working space in laparoscopy: CT-measurement of the effect of neuromuscular blockade and its reversal in a porcine model.
Submitted for publication

Vlot J, Wijnen R, Stolker RJ, Bax KN. Optimizing working space in laparoscopy: CT measurement of the effect of pre-stretching of the abdominal wall in a porcine model. Surg Endosc 2013.

van Beelen NW, Mous DS, Brosens E, Klein AD, Ven CP, Vlot J, IJsselstijn H, Wijnen R. Increased Incidence of Hypertrophic Pyloric Stenosis in Esophageal Atresia Patients.
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CURRICULUM VITAE

John Vlot was born on Saturday February 5th, 1972 in Schiedam. After graduating from high school at Stedelijk Gymnasium Schiedam in 1990, he studied Aeronautical Engineering at the Technical University Delft for two years (propaedeutic diploma *cum laude*). He then decided to switch careers and between 1992 and 1998 attended medical school at Erasmus University Rotterdam (propaedeutic diploma *cum laude*). After working for two years as a surgical house officer he trained as a surgeon between 2001 and 2007 at the Westeinde Hospital in The Hague (Dr. J.C.A. de Mol van Otterloo) and the Leids Universitair Medisch Centrum in Leiden (Prof. dr. J.F. Hamming). From 2007 until 2008 he did his specialist training in pediatric surgery at the Sophia Children's Hospital (Prof. dr. N.M.A. Bax). Since 2008 he has been working as a consultant surgeon at the department of pediatric surgery of the Erasmus MC in Rotterdam. The work presented in this thesis is part of his ongoing research on minimal access surgery. John is married to Anne-Marie and has two daughters, Sophie and Emma.

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student:	John Vlot
Erasmus MC department:	Pediatric Surgery
Research School:	
PhD period:	2009-2014
Promotor(s):	Prof. dr. N.M.A. Bax
	Prof. dr. R.M.H. Wijnen
Supervisor:	

1. PhD Training

General courses	Year	Workload (ECTS/hours)
- BROK ("Basiscursus Regelgeving Klinisch Onderzoek") Erasmus University	2011	1 ECTS
- Artikel 9 ("Laboratory Animal Science") Erasmus University	2011	3 ECTS
Seminars and workshops		
- Tricks of the trade in pediatric surgery Case Western Reserve University (USA)	2010	6 hrs
- Symposium endoscopic surgery in children and neonates Wilhelmina children's hospital, Utrecht (NL)	2010	12 hrs
- Ultrasound guided venous access Sonosite, Hertfordshire (UK)	2010	5 hrs
- State of the art MIS Presbytarian St. Luke, Denver (USA)	2011	20 hrs
- Pediatric chest wall deformities Case Western Reserve University (USA)	2011	6 hrs
- Live (MIS) donor nephrectomy Skillslab Erasmus University (NL)	2012	15 hrs
Presentations		
- SAGES, San Diego (USA) (poster)	2012	
- SAGES 2013, Baltimore (USA) (poster)	2012	
- EAES Brussels (Belgium) (oral, Technology Award Session)	2012	
- EAES Vienna (Austria) (poster with oral presentation)	2013	

International conferences

- European Paediatric Surgeons' Association (EUPSA) congress, Graz, Austria	2009	26 hrs
- European Paediatric Surgeons' Association (EUPSA) congress, Leipzig, Germany	2013	24 hrs
- Annual congress British Association of Paediatric Surgeons (BAPS), Aberdeen, UK	2010	20 hrs
- Annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) San Diego, USA	2012	20 hrs
- Annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Baltimore, USA	2013	24 hrs
- International Congress of the European Association of Endoscopic Surgeons (EAES), Brussels, Belgium	2012	25 hrs
- International Congress of the European Association of Endoscopic Surgeons (EAES), Vienna, Austria	2013	20 hrs

Other

- REPAIR meetings (Erasmus MC)	0.5 ECTS
- Research meetings with vision robotics (TU Delft)	2 ECTS
- Research meetings with Industrial Design/ 3ME (TU Delft)	2 ECTS

2. Teaching

- Supervising medical student (research project)	2013	1.5 ECTS
- Presentations for visiting professors, PhD students and different departments at Erasmus MC and TU Delft	2009-2014	0.3 ECTS