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Pathophysiological and Clinical Aspects of Carbonic Dioxide Pneumoperitoneum

Ph.D thesis

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2004

This thesis is based on the following papers,which will be referred to by their roman numerals:

I. Larsen JF, Svendsen FM, Ejstrud P, Kristensen JU, Pedersen V, Redke F. Randomized comparison of conventional and gasless laparoscopic cholecystectomy in regard to operative technique, postoperative course and recovery. J Gastrointestinal Surg 2001;5:330-6.

II. Larsen JF, Ejstrud P, Svendsen F, Redke F, Pedersen V. Randomized study of coagulation and fibrinolysis during and after gasless and conventional laparoscopic cholecystectomy. Br J Surg 2001;88:1001-5

III. Larsen JF, Ejstrud P, Svendsen F, Pedersen V, Redke F. The systemic response in patients undergoing laparoscopic cholecystectomy using gasless or carbonic dioxid pneumoperitoneum: a randomized study. J Gastrointestinal Surg 2002;6:582-586.

IV. Larsen JF, Svendsen FM, Pedersen V. Pneumoperitoneum affects cardiac function and haemodynamics during laparoscopic cholecystectomy in ASA I and II patients. A randomized study. Accepted Br J Surg march 2004.

V. Larsen JF , Svendsen F, Redke F, Pedersen V. Perioperative lung function and gas exchange during carbonic dioxide pneumoperitoneum and gasless laparoscopic cholecystectomy. A randomized comparison. Submitted Br J Surg 2004.

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Contents

1. Introduction

Since the introduction in 1987 by Phillip Mouret of the first laparoscopic cholecystectomy (LC) in the human and since the publishing in 1989 of the first experience with the laparoscopic technique by Périssat et al [1], this technique rapidly became the standard of care for the management of symptomatic cholelithiasis. The introduction of LC caused a revolutionary development of the laparoscopic technique within general surgery, and several laparoscopic procedures are now 'the gold standard' within this field, e.g. laparoscopic reflux surgery[2], appendectomy[3], adrenalectomy[4], some forms of obesity surgery [5], and within the treatment of subgroups of inguinal hernia[6]. The indications for laparoscopic resection of potentially curable colo-rectal cancer have not been defined yet and are awaiting the the results of the ongoing, randomized trials to address the overall important issues of cancer recurrence and survival. However, so far the primary results suggest that laparoscopic surgery will also get an important role within oncologic surgery[7].

The prerequisite for laparoscopic surgery is a working cavity. Positive pressure CO_2 -pneumoperitoneum (CO_2-PP) and positional changes of the patients are the general techniques by which to expose the intraperitoneal organs. Carbonic dioxide (CO_2) is the preferred gas, because it is inexpensive, highly soluble, and chemically stable. In addition, it is a normal product of human metabolism and suppresses combustion. With respect to CO_2-PP there is concern, however, that it may affect the cardiovascular and pulmonary functions. CO_2 is absorbed from the peritoneal cavity into the circulation, where it may result in hypercarbia, acid-base disturbances and affect the systemic response and the plasma cascade systems. In addition to the effect of positive pressure pneumoperitoneum and the absorbed CO_2 , the positional changes of the patients from Trendelenburg to reverse Trendelenburg positions may add to the pathophysiological effects, e.g. stimulate the coagulation system.

As the numbers of laparoscopic procedures are rising and now also offered to patients with co-morbidity, it is mandatory to be aware of the specific, intraoperative, pathophysiological effects that are related to laparoscopic surgery, when using positive pressure CO_2-PP and to evaluate alternative, minimally invasive methods.

2. Background

2.1 Clinical background

It is a common belief that minimally invasive surgery has important effects on the clinical outcome. However, controlled evaluation of the laparoscopic technique has been scarce, and relatively few prospective, randomized trials have been performed to define the indications for the laparoscopic approach and to confirm its benefits, when compared with standard operations of open surgery [3,7-32]. Table 1 summarizes the trials regarding intervention, number, perioperative outcome, follow-up, and recommendations within various laparoscopic procedures. The randomized studies suggest that the surgical trauma represents an important factor in determining the outcome. Other factors - e.g. CO_2-PP - may contribute to the postoperative morbidity , as stated by Kehlet [33,34]. Five studies randomly comparing CO_2-PP with the gasless technique[10,13,14,17,35] showed reduced nausea [10,14], vomitting [10,14] and shoulder pain [10,13,14] in the gasless group. However, in a small study, including 17 patients, randomly assigned to CO_2-PP or gasless laparoscopic colon resection, less pain, but more fatigue was found in the CO_2-PP group [35]. Further studies are needed to investigate the effects of CO_2-PP regarding perioperative course and convalescence.

2.2 Coagulation and fibrinolysis

Although conventional, laparoscopic cholecystectomy is regarded as a minimally invasive procedure, avoiding much of the tissue injury associated with traditional laparotomy, the perioperative changes in plasma levels of these markers do not seem substantially different from those found in open cholecystectomy [36-39]. This has been confirmed in randomized, controlled trials comparing patients undergoing laparoscopic vs. open colon resection [40], and laparoscopic gastric bypass vs. open gastric bypass [41]. The clinical consequences of these changes regarding e.g. thromboembolic complications are not known, nor are the pathophysiological mechanisms releasing the coagulation system. PP and reverse Trendelenburg position may lead to venous stasis in the legs [42,43]. In addition, the venous stasis during PP could affect the endothelium and induce changes in coagulation and fibrinolysis. These factors could mask true differences between laparoscopic and open surgery[44,45]. Based on these observations it may be hypothesized that CO_2-PP may trigger the coagulation and fibrinolytic systems.

2.3 Endocrine, metabolic, and immune responses

Major surgical injury is followed by changes in the metabolic, endocrine, and inflammatory responses. Together with the increased demands on organ functions this constitutes the stress response [33,46]. The response may lead to postoperative hypermetabolism, catabolism, increased demands on body organs and changes in host defense mechanism [46,47]. Within open surgery the responses apparent are proportional to the degree of injury [48] and support the hypothesis that surgical stress response may have harmful effects on the postoperative course and be correlated with clinical development of complications [33,49]. Therefore, it is important to investigate the pathophysiological role of the various components of the surgical stress response and to determine if modifications of such responses may improve surgical outcome. In 1998 Kehlet [47] when reviewing the literature concluded that laparoscopic surgery as compared with that of open has no important effects on the endocrine, metabolic response, but may result in a reduced, inflammatory response. Additional randomized studies published since have shown a tendency towards a reduced, metabolic, endocrine, and inflammatory response, when using $C0_2$-PP, as compared with open surgery [9,35,50-59]. Table 2 summarizes the results of the randomized, controlled and observational trials performed since 1998.

It has been suggested that the cellular acidification induced by CO_2-PP may contribute to the blunting of the inflammatory response during laparoscopic surgery [60]. Apparently Helium, which does not result in acidosis, is more capable than CO_2-PP of preserving cell-mediated, intraperitoneat immunity, causing less pronounced cytocin response[61], However, Helium pneumoperitoneum does not appear to protect against increase in stress hormones[62]. Few studies have investigated the systemic response in patients undergoing gasless laparoscopy and compared it with that of CO_2-PP technique [35,50,52,59]. Two studies demonstrated reduced hormonal response in the gasless group [52,59], and two studies did not find any difference [35,50,59]. As CO_2-PP results in absorption of CO_2, resulting in acidosis, and as the positive, intraabdominal pressure has systemic effects, it is relevant to perform further studies comparing the systemic response and outcome in patients undergoing CO_2-PP or gasless laparoscopy

2.4 Haemodynamics

Alterations in haemodynamics depend on the interaction of several patient and procedure related factors: concomitant disease, intraabdominal pressure, patient position, CO_2 absorption, neurohumeral response, and the nature and duration of the procedure. In addition, the intravascular volume, the preexisting cardiovascular status of the patients, and the anaesthetic agents used can influence the cardiovascular response during CO_2-PP. In the light of this complexity it is not surprising that the published data are inconsistently reported (Tabel 3). Most studies report an increased systemic resistance, increased mean arterial pressure, and little change in heart rate. Similarly, the results of studies investigating the effect of CO_2-PP on heart performance are conflicting, some showing a decrease, few an increase and many no change in cardiac output (CO) or cardiac index (CI) during PP. To evaluate the influence of CO_2-PP, a randomized design involving the same surgical and anaesthetic procedure with and without CO_2-PP seems logical. When we planned our study, six studies had already been published comparing CO_2-PP with gasless technique (Table 4) [10,63-67], without, however, using transoesophageal echocardiography (TOE) for the monitoring of heart function. At that time it was stated that further studies using TOE were needed to examine more closely the intracardiac consequences of CO_2-PP and to compare mechanical technique with CO_2-PP [68].

2.5 Intraoperative lung function

CO_2-PP in various ways affects the intraoperative lung function: the lung mechanics, gas exchange and CO_2 homeostasis. During CO2-PP the airway pressure is increased [50,69,70] and the diaphragma cephalicly displaced. Additionally, the intrathoracic pressure increases, the abdominal part of the chest wall stiffens and the expansion of the lungs is restricted, reducing the functional, residual capacity [71] and compliance [72]. The combination of posture and positive intraabdominal pressure may affect the respiratory mechanism during surgery [73,74]. Further, CO_2-PP may impair gas exchange by mechanical compression of basal lung regions causing atelectasis and secondary, uneven ventilation-perfusion. However, only few studies have shown significant shunting with increased venous admixture during CO_2-PP [73,75,76], and most authors have failed to show any change in oxygenation during CO_2-PP. CO_2 is absorbed from the peritoneum into the circulation. If the increased CO_2 load cannot be eliminated by the lungs, retension in the body, hypercarbia and acidosis may follow [77]. Few have investigated gas exchange keeping the ventilation constant during CO_2-PP [78-80] and compared it with the gasless technique and during changes in positioning as well[81,82].

2.6 Hypotheses and aims

The effects of positive pressure pneumoperitoneum, CO_2 absorption, and position of the patients may be considered important factors for the interpretation of the differences in clinical and physiological responses between open, conventional laparoscopy using CO_2-PP and gasless techniques. It can be hypothesized that CO_2-PP may affect:

- The outcome after laparoscopic surgery by increasing visceral and shoulder pain, nausea, and vomitting, resulting in prolonged convalescence compared with that of gasless laparoscopy.
- The coagulation and fibrinolytic system as a consequence of venous stasis in the legs.
- The inflammatory responses which may be caused by hypercarbia and acidosis during insufflation of CO_2 .
- The haemodynamic and heart performance caused by affection of preload, afterload, and contractility during CO_2-PP.
- The perioperative lung mechanism, CO_2 –homeostasis with hypercabnia, acidosis and accumulation of CO_2 .

In paper I the feasibility of gasless LC is investigated and the clincal course regarding operative time, postoperative pain, hospital stay and convalescence is compared with that of CO_2-PP LC. Papers II and III compare the perioperative coagulation, fibrinolytic and surgical stress responses during CO_2-PP and gasless LC. Paper IV compares the effect of CO_2-PP and the positional changes with that of gasless LC on the haemodynamics and cardiac function as determined by TOE. In paper V the perioperative lung function, oxygenation, CO_2 homeostasis, and accumulation of CO_2 is investigated.

3. Methodological considerations

3.1 Mechanical abdominal wall lift (AWL)

In laparoscopic surgery AWL is an alternative gasless technique to CO_2-PP for exposure of the operative field. Most AWL systems consist of an anchoring device, inserted either into the subcutaneous layer of the the anterior abdominal wall or into the the peritoneal cavity, and a traction device fixed to the operating table. Depending on which device used, a tentlike cavity is created that often gives a small, intraabdominal working space. In this study we used the Laparotensor® (Lucini, Milan, Italy) with a curved subcutaneous anchoring system, theoretically having the advantages of avoiding damage to the intraabdominal organs, pressure trauma to the parietal peritoneum and creating a more domelike working cavity[83]. Generally, AWL systems are connected with a reduced working space compared with that of CO_2-PP, which make them particularly unsuitable for patients with high intraperitoneal fat content [83], for which reason patients with a body mass index over 30 were excluded from the study.

3.2 Design

The surgical techniques using AWL laparoscopy or conventional CO_2-PP are comparable, which forms the basis for comparison of different clinical and physiological factors in patients undergoing laparoscopy with and without CO_2-PP. As several individual and procedure related factors may interact in the performing of laparoscopic surgery, we found the randomized, controlled trial comparing patients undergoing laparoscopy with and without CO_2-PP to be most capable of evaluating the effect of CO_2-PP. Experience, however, with the technique was essential for the conducting of the trial, for which reason a pilot study was performed. In order to minimize variation between the groups, a welldefined patient group was selected, and the anaesthesia, operative procedure, and postoperative treatment standardized. Patients and data collectors were blinded.

3.3 Sample size

The sample size was calculated under the following assumptions: expected difference in mean of 10 procent, expected standard deviation 10 per cent, $\alpha = 0.05$, power =0.90. A sample size of 46 patients was sufficient to detect these differences. The operations were carried out once a week, except on holidays etc. Data was collected from 1 December 1998 to 1 October 1999. The patients were recruited from a waiting list, except for the inclusion and exclusion criteria, no selection bias was made. A total number of 54 patients were included. The five studies are based on the same material.

3.4 The endocrine, metabolic, and inflammatory responses

The stress response may be summarized as follows:

Effects	General response		Local response	
	Endocrine metabolic	Immune	Neural	Humoral
↑	Catabolic acting hormones: Catecholamines Glucagon **Cortisol**	Interleukin-1 Interleukin-6 Tumour necrosis factor Prostaglandin E_2s CRP plasmaconcentration Oxygen free radical release **CRP-synthesis**	Peripheral neural stimulation	Complement system Arachnoid acid system Coagulation Fibrinolysis Histamine Serotonin cytokins
↓	Anabolic acting hormones: Growth hormone **Insulin**	Delayed -type hypersensitivity response T cell-dependent antibody response Interleukin-2 production Interleukin-2 expression Interferon -γ production NK cell activity Neutrophil chemotaxies Phagocytocis		
Outcome	Increased organ demands, catabolism, immunosuppression, organ dysfunction **hyperglycaemia**	Increased infectious complications and possible cancer recurrence[7]	Initiation of the stress response by transmitting the pain response to central nervosystem stimulating the adrenocortical response. Postoperative pain hypersensitivity	Facilitation of afferent neural stimuli. Coagulation Fibrinolysis Activation of kinins and complement system

The effects on the intraoperative and postoperative, endocrine, metabolic responses were assessed by measuring the serum insulin (s-insulin), serum glucose (s-glucose) and serum cortisol (s-cortisol). The inflammatory response was assessed by measuring serum C-reactive protein (CRP).

3.5 Coagulation and fibrinolysis

The aim of this study was to detect activation of coagulation and fibrinolysis in vivo. Traditional assays are not well suited for this purpose, as they measure either plasma levels of clotting factors or the velocity of in vitro clotting or fibrinolysis (i.e. processes taking place in the laboratory). Instead, we used commercially available immunoassays for products generated by activation of coagulation or fibrinolysis. Prothrombin fragment 1+2 (F1+2) is a short-lived peptide released when prothrombin is converted into thrombin. Soluble fibrin is the soluble precursor of clots or thrombi, which form by aggregation of soluble fibrin and subsequent cross-linking. Lysis of such clots by plasmin releases cross-linked fibrin degradation products that may be identified by their neoantigen D-dimer (DD). Key steps in coagulation and fibrinolysis (i.e. thrombin generation, fibrin generation, and fibrinolysis) may thus be monitored by measurement of these markers

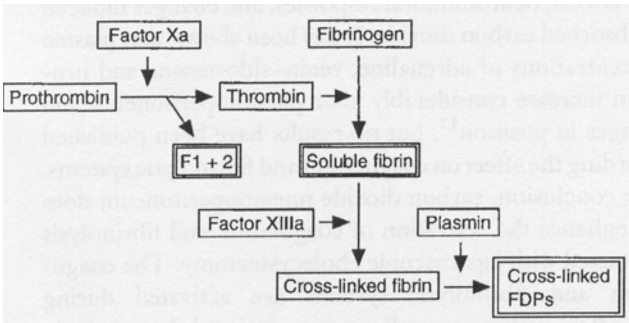

Figure 1. Markers of coagulation and fibrinolysis shown in the double boxes

3.6 Heart performance

Transoesophageal echocardiography (TOE) can be used to monitor cardiac left ventricular function throughout surgical procedures. It is a safe procedure, rendering high-quality two-dimension images and dobbler information. There are, however, some technical difficulties, e.g. poor transmission of ultrasound through air-containing structures. In study IV, TOE was performed using a 5 Mhz 2 element annular monoplane probe. TOE included the short axis view at the mid papillary level, mitral annulus diameter in diastole and mitral flow curves at the mitral annular level. Measuring the short axis dimensions may be difficult, as the heart may change its relation to the transducer during insufflation and positional changes of the patient in addition to poor transmission caused by the CO_2-PP. Especially in the reverse Trendelenburg position we noticed this problem. In half of the patients we were not able to obtain reliable short axis view. The left ventricular end diastolic diameter (LVEDD) was measured at mid papillary level and used as an estimate of the left ventricular filling (preload). Left ventricular end systolic diameter (LVESD) was measured at mid papillary level and used as an estimate of the systolic volume. The fractional shortening (FS) of the left ventricle of the heart was calculated ((LVEDD-LVESD)/LVEDD) and used as an estimate of the left ventricular performance integrating the three determinants. An echocardiographically determined left ventricular end systolic and diastolic dimension can be used as a surrogate for left ventricular volume in the left ventricular pressure-volume relation[84].

Cardiac output (CO) was calculated by multiplying the time velocity integral of the mitral flow (TVI) with cross sectional area of the mitral ostium (A) and the heart rate (HR): CO (l /min) = TVI · A · HR . Calculations like these are, however, problematic, the greatest limitation being calculation of the sectional area. Thus, we were unable to calculate CO in 20-25% of our measurements. In addition, the diameter measured must be squared in the calculation of blood flow any errors would also be squared. Terai et al [85]have shown, however, a close correlation (r = 0.97) of CO calculated from TOE with CO, determined by the thermodilution technique. Furthermore, as the same method was used to evaluate the heart performance, changes between and within the groups may reflect true differences.

3.7 Statistics

In papers I, II, and III the non-parametric Mann-Whitney test was used to compare two groups. Fischer's exact test was applied in case the frequency was less than five. Friedman's analysis was used to detect changes with time within each group. The data are expressed as median and range. P-values of < 0.05 were considered significant.

In paper IV analysis of variance (ANOVA) statistics was used to compare differences between and within more than two groups. Data was tested for normality. Three-way ANOVA was used to consider the effect of which method used during LC: CO_2-PP or wall traction (factor 1), the position: supine, Trendelenburg, or reverse Trendelenburg (factor 2) and the time during operation (factor 3). Missing data was treated by using a general, linear model. A P value less than 0.05 was considered significant. To isolate the group or groups that differed from the others, Student-Newman-Keuls Method for pairwise multiple comparison was used. Two-way ANOVA was used to consider the effect of positional changes (factor 1) and the phases (factor 2) within the groups,. P value less than 0.05 was considered significant. Patient data were included in the analysis, until time of conversion. Results are reported as mean ± SD. Statistical analysis was performed using the Jandel Sigmastat version 2.0 statistical package (SPSS Science Chicago, USA).

In paper V we simplified the analysis by pooling data into two groups, CO_2-PP group and gasless group. Data was tested for normality and the two groups compared using two-tailed version of Student's t test. Changes within one group were tested using One-way ANOVA. Multiple pairwise comparison was made with Student-Newman-Keuls Method metod, with the overall alpha level set at 0.05.

4.Papers

Se appendix

I. Larsen JF, Svendsen FM, Ejstrud P, Kristensen JU, Pedersen V, Redke F. Randomized comparison of conventional and gasless laparoscopic cholecystectomy in regard to operative technique, postoperative course and recovery. J Gastrointestinal Surg 2001;5:330-6.

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V. Larsen JF , Svendsen F, Redke F, Pedersen V. Perioperative lung function and gas exchange during carbonic dioxide pneumoperitoneum and gasless laparoscopic cholecystectomy. A randomized comparison. Submitted Br J Surg 2004.

5. General discussion

5.1 Clinical outcome

Pain is a common complaint after laparoscopic surgery. Many hypotheses have been put forward in the attempt to explain the aetiology of postlaparoscopic pain, which may be classified into three groups: visceral, incisional, and shoulder pain[86,87]. Traction of the triangular ligament, overstretching of the diaphragmatic muscle fibers due to a high rate of insufflation[88], hypothermia caused by the gas used , direct peritoneal irritation by CO_2 and /or the acidosis caused by hypercarbia[89], and residual CO_2 [90] are some of the hypotheses. The multifactorial nature of postoperative pain, and the great inter-individual variation in early postoperative pain [87] may explain the contradictory results of the published data [91]. If CO_2-PP per se is an important factor, it may be expected that gasless laparoscopy result in reduced visceral and shoulder pain. Three randomized, controlled trials have been performed, comparing gasless with CO_2-PP technique as regards postoperative pain[10,14,17]. In neither of these studies local anaesthesia was administered. Two of the studies showed reduced shoulder pain [10,14] and one study increased shoulder pain, but no difference was found in visceral pain score [17]. We did not register any shoulder pain in patients operated by the gasless technique and only little in the CO_2-PP group four hours postoperatively (I). Wound pain, dominant 8 to 24 hours postoperatively, was less pronounced than visceral pain (I), which is contrary to the findings by Bisgaard et al [86], who showed that incisional pain dominated over shoulder and visceral pain, irrespective of administration of intraperitoneal, local anaesthesia. However, we did not find any significant differences in pain score, nor in morphine consumption at rest or during mobilization within or between the groups during hospital stay (I). One possible explanation could be that local anaesthetics (bupivacaine 0.5 %) was administered in the port sites and subdiaphragmatically after removal of the gallblader, although the results of randomized, controlled trials, regarding intraperitoneal installation of local anaesthetics are conflicting [91].

An important parameter for the evaluation of the advantages of minimally invasive surgery is duration of convalescence or sick leave. It has been shown that improved patient information may reduce convalescence [92].We did not recommend a specific period of postoperative convalescence, but asked the patients to score activity, pain, nausea, and fatique for 14 days. The two groups of patients received the same information. Patients in the gasless group returned to their normal activities sooner and tended to be painfree earlier than those of CO_2-PP group (I). To our knowledge, no other studies have compared gasless with CO_2-PP technique in regard to sick leave or duration of convalescence. Koivusalo et al [14] showed that gasless cholecystectomy resulted in more uneventful and faster postoperative recovery than conventional CO_2-PP. However, further studies are needed to clarify whether this observed difference is due to the distended peritoneum, the absorbed CO_2, or the associated acidosis.

5.2 Systemic response

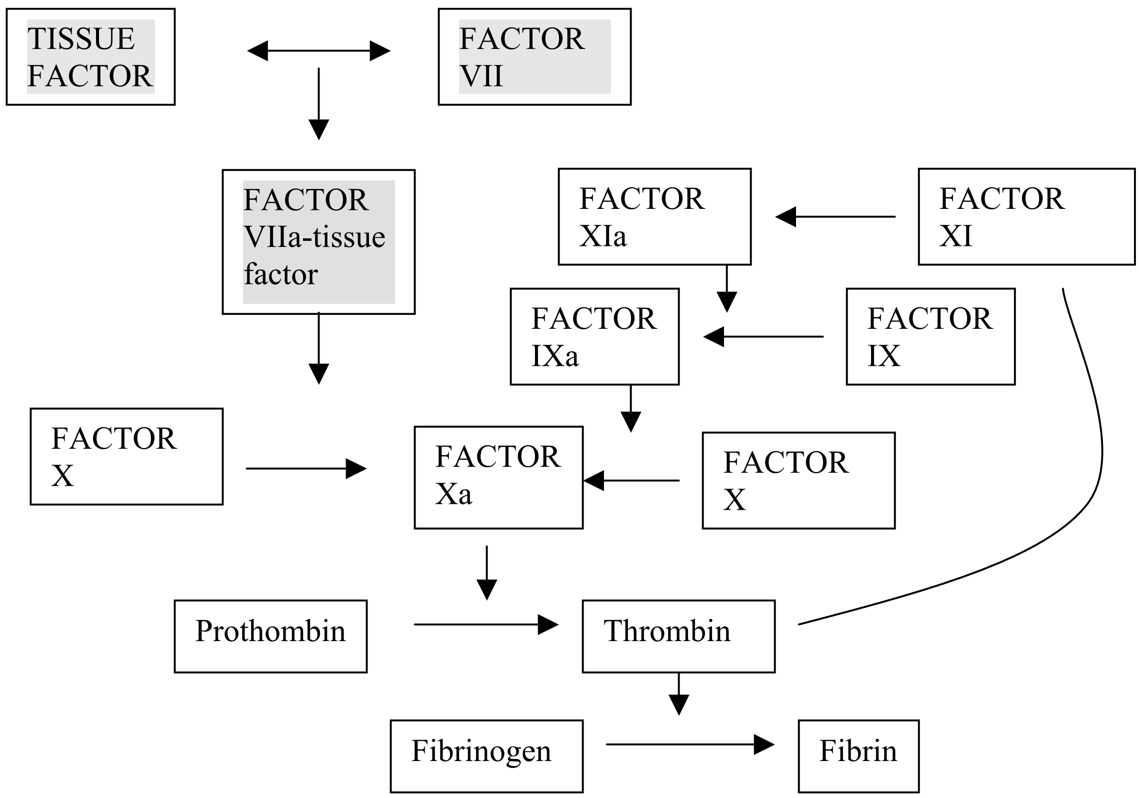
Surgical stress response

The clinical consequences of perioperative systemic changes – immunosuppression - are increased susceptibility to infective complications[93] and probably increased risk of recurrence after cancer surgery[7]. As CO_2-PP may blunt the inflammatory response, it is of interest to compare the post traumatic immune function during CO_2-PP with that of gasless laparoscopy. The effect of CO_2 on the stress response has been investigated in eight randomized studies comparing CO_2-PP with the gasless technique (Table 3). Most of them have investigated the response during and after laparoscopic cholecystectomy, showing no change or only a slight decrease in the inflammatory response using CO_2-PP [35,50,51,94,95], while data on the endocrine, metabolic response are conflicting: two studies showed increased [52,59] two showed decreased metabolic and endocrine response [50,94], and one study no difference [35]. Paper III suggests a reduced, inflammatory reponse after CO_2-PP compared with that of gasless laparoscopy, supporting the above-mentioned hypotheses. We did not expect to find any clinical difference in outcome because of the relatively small study group. However, our results support the hypothesis that an reduced metabolic and endocrine response may be followed by a more uneventful course[47]. It remains to be proven if these changes have any clinical importance regarding postoperative complications.

Coagulation and fibrinolysis

Fibrin formation and subsequent resolution are fundamental mechanisms involved in haemostasis and physiological tissue repair. Clotting involves plasma, platelets, and components in the vessel wall. Blood coagulation can be initiated by two pathways: the extrinsic pathway, the most important in vivo system triggered by release of tissue factor from the site of injury, and the intrinsic pathway stimulated by contact with a negatively charged surface, now supposed to be an in vitro artefact[96]. Following initial triggering a series of serine proteases are sequentially activated, culminating in the formation of thrombin, the enzyme responsible for the conversion of soluble fibrinogen into the insoluble fibrin clot (Figure 2).

Figure 2
Coagulation system, extrinsic pathway



The coagulation system is a cascade system [96] which:

- stimulated by extern activation or autoactivation converts inert proenzymes into active enzymes, which by
- limited proteolysis cleavage activates several molecules at the next step, yielding an exponential amplification
- the response may be amplified by positive feedback and by use of binding proteins to bring reactants together
- the response may be inhibited by destruction of active proteins and
- formation of inhibitor-complex formation.

Both genetic and environmental factors can influence the activation of coagulation and may predispose to thrombosis. The CO_2-PP and positioning of the patients in reverse Trendelenburg position may lead to venous stasis [42,97-99]. As venous stasis predisposes to venous thombosis, it may be speculated that CO_2-PP result in increased markers of coagulation and fibrinolysis. In study II we investigated this hypothesis showing no differences between the the gasless and CO2-PP groups, which suggests that the CO_2-PP does not affect the coagulation and fibrinolytic system. Supporting our results, Dabrowiecki et al [100] demonstrated that blood samples obtained from the cubital vein and femoral vein during CO_2-PP showed no difference in markers of coagulation and fibrinolysis, suggesting that venous stasis in lower extremities during laparoscopic cholecystectomy does not cause alterations in haemostasis.

5.3 Haemodynamics

Preload

It has been suggested that the increased, intraabdominal pressure forces blood out of the abdominal organs, which may result in autotransfusion and increased preload. The increased, central venous pressure (CVP) and pulmonary artery occlusive pressure shown in many studies [101] [10,52] may, however, be increased secondary to the transmission of the abdominal pressure to the thoracic cavity. Transoesophageal echocardiography may be helpful in the monitoring of the ventricular filling [102]. It has been shown that the left ventricular filling pressure is not associated with increased left ventricular diastolic area [102,103], which seriously questions the relevance of CVP measurements during CO_2-PP . The results of the prospective studies investigating the left ventricular dimensions (end diastolic diameter/area) using TOE are conflicting (Table III). Cunnigham et al [103], Dorsay et al.[104] ,and D'Ugo [105] found no changes in the left ventricular end diastolic area during CO_2-PP in supine position. However, after head-up positioning a decrease was registered in two of the studies. Zuckerman et al.[106] showed a significant reduction in left ventricular end diastolic volume placing the patients in reverse Trendelenburg position. Contrary to this, Gannedahl et al. [107] showed increased left ventricular volume during PP, irrespective of posture in cardiovascularly healthy patients. As many factors may affect the filling condition of the heart during surgery it is important to include a control group. To our knowledge, however, no control group has been included in the studies investigating the left ventricular filling during CO_2-PP. We found a significantly increased diastolic diameter during CO_2-PP compared with that of gasless technique, reflecting an increased venous return during CO_2-PP (IV) .

Afterload

In agreement with paper IV most studies have shown increased systemic, vascular resistance. It has been suggested that the increased SVR and MAP may result from stimulation of hormonal mediators: catecholamines, renin, and vasopressin. Ogihara et al [59] showed a significantly increased plasma epinephrine, norepinephrine, and dopamine in patients undergoing laparoscopic ovarian resection by CO_2-PP compared with that of gasless technique, whereas Koivusalo et al found no difference between the groups [52,66]. Clonidine inhibits the release of catecholamines, and it has been shown that MAP, HR, and SVR are significantly reduced, when clonidine is infused one hour prior to CO_2-PP. This suggests an effect of the sympathetic system on the haemodynamics during CO_2-PP [108] . A time relationship between elevated plasma vasopressin and increased MAP/SVR has also been found [108,109], and O'Leary et al [110] reported a fourfold increase in plasma renin and aldosterone concentration during LC, correlating with changes in the haemodynamics, which was in accordance with the findings by Koivasalo et al [52]. Thus, the sympathetic, renin-angiotensin and vasopressin system may all be factors involved in the increase of afterload during CO_2-PP. If absorbed CO_2 per se does stimulate neurohumoral mediators, it might be expected that different insufflated gasses would result in different reponses, as shown in an animal study comparing CO_2 with nitrogen PP [111]. However, a human study showed no difference in haemodynamic parameters comparing CO_2 with N_2O [112].

Left ventricular performance

Left ventricular systolic performance is the ability of the left ventricle to empty. Because myocardial contractility is an important determinant of the left ventricle systolic performance, systolic performance and contractility are frequently considered to be interchangeable. However, they are not the same, because the systolic performance is also influenced by load. Myocardial contractility refers to the fundamental property of cardiac tissue, reflecting the level of activation. The more the amount of contraction, the more the amount of shortening. At constant preload and afterload increased contractility results in a greater extent and velocity of shortening. Our study showed a significantly reduced FS during CO_2-PP compared with that of the gasless group, suggesting a reduced cardiac performance as a consequence of CO2-PP. In accordance with our results Irwin et al.[113] demonstrated reduced fractional area during CO_2-PP, using a two-dimensional echocardiographic backscatter imaging technique. However, Gannedahl et al[107], did not show any changes of end systolic area, nor of the fractional area during PP. Hypercarbia and acidosis may occur during CO2-PP [77] and may decrease the contractility of the heart, as shown in an animal study [114].

A temporal relationship between changes in pH and FS during CO_2-PP was found. However, no correlation was found between changes in FS and pH (n = 191, Pearson's r = -0.073,)

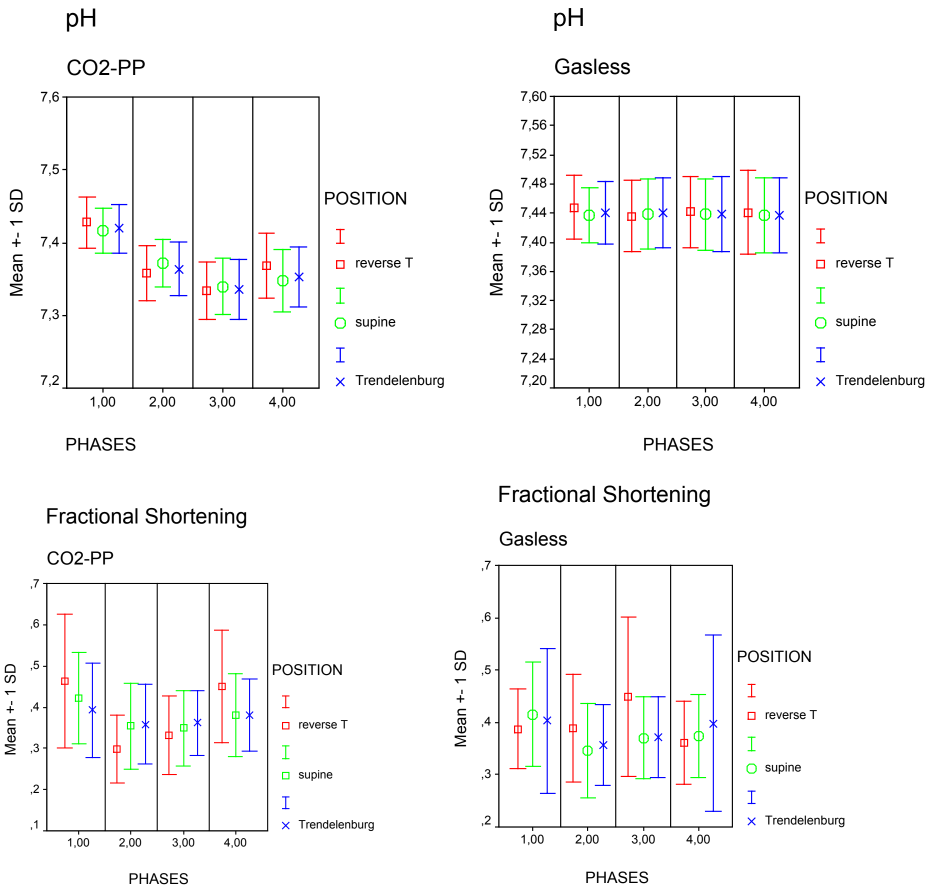


Figure 3. Fractional shortening and pH measured preoperatively (phase 1), peroperatively (phases 2 and 3) and postoperatively (phase 4) in three positions.

This association may as well be a consequence of increased afterload. As stated in paper IV afterload is the load that the myocardium must bear to contract; the greater the afterload, the less the amount of shortening. In a simple sense MAP represents the afterload, so a relationship between FS and MAP may be expected. We found a low, though significant correlation between MAP and FS (CO_2-PP n = 268, Pearson's r = -0,199, P < 0,001; Gasless n = 202, Pearson' r = -

0,197).

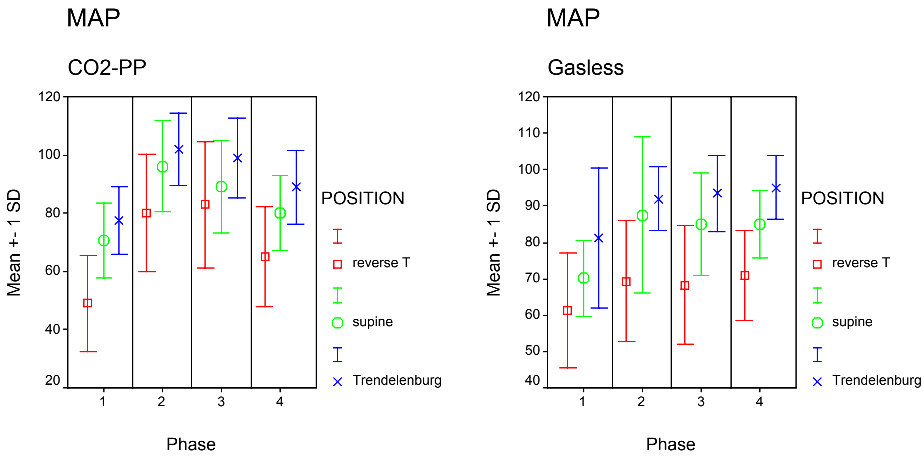


Figure 4. MAP measured preoperatively (phase 1), peroperatively (phases 2 and 3) and postoperatively (phase 4) in three positions.

Cardiac output

The integrated pumping function of the cardiovascular system ultimately results in the cardiac output. Four randomized studies have compared cardiac output during CO_2-PP with gasless or low pressure laparoscopy, suggesting reduced cardiac output during CO_2-PP [80,80,115] or no changes [64,65] (Table 4). We used TOE for measurements of the CO and found no difference in CO comparing gasless and CO_2-PP techniques (IV). Several observational studies have investigated the effect on the cardiac output during laparoscopy (Table 3). In an investigation by Joris et al [101] 15 patients, ASA physical class I, showed a reduction of 50% of the preoperative values during PP using Swan-Ganz catheter measurements. No extra volume loading was given before laparoscopy, but a basal infusion of 4mL/kg/h of lactated Ringer's solution was given to compensate for intraoperative loss. In a similar study Hirvonen et al [116] showed a less than 20% reduction in CO by giving the patients extra volume loading before laparoscopy, however. Using transoesophageal doppler Alishahi et al[117] found a similar reduction in CO during PP and head up tilt. The question is, however, whether the PP or other factors are responsible for the decrease in CO. In a small, prospective, randomized study cardiac output was measured using Swan-Ganz catheter and thermodilution method in 15 patients assigned to open cholecystectomy, conventional laparoscopic cholecystectomy or gasless laparoscopic cholecystectomy[80]. Contrary to the results of our study, which showed no difference, the cardiac index was significantly reduced by 15% in patients undergoing conventional laparoscopic cholecystectomy.

Position

Patient position has important effect on the haemodynamic consequences of pneumoperitoneum. Maximum haemodynamic changes have been observed, when PP is created with the patients in reverse Trendelenburg with a decline in cardiac index of 50% [101]. The change from supine to reverse Trendelenburg positions may be accompanied by a fall in venous return, reflected by change in left ventricular end diastolic area[103]. In our study LVEDD, reflecting left ventricular filling ,was significantly increased immediately after CO2-PP (phase 2) compared with that of the gasless technique. Compared with basic values this suggests improved left ventricular filling during CO2-PP. However, the LVESD was significantly increased during CO_2-PP compared with that of the gasless technique, the result being a reduced FS during CO2-PP. This suggests a reduced left ventricular performance during reverse Trendelenburg position immediately after insufflation of CO2. The increased LVESD may be a result of increased afterload; however, the correlation between LVESD and MAP was low.

Conclusion

CO_2-PP affects haemodynamics by increasing heart rate and mean arterial pressure. The sympathetic, renin-angiotensin and vasopressin system may be involved. It remains to be demonstrated whether pneumoperitoneum or CO_2 is responsible for the activation of the systems. CO_2-PP increases left ventricular filling immediately after insufflation of CO_2, however, left ventricular performance of the heart is reduced simultaneously. CO2-PP has little , if any, effect on the CO in cardiovascularly healthy patients on the assumption that the patients are given extra volume. The consequence of CO_2-PP on the left heart performance is most pronounced in the reverse Trendelenburg position.

5.4 Intraoperative lung function

Lung mechanism and oxygenation

Four randomized studies have compared high/ low pressure CO_2-PP with gasless laparoscopy regarding respiratory mechanism during laparoscopic surgery. All of them showed reduced pulmonary compliance during CO_2-PP[10,59,63,67], agreeing with our results that showed reduced compliance during CO_2-PP and further reduction, when placing patients in Trendelenbourg position. The reduced compliance did not have any effect on the oxygenation. Contrary to what may be expected, Odberg et al. [70] showed a 15 per cent elevation in PaO2 and a 31 per cent reduction in venous admixture in healthy patients during CO_2-PP, suggesting reduced shunting during CO_2-PP. This was confirmed by Anderson et al [69] who used multiple inert gas technique, showing decreased pulmonary shunt and increased PaO2 during CO_2-PP in cardio-pulmonarily healthy patients.

CO_2 homeostasis

During CO_2-PP the volume of absorbed CO_2 is estimated to 39 ml/min [118], matching excess CO_2 output during CO_2-PP, to 32-54 ml/min in steady state [77,119]. During insufflation of CO_2 , a significant increase in paCO_2 and a decrease in pH was registered (V). PaCO_2 correlated well with pH (CO_2-PP group n = 334, Pearson's r = -0,852, P < 0,001) (gasless group n = 249, Pearson's r = -0,883, P < 0,001) .

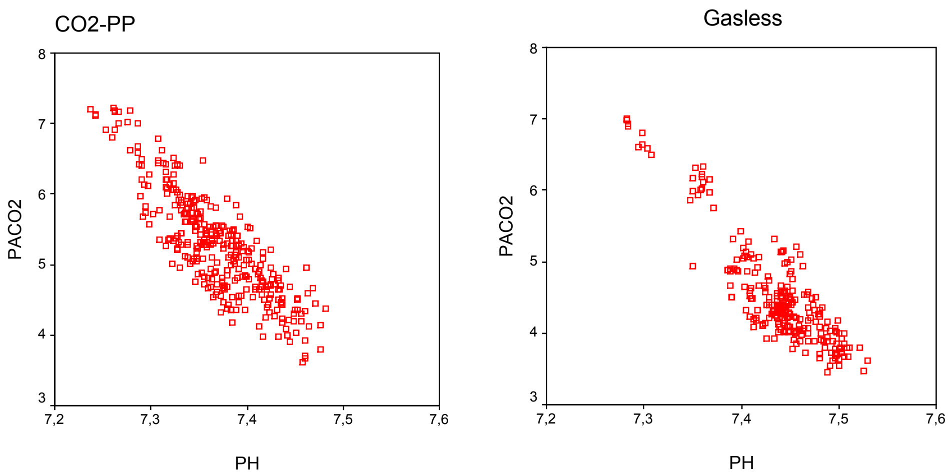


Figure 5. Correlation between PaCO_2 and pH

During CO_2-PP carbonic dioxide output may increase by 50% [77]. Even in patients with normal lung function CO_2-PP results in increased CO_2-PP and acidosis, if the increased CO_2 load is not eliminated by increased minute ventilation, as shown in our study. With increased ventilation, normocarbenia can be maintained and acidosis avoided, but in patients who are cardio-pulmonarily compromised, this is not always possible, however [75]. To adjust ventilation to the requirements of carbonic dioxide excretion, close monitoring of etCO2, which we found is well correlated to PaCO_2 , is essential. By using gasless technique or other gases it is possible to avoid hypercarbnia and acidosis, as shown in our study (V) and other studies as well [120,121]. .

6. General conclusions

The aim of this thesis was to evaluate the pathophysiological effects of CO_2-PP in patients undergoing laparoscopy. As several individual and procedure related factors may interact, we used the randomized, controlled trial to compare the clinical, systemic, and cardiopulmonary factors of importance for the outcome in patients undergoing LC with and without CO_2-PP. The greatest limitation of the present study was lack of patients with comorbidity (ASA III and IV) and inclusion of major abdominal surgery.

Paper I reveals that CO_2-PP and the gasless techniques are comparable as regards operative time, and intraoperative and postoperative complications. The sampling time was standardized , making it possible to investigate the differences between CO_2-PP and the gasless technique. During hospital stay no significant difference was registered in pain score nor in morphine consumption at rest or during mobilization within or between the groups (I). However, patients in the gasless group returned to their normal activities sooner and tended to be painfree earlier than those of CO_2-PP group (I). CO_2-PP did not affect coagulation or fibrinolytic markers (II), however, it was not possible in the present study to clarify if CO_2-PP may be followed by a higher rate of thromboembolic complications than gasless or open surgery. During insufflation of CO_2 a significant increase in $paCO_2$ and decrease in pH is registered, whereas no changes are observed during gasless LC (V). It has been suggested that the cellular acidification induced by CO2-PP may contribute to the blunting of the inflammatory response during laparoscopic surgery. Paper III suggests that the postoperative inflammatory response is reduced, whereas the metabolic and endocrine responses are increased in patients undergoing CO_2-PP compared with that of the gasless technique. The clinical implications of this observation is difficult to evaluate, however, faster postoperative recovery in the gasless group may be associated with the specific effects of CO_2-PP. Whether it is the distended peritoneum or the acidosis associated with CO_2-PP which results in this observed difference has to be further investigated. CO_2-PP affects the haemodynamics by increasing heart rate and mean arterial pressure (IV). The sympathetic, renin-angiotensin and vasopressin system may be involved. It remains to be seen whether pneumoperitoneum or CO2 is responsible for the activation of the systems. CO_2-PP increases left ventricular filling immediately after insufflation of CO_2, however, left ventricular performance of the heart is reduced simultaneously (IV). The simultaneous respiratory acidosis after insufflation of CO_2 could be an important factor determining part of the decreasing heart performance.

However, no correlation between heart performance measured by fractional shortening and mean arterial pressure was found. The observed haemodynamic effects of CO_2-PP did not have any consequenses on the cardiac output (IV). However, our study was limited to cardiopulmonarily healthy patients only. Clinical studies on ASA III and IV patients have shown serious haemodynamic changes during CO_2-PP.

Table 5 summarizes the overall effects of CO_2-PP shown in papers I-V:

Study	Parameter	Pre. operative	Induction	Operation 5 minutes	Operation 30 minutes	Post.op.	Post.op 24 h	Conval escence
I	Wound pain					→	→	↑
Clinical	Visceral pain					→	→	↑
Outcome	Convalescen ce							↑
II	F1 + 2	→	→	→	→	→		
Coagulation	Soluble fibrin	→	→	→	→	→		
Fibrinolysis	d-Dimer	→	→		→	→		
III	Cortisol	→	→	↑	↑	→	→	
Systemic	Insulin	→	→	→	↑	→	→	
response	Glucose	→	→	→	→	→	→	
	CRP	→	→	→	→	→	↓	
IV	LVEDD		→	↑	↑	↑		
Heart	LVESD		→	↑	↑	↑		
haemodyna mics	FS		→	→	↓	→		
	CO		→	→	→	→		
	HR	→	→	↑	↑	→		
	MAP	→	→	↑	↑	→		
V	Compliance		→	↓	↓	→		
Lung	$PaCO_2$	→	→	↑	↑	→ (↑*)		
function	PaO_2	→	→	→	→	→		
	pH	→	→	↓	↓	→ (↓*)		
	$etCO_2$		→	↑	↑	→ (↑*)		

Tabel 5. Overall effects and outcome in patients undergoing CO_2-PP or gasless LC.
↑: Significantly increased effect of CO_2-PP compared with that of gasless technique.
→: No difference between CO_2-PP and gasless technique.
↓: Significantly reduced effect of CO_2-PP compared with that of gasless technique .
* Significant difference between parameters compared with that of induction phase.

7. Future research

7.1 Inflammatory and immune response.

The *clinical* outcome after laparoscopic surgery concerning sepsis, pneumonia, urinary tract infections, local tumour growth and metastases are important issues which are poorly evaluated, however. There is evidence that surgical stress impairs immunity and that this is more intense within open than laparoscopic surgery (Table 2). Immunity plays a significant role in tumour progression and metastatic spread {Bouvy, 1997 1167 /id. A large-scale, randomized, controlled trial suggests that laparoscopically assisted colectomy is more effective than open colectomy for the treatment of colon cancer in terms of tumour recurrence and cancer-related survival [7]. However, use of CO_2-PP has been intensively debated regarding port-site recurrence and intraperitoneal tumour growth [91,122]. Large-scale, multicentre, clinical studies are currently being performed in Europe and the United States, the oncological results of which will be available in a few years.

- Further experimental studies are needed concerning mobilization and spread of neoplastic cells in relation to choice of
    - Surgical technique
    - Insufflated gas
    - Pressure
    - Gasless technique

    in addition to
- clinical studies comparing open fast trac surgery with laparoscopic technique concerning long time cancer related survival.

7.2 Haemodynamics

- Heart performance. The haemodynamic changes in high risk ASA III and IV patients need further investigations such as
    - Evaluation of methods for the monitoring of cardiac function
        - TOE
        - Pulmonary arterial catheter

- Additional, randomized, controlled studies are needed to evaluate the effect of different interventions on the haemodynamic parameters
    - Pharmacotherapy
    - Gasless technique
    - Inert gas

- Circulation. In patients with cardiovascular disease or organ disorders prolonged CO_2-PP may result in reduced perfusion and organ function. Further experimental and clinical studies are needed regarding
  - Splanchnic perfusion.
    - measured by microdialysis technique
  - Renal perfusion
    - Measured by microdialysis technique
  - Hepatic perfusion.
  - CNS

7.3 Lung Function

- Patients with pulmonary disease may have retention of CO_2 postoperatively. However, little is known about the clinical, postoperative, pulmonary complications and the CO_2 – homeostasis in patients with obstructive pulmonary disease. Further studies are needed regarding:
  - Per- and postoperative excretion of CO_2 in patients with pulmonary disease.
  - Postoperative clinical, pulmonary complications in patients with pulmonary disease.

8. English summary

The number of laparoscopic procedures is still rising and within the field of gastro-intestinal surgery, urology, and gynaecology the laparoscopic procedure has now become the gold standard. The prerequisite for laparoscopic surgery is a working cavity. Positive pressure carbonic dioxide pneumoperitoneum (CO_2-PP) and positional changes of the patients are the general methods of exposing the intraperitoneal organs. Carbonic dioxide (CO_2) is the preferred gas, because it is inexpensive, highly soluble, and chemically stable. In addition, it suppresses combustion and is a normal product of human metabolism. There is, however, some concern in regard to CO_2-PP, which may affect the cardiovascular and pulmonary functions. CO_2 is absorbed from the peritoneal cavity into the circulation, where it may result in hypercarbia, acid-base disturbances, and may affect the systemic response and the plasma cascade systems. As the laparoscopic procedures are also offered to patients with co-morbidity, it is mandatory to be aware of the specific, intraoperative, pathophysiological effects that are related to laparoscopic surgery, when using positive pressure CO_2-PP and to evaluate alternative, minimally invasive methods.

Based on a randomized design comparing conventional with gasless laparoscopy the effects of CO_2-PP are investigated in regard to:

- outcome, pain, convalescence,
- coagulation and fibrinolysis
- surgical stress response
- perioperative haemodynamics and heart performance
- perioperative respiratory function

The studies revealed that:

- convalescence is significantly prolonged in patients undergoing surgery with CO_2-PP compared with gasless technique. However, no difference is registered in postoperative pain or hospital stay
- coagulation and fibrinolysis is not enhanced by CO_2-PP
- endocrine and metabolic response may be activated and the inflammatory response blunted by CO_2-PP
- mean arterial pressure and heart rate is increased during CO_2-PP

- preload and afterload is increased, heart performance decreased, but cardiac output not affected during CO_2-PP
- the haemodynamic effects are most pronounced in the reverse Trendelenburg position
- static lung compliance is reduced, hypercarbia and acidosis follows CO_2-PP
- postoperative hypercarbia and acidosis may be due to hypoventilation rather than CO_2 accumulation after CO_2-PP laparoscopy.

Further studies are needed to evaluate the long time effects on cancer related survival in patients undergoing laparoscopic surgery compared with that of open fast trac surgery and different laparoscopic techniques. In addition, the evidence of the effect of CO_2-PP on high risk cardio-pulmonary patients are insufficient.

9. Danish summary – dansk resumé

Laparoskopisk kirurgi har vundet stigende udbredelse inden for mave-tarm kirurgi, urologi og gynækologi pga. det reducerede kirurgiske traume, som i forhold til åben kirurgi medfører kortere indlæggelsestid og rekonvalescens. Forudsætningen for at udføre kikkert kirurgi i bughulen er etablering af en arbejdskavitet. Traditionelt anvendes kuldioxid (CO_2), som er ufarligt, hurtigt opløseligt, ikke-brændbart og billigt, ligesom det normalt ikke danner luftbobler ved optagelse i blodbanen. Overtryks CO_2-pneumoperitoneum har imidlertid nogle virkninger, som i kombination med de til tider ekstreme lejeændringer kan have en række uheldige konsekvenser for forskellige organsystemer. Da laparoskopi i stigende omfang også tilbydes patienter med konkurrerende lidelser, er det vigtigt at have viden om bivirkningerne af CO_2 –pneumoperitoneum.

Baseret på et randomiseret design sammenlignes konventionel med gasløs laparoskopi mhp. at analysere virkningen af CO_2 –pneumoperitoneum på:

- klinisk forløb, postoperative smerter og rekonvalescens
- koagulations- og fibrinolysemarkører
- kirurgisk stress respons
- perifer kredsløb og perioperativ hjertefunktion
- perioperativ lungefunktion og blodgasser

Undersøgelserne viser, at CO_2 –pneumoperitoneum

medfører længere rekonvalscens sammenlignet med gasløs teknik, men øger ikke de postoperative smerter eller indlæggelsestiden

- påvirker ikke koagulations- og fibrinolysemarkørerne
- påvirker det kirurgiske respons ved at øge det endokrine og metabolske respons og hæmme det inflammatoriske
- øger pulsfrekvensen og blodtrykket
- øger hjertets preload og afterload samt hjertefunktionen, dog uden at påvirke cardiac output
- påvirkningen af hjertefunktionen er mest udtalt i anti Trendelenburg
- øger lungernes statiske compliance og medfører hyperkapni samt respiratorisk acidose uden at påvirke iltningen af det arterielle blod.

Der mangler viden om, hvilken langsigtet effekt, laparoskopi har på den cancer relaterede overlevelse. Ligeledes mangler der viden om de kort- og langsigtede, patofysiologiske virkninger af CO_2 –pneumoperitoneum blandt patienter med alvorlige hjerte-lunge problemer.

10. Tables

Table 1. Controlled, clinical trials.

Operation	**author/year References**	**Intervention**	**Number**	**Outcome Perioperative**	**Outcome Follow-up**	**Recommendation**
Cholecystectomy	Barkun, 1992 [15]	Laparoscopic vs. mini	70	↓Hospital stay	↓Convalscense	LC preferred
	Super, 1996 [24]	Laparoscopic vs mini	100	↓Pain →Hospital stay	→Convalscense	Comparable Procedures
	Majeed, 1996 [25]	Laparoscopic vs mini	200	↑Operative time →Hospital stay	→convalescense	LC no significant advantages
	Kunnz, 1992 [26]	Laparoscopic vs mini	77	→Operative time ↓Postop pain ↓Hospital stay		LC preferred
	McGinn, 1995[12]	Laparoscopic vs mini	310	→Hospital stay ↓Pain	↓Convalscense	LC preferred
	McMahon,1995 [11]	Laparoscopic vs. mini	299		1 year follow- up: 90% symptomatic benefit both groups	No difference long time follow up
	Hendolin, 2000 [9]	Laparoscopic vs Open	49	↓Hospital stay ↓Pain	↓Sick leave	LC preferred

Table 1 cont.						
Operation	**References author/year**	**Intervention**	**Number**	**Outcome Perioperative**	**Outcome Follow-up**	**Recommendation**
cholecystectomy	Koivusalo, 1996 [14]	Gasless Laparoscopic vs Conventional Laparoscopic	26	↓Nausea ↓Vomiting ↓Shoulder pain ↓Recovery		Gasless preferred
	Lindgren, 1995 [10]	Abd wall lift vs Conventional laparoscopic	25	↓Nausea ↓Vomiting ↓Shoulder pain		Abd wall lift preferred
	Sarli, 2000 [13]	Low vs high pressure	90	↓Shoulder pain		Low pressure preferred
	Vezakis, 1999 [17]	Gasless vs Low pressure Laparoscopic	36	↓Exposure →Pain ↑Operative time		Gasless value in high risk patients
Inguinal hernia	Cochrane, 2003 Review [6]	Laparoscopic mesh vs open mesh	7161	↑Operative time ↓haematoma ↑Seroma ↓infection →hospital stay	↓Normal activity ↓Persistent pain ↓numbness →recurrence	No
Ventral hernia	Carbajo 1999 [18]	Laparoscopic mesh vs open mesh	60	↓Operative time ↓Hospital stay	↓Recurrence rate	No

Table 1 cont.						
Operation	**References author/year**	**Intervention**	**Number**	**Outcome Perioperative**	**Outcome Follow-up**	**Recommendation**
Appendicitis	Cochrane Review [3]	Laparoscopic vs open	39 studies	↓Wound infection ↑Operative time ↓Pain ↓Hospital stay ↓Negative app.	↓Convalscence	Laparoscopy
Gastro-oesophageal reflux	Nilsson 2000 [19,21]	Laparoscopic vs open fundoplicatio	60	↑Operative time ↓Pain ↓Hospital stay	→Convalscence →well being	
	Bais 2000 [22]	Laparoscopic vs open fundoplication	42		Cured →oesophagitis →quality of life	
	Laostarnen 2001 [20]	Laparoscopic vs open fundoplication	28			
	Laine 1997 [23]	Laparoscopic vs open fundoplication	110			

Table 1 cont.						
Operation	**References author/year**	**Intervention**	**Number**	**Outcome Perioperative**	**Outcome Follow-up**	**Recommendation**
Colo-rectal neoplasms	Lacy 2002 [7]	Laparoscopy vs open	219	Recovery faster Bowel function faster Oral intake faster ↓Morbidity Periop →mortality ↓Hospital stay	5-year survival↑	Laparoscopy
	Delgado 2000 {Delgado, 2000 716 /id}	Laparoscopy vs open	255	Operative time →Morbidity< 70 years ↓Morbidity > 70 years		> 70 years laparoscopy
	Schwenk 1998 [123]	Laparoscopy vs open	60	Bowel function faster Oral feeding faster		short term laparoscopy Long term ?
	Milsom 1998 [29]	Laparoscopy vs open	109	↓Pain Bowel function faster		Short term laparoscopy Long term ?
	Stage 1997 [27]	Laparoscopy vs open	29	↓Hospital stay ↓Pain		No

Table 1 cont.						
Operation	**References author/year**	**Intervention**	**Number**	**Outcome Perioperative**	**Outcome Follow-up**	**Recommendation**
Obesity	De Wit 1999 [32]	Laparoscopic adj. Silicone banding vs open	50	↓Operative time ↓Hospital stay →Complications	↓Readmission →Weight loss	Laparoscopy
	Westling 2001 [31]	Laparoscopic gastric bypass vs open	51	↓Pain ↓Hospital stay ↑Reoperation ↑Conversion	→Weight loss	No
	Nguyen 2001 [30]	Laparoscopic gastric bypass vs open	150	↑Operative time ↓Hospital stay ↓Wound infecti	↓Incisional hernia Anastomosis ↑stricture →Weight loss ↑Quality of life	Laparoscopy
Splenectomy	No randomized trials					
Staging	No randomized trials					
Inflammatory Bowel Disease	Milson 2001 [16]	Laparoscopic vs open ileocecal Crohn	60	→Pain Bowel function ↑faster ↓Hospital stay Minor ↓complications Major →complications	→Clinical recurrence	Laparoscopy

Table 2. Endocrine, metabolic, and inflammatory reponse.

Effects of laparoscopic surgery on intraoperative and postoperative endocrine, metabolic, and immune responses (clinical studies). → : no difference between laparoscopic vs open/gasless surgery; ↓ : Reduced response in laparoscopic vs. open/gasless surgery; ↑increased response in laparoscopic vs. open/gasless surgery.
Lap.: laparoscopic; chol.: cholecystectomy; IL: Interleucin; CRP: C-reactive protein;
ACTH: adrenocorticotrophic hormone; u: urine

Reference	**Year**	**Operation**	**Intervention**	**Duration**	**Parameter**	**Comments**
Anone et al [53]	1998	Lap . chol.	General anaesthesia vs general + fentanyl vs general + epidural	perioperative	↑ cortisol all groups ↑Cathecholamines group I	Randomized N=52
Bello et al [124]	1998	Cholecystectomy.	Laparoscopic vs. open	7 days	→IL-1, IL-6, →IL-10, →Prolactin, →Cortisol, →Growth H	Non randomized N=40
Engin et al [58]	1998	Cholecystectomy	Laparoscopic vs. open	perioperative	↓glucagon, ↓Insulin	Randomized N=32
Koivusalo et al [52]	1998	Cholecystectomy	CO2-PP vs. gasless	perioperative	↑cathecholamines	Randomized N=26

Table 2 cont.						
Reference	**Year**	**Operation**	**Intervention**	**Duration**	**Parameter**	

						Comments
Nanashima et al [95]	1998	Cholecystectomy	CO2-PP vs. gasless	2 days	→ IL-6	Non randomized N=27
Ninomiya et al [51]	1998	Cholecystectomy	CO2-PP vs. gasless		→IL-6, →CRP →neutrophil elastase	Non randomized N=20
Holub et al [125]	1999	Hysterectomy	Laparoscopic vs. open	?	↓CRP	Non randomized N=32
Ogihara et al [59]	1999	Lap ovarian resection	CO2-PP vs. gasless	perioperative	↑cathecolamines ↑dopamin ↑Anti diuretic hor →cortisol	Randomized N=12
Schulze et al [35]	1999	Lap. Colon resection	CO2-PP vs gasless	10 days	→ IL-6 → CRP	Randomized N=17
Blanc-Louvry et al [56]	2000	Cholecystectomy	Laparoscopic vs. open	1 day	↓ACTH ↓urine cortisol ↓urine catechol	Randomized N=41
Hendolin et al [9]	2000	Cholecystectomy	Laparoscopic vs. open	?	→catecholamines →cortisol, →glucose	Randomized N=49
Ishizuka et al [94]	2000	Lap.chol	CO2-PP vs gasless	1 day	↓catecholamines ↓IL-6 ↑cortisol	Non randomized N=31

Table 2 cont.						
Reference	**Year**	**Operation**	**Intervention**	**Duration**	**Parameter**	**Comments**
Uzunkoy et al [57]	2000	Herniotomy	Laparoscopic vs. open	2 days	↓CRP →Cortisol →Glucose	Randomized N=50
Rorarius et al [126]	2000	Hysterectomy	Laparoscopic vs. vaginal	?	→CRP →ACTH →Cortisol →Glucose	Non randomized N=20
Nguyen et al [54]	2002	Gastric bypass	Laparoscopic vs. open	3 days	→Insulin →Glucose →Catecholamines →Dopamine ↓ACTH ↓Cortisol ↓CRP ↓IL-6 →Nitrogen balance	Randomized N=48
Solomon et al [55]	2002	Rectopexy vs	Laparoscopic vs. open	?	↓Urine- ↓catecholamine IL-6 ↓Cortisol ↓CRP	Randomized N=40
Uen et al [50]	2002	Cholecystectomy	CO2-PP vs gasless	2 days	↓u-Cortisol ↓CRP ↓IL-6	Randomized N=95

Table 2 cont.						
Reference	**Year**	**Operation**	**Intervention**	**Duration**	**Parameter**	**Comments**
Larsen et al[127]	2002	Cholecystectomy	CO2-PP vs gasless	1 day	↑Cortisol ↑Insulin →Glucose ↓CRP	Randomized N=50
Hildebrant et al [128]	2003	Colon resection for inflammatory bowel disease	Laparoscopic vs. open	?	IL-6 IL-10 CRP Granulocyte elastase	Non randomized N=42

Table 3. Haemodynamics, clinical trials.

Haemodynamic parameters	**Decrease**		**Unaltered**		**Increase**	
	Authors, year	Ref.		Ref.	Authors, years	Ref.
Heart Rate			Joris, 1993 Myre, 1997 Joris, 1998 Elliott, 1998 Myre, 1998 Zuckerman,2001, Irwin, 2001 Galizia, 2001 Uen, 2002	50,80,101,102,106,108,113,129,130	Andersson,1999 Hirvonen, 2000	116,131
Mean Arterial Pressure			Uen, 2002	50	Joris, 1993, Koivusalo, 1997, Myre 1998, 1998	52,63,101,108,113,129,131
Systemic Vascular Resistance			Dhoster, 1996	132	Critchley, 1993 Joris 1993, 1998 Walder, 1997 Zollinger, 1997 Volpino, 1998 Hirvonen, 2000	101,108,109,116,133-135
Cardiac output	Westerband, 1992 Safran, 1993 Joris, 1998	76,108,136	Andersson, 1999	131	Dhoster, 1996	132

Table 3 cont.						
Haemodynamic parameters	**Decrease**		**Unaltered**		**Increase**	
	Authors, year	Ref.		Ref.	Authors, years	Ref.
Cardiac index	Dorsay, 1995 Koksoy, 1995 Elliot, 1998 McLaughlin, 1995 Walder, 1997 Wallace, 1997 Elliot, 1998 Galizia, 2001	65,80,104,109,130,134,137,138	Critchley, 1993 Walder, 1997 Odeberg, 1994 Zuckerman, 2001	102,106,109,135,139	Hashimoto 1993, Dhoster 1996	72,132
End diastolic diameter			D'Ugo, 2000	105		
End systolic diameter			D'Ugo, 2000	105		
Fractional area	Irwin, 2001	113				
End diastolic area	Cunnigham, 1993	103	Couture, 1997	140,141	Gannedahl 1996	107

Table 4 Haemodynamics, randomized, controlled trials

.Hemodynamics. Randomized, controlled trials. ↑: higher; →: no difference; ↓: reduced

Author	Reference	Operation	Intervention	Parameter	Comments
Lindgren et al 1995	10	Lap. chol.	CO_2-PP vs. gasless	↑MAP, → HR ↑CVP	Randomized N=25, Human
Koivusalo et al 1996	66	Lap. chol.	CO_2-PP vs. gasless	↑p-renin → noradrenalin	Randomized N=24
Koivusalo et al 1997	63	Lap.chol.	CO_2-PP vs. gasless	↑MAP, →HR	Randomized N=29
Casati 1997	67	Gynaecological laparoscopy	CO_2-PP vs. gasless	↑ diastolic pressure → HR	Randomized N=20
Wallace 1997	65	Lap.chol	CO_2-PP high (15 mmHg) vs. CO_2-PP low (7.5mmHg)	→HR →CI	Randomized N=20
Miejer 1997	64	Lap. Chol.	CO_2-PP vs wall traction and low CO_2-PP	→Diastolic press. →Systolic press. →HR →CO	Randomized N=18
Koivusalo 1998	52	Lap.chol.	CO_2-PP vs. gasless	↑MAP ↑HR →norepinephrine →epinephrine	Randomized N=13

Table 4 cont.					
Author	**Reference**	**Operation**	**Intervention**	**Parameter**	**Comments**
Ogihara et al 1999	52,59	Laparoscopic ovarian resection	CO_2-PP vs. gasless	↑MAP →HR ↑Dopamine ↑Epinephrine ↑Norepinephrine	Randomized N=12
Schulze et al 1999	35	Laparoscopic colon resection	CO_2-PP vs gasless	→ MAP ↑ HR ↑ CVP	Randomized N=17
Dexter et al 1999	115	Lap. chol.	CO_2-PP high (15 mmHg) vs. CO_2-PP low (7mmHg)	↑MAP ↑HR ↓SV ↓CO	Randomized N=20
Galizia et al 2001	52,80	Lap.chol.	CO_2-PP vs. Gasless vs open	↑MAP →HR ↑SVR ↓CO ↓CI	Randomized N=15
Uen et al 2002	50,52	Lap.chol.	CO_2-PP vs. gasless	→MAP →HR	Randomized N=95
Tsereteli et al 2002	112	Elective laparoscopic surgery	CO_2-PP vs. N2O	→MAP →HR	Randomized N=103

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12. Appendix