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Publication date:
2004

Document Version
Publisher’s PDF, also known as Version of record

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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:


Acknowledgement

Data collection to the five papers on which this review is based was carried out during my employment as a consultant surgeon at the Department of Surgical Gastroenterology, Aalborg Hospital.

This work would not have been possible without the support from the Department of Surgical Gastroenterology, Anaesthesiology and Cardiology. I am grateful to Dr. Flemming Svendsen with whom I have spent many hours discussing and analyzing the data. Flemming’s permanent humorousness and encouraging telephone calls and emails kept the process running. I am also very grateful to Dr. Vivi Pedersen for her performance of the echocardiography, to the consultants at the Department of Cardiology helping analyzing the data and to Dr. Per Ejstrud, Dr. Jørgen Ulrik Kristensen and Dr. Finn Redke for their efforts during data collection. Dr. Hans Rahr contributed with important detail and critical review of the paper regarding coagulation and fibrinolysis. The excellent and precise laboratory work was performed by the laboratory technologists, Dorte Reffeld Lund and Jane Hillingsøe to whom I’m very thankful. Also thanks to Professor Hans Gregersen for his support and guidance and to Per Gandrup and Tove Nilsson for their encouraging me to make this review.

Great patience from my colleagues and from the nurses at the Department of Surgical Gastroenterology formed the basis for the establishment of this work.

The most patient co-worker, however, has been my wife, Grete, without whose assistance with the manuscripts this work would never have been possible.

The studies were financially supported by Aalborg Hospital and fundings from Nordjyllands Amts Forskningsraad, Aalborg Stifts Julelotteri and Det Obelske Familefond.
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 Périsat et al, 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, appendectomy, adrenalectomy, some forms of obesity surgery, and within the treatment of subgroups of inguinal hernia. The indications for laparoscopic resection of potentially curable colo-rectal cancer have not been defined yet and are awaiting 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.

The prerequisite for laparoscopic surgery is a working cavity. Positive pressure CO₂-pneumoperitoneum (CO₂-PP) and positional changes of the patients are the general techniques by which to expose the intraperitoneal organs. Carbonic dioxide (CO₂) 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 CO₂-PP there is concern, however, that it may affect the cardiovascular and pulmonary functions. CO₂ 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 CO₂, 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 CO₂-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\(^10,14\), vomiting\(^10,14\) 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. The response may lead to postoperative hypermetabolism, catabolism, increased demands on body organs and changes in host defense mechanism. Within open surgery the responses apparent are proportional to the degree of injury and support the hypothesis that surgical stress response may have harmful effects on the postoperative course and be correlated with clinical development of complications. 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 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 CO₂-PP, as compared with open surgery. 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 CO₂-PP may contribute to the blunting of the inflammatory response during laparoscopic surgery. Apparently Helium, which does not result in acidosis, is more capable than CO₂-PP of preserving cell-mediated, intraperitoneal immunity, causing less pronounced cytokine response. However, Helium pneumoperitoneum does not appear to protect against increase in stress hormones. Few studies have investigated the systemic response in patients undergoing gasless laparoscopy and compared it with that of CO₂-PP technique. Two studies demonstrated reduced hormonal response in the gasless group, and two studies did not find any difference. As CO₂-PP results in absorption of CO₂ 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 CO₂-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, CO₂ 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 (Table 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 CO$_2$-PP the airway pressure is increased $^{50,69,70}$ and the diaphragma cephalically 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\textsubscript{2}-PP may affect:

- The outcome after laparoscopic surgery by increasing visceral and shoulder pain, nausea, and vomiting, 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\textsubscript{2}.
- The haemodynamic and heart performance caused by affection of preload, afterload, and contractility during CO\textsubscript{2}-PP.
- The perioperative lung mechanism, CO\textsubscript{2}—homeostasis with hypercapnia, acidosis and accumulation of CO\textsubscript{2}.

In paper I the feasibility of gasless LC is investigated and the clinical course regarding operative time, postoperative pain, hospital stay and convalescence is compared with that of CO\textsubscript{2}-PP LC. Papers II and III compare the perioperative coagulation, fibrinolytic and surgical stress responses during CO\textsubscript{2}-PP and gasless LC. Paper IV compares the effect of CO\textsubscript{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\textsubscript{2} homeostasis, and accumulation of CO\textsubscript{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 anterior abdominal wall or into 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. 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, 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 percent, expected standard deviation 10 percent, $\alpha = 0.05$, 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:

<table>
<thead>
<tr>
<th>Effects</th>
<th>General response</th>
<th>Local response</th>
<th>Humoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>Catabolic acting hormones: Catecholamines Glucagon <strong>Cortisol</strong></td>
<td>Interleukin-1 Interleukin-6 Tumour necrosis factor Prostaglandin E&lt;sub&gt;2&lt;/sub&gt; CRP plasmoncentration Oxygen free radical release <strong>CRP-synthesis</strong></td>
<td>Peripheral neural stimulation</td>
</tr>
<tr>
<td>↓</td>
<td>Anabolic acting hormones: Growth hormone <strong>Insulin</strong></td>
<td>Delayed -type hypersensitivity response T cell-dependent antibody response Interleukin-2 production Interleukin-2 expression Interferon-γ production NK cell activity Neutrophil chemotaxies Phagocytosis</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Increased organ demands, catabolism, immunosuppression, organ dysfunction <strong>hyperglycaemia</strong></td>
<td>Increased infectious complications and possible cancer recurrence</td>
<td>Initiation of the stress response by transmitting the pain response to the central nervous system stimulating the adrenocortical response. Postoperative pain hypersensitivity</td>
</tr>
</tbody>
</table>

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.

![Diagram showing markers of coagulation and fibrinolysis](image)

*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-dimensional images and doppler 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 CO₂-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.\textsuperscript{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): \[
\text{CO (l/min) = TVI \cdot A \cdot HR.}
\]
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\textsuperscript{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: \text{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,
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


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\textsuperscript{86,87}. Traction of the triangular ligament, overstretching of the diaphragmatic muscle fibers due to a high rate of insufflation\textsuperscript{88}, hypothermia caused by the gas used, direct peritoneal irritation by CO\textsubscript{2} and/or the acidosis caused by hypercarbia\textsuperscript{89}, and residual CO\textsubscript{2} \textsuperscript{90} are some of the hypotheses. The multifactorial nature of postoperative pain, and the great inter-individual variation in early postoperative pain may explain the contradictory results of the published data\textsuperscript{91}. If CO\textsubscript{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\textsubscript{2}-PP technique as regards postoperative pain\textsuperscript{10,14,17}. In neither of these studies local anaesthesia was administered. Two of the studies showed reduced shoulder pain\textsuperscript{10,14} and one study increased shoulder pain, but no difference was found in visceral pain score\textsuperscript{17}. We did not register any shoulder pain in patients operated by the gasless technique and only little in the CO\textsubscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{92}. We did not recommend a specific period of postoperative convalescence, but asked the patients to score activity, pain, nausea, and fatigue 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\textsubscript{2}-PP.
group (I). To our knowledge, no other studies have compared gasless with CO₂-PP technique in regard to sick leave or duration of convalescence. Koivusalo et al. showed that gasless cholecystectomy resulted in more uneventful and faster postoperative recovery than conventional CO₂-PP. However, further studies are needed to clarify whether this observed difference is due to the distended peritoneum, the absorbed CO₂ 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 and probably increased risk of recurrence after cancer surgery. As CO₂-PP may blunt the inflammatory response, it is of interest to compare the post traumatic immune function during CO₂-PP with that of gasless laparoscopy. The effect of CO₂ on the stress response has been investigated in eight randomized studies comparing CO₂-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 CO₂-PP, while data on the endocrine, metabolic response are conflicting: two studies showed increased, two showed decreased metabolic and endocrine response, and one study no difference. Paper III suggests a reduced, inflammatory response after CO₂-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. 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. 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).
The coagulation system is a cascade system which:

- stimulated by external 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 thrombosis, 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 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). Cunningham 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. showed a significantly increased plasma epinephrine, norepinephrine, and dopamine in patients undergoing laparoscopic ovarian resection by CO₂-PP compared with that of gasless technique, whereas Koivusalo et al. found no difference between the groups. 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 CO₂-PP. This suggests an effect of the sympathetic system on the haemodynamics during CO₂-PP. A time relationship between elevated plasma vasopressin and increased MAP/SVR has also been found, and O’Leary et al. 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 Koivusalo et al. Thus, the sympathetic, renin-angiotensin and vasopressin system may all be factors involved in the increase of afterload during CO₂-PP. If absorbed CO₂ per se does stimulate neurohumoral mediators, it might be expected that different insufflated gases would result in different responses, as shown in an animal study comparing CO₂ with nitrogen PP. However, a human study showed no difference in haemodynamic parameters comparing CO₂ with N₂O.

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 CO₂-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. demonstrated reduced fractional area during CO₂-PP, using a two-dimensional echocardiographic backscatter imaging technique. However, Gannedahl et al. 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’s \(r = -\)
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 \(^{64,65}\) (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%. 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. 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 CO2-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**

CO2-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 CO2 is responsible for the activation of the systems. CO2-PP increases left ventricular filling immediately after insufflation of CO2, 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 CO2-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 CO2-PP with gasless laparoscopy regarding respiratory mechanism during laparoscopic surgery. All of them showed reduced pulmonary compliance during CO2-PP, agreeing with our results that showed reduced compliance during CO2-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.\textsuperscript{70} showed a 15 per cent elevation in PaO2 and a 31 per cent reduction in venous admixture in healthy patients during CO\textsubscript{2}-PP, suggesting reduced shunting during CO\textsubscript{2}-PP. This was confirmed by Anderson et al.\textsuperscript{69} who used multiple inert gas technique, showing decreased pulmonary shunt and increased PaO2 during CO\textsubscript{2}-PP in cardio-pulmonarily healthy patients.

\textit{CO\textsubscript{2} homeostasis}

During CO\textsubscript{2}-PP the volume of absorbed CO\textsubscript{2} is estimated to 39 ml/min\textsuperscript{118}, matching excess CO\textsubscript{2} output during CO\textsubscript{2}-PP, to 32-54 ml/min in steady state\textsuperscript{77,119}. During insufflation of CO\textsubscript{2}, a significant increase in paCO\textsubscript{2} and a decrease in pH was registered (V). PaCO\textsubscript{2} correlated well with pH (CO\textsubscript{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).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Correlation between PaCO\textsubscript{2} and pH}
\end{figure}

During CO\textsubscript{2}-PP carbonic dioxide output may increase by 50\%\textsuperscript{77}. Even in patients with normal lung function CO\textsubscript{2}-PP results in increased CO\textsubscript{2}-PP and acidosis, if the increased CO\textsubscript{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\textsuperscript{75}. To adjust ventilation to the requirements of carbonic dioxide excretion, close monitoring of etCO\textsubscript{2}, which we found is well correlated to PaCO\textsubscript{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 \(\text{CO}_2\)-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 \(\text{CO}_2\)-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 \(\text{CO}_2\)-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 \(\text{CO}_2\)-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 \(\text{CO}_2\)-PP group (I). \(\text{CO}_2\)-PP did not affect coagulation or fibrinolytic markers (II), however, it was not possible in the present study to clarify if \(\text{CO}_2\)-PP may be followed by a higher rate of thromboembolic complications than gasless or open surgery. During insufflation of \(\text{CO}_2\) a significant increase in \(p\text{aCO}_2\) 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 \(\text{CO}_2\)-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 \(\text{CO}_2\)-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 \(\text{CO}_2\)-PP. Whether it is the distended peritoneum or the acidosis associated with \(\text{CO}_2\)-PP which results in this observed difference has to be further investigated. \(\text{CO}_2\)-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 \(\text{CO}_2\) is responsible for the activation of the systems. \(\text{CO}_2\)-PP increases left ventricular filling immediately after insufflation of \(\text{CO}_2\), however, left ventricular performance of the heart is reduced simultaneously (IV). The simultaneous respiratory acidosis after insufflation of \(\text{CO}_2\) 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\textsubscript{2}-PP did not have any consequences 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\textsubscript{2}-PP.

Table 5 summarizes the overall effects of CO\textsubscript{2}-PP shown in papers I-V:

<table>
<thead>
<tr>
<th>Study</th>
<th>Parameter</th>
<th>Pre-operative</th>
<th>Induction</th>
<th>Operation 5 minutes</th>
<th>Operation 30 minutes</th>
<th>Post.op. 24 h</th>
<th>Convalescence</th>
</tr>
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<td>↑</td>
<td>↑</td>
<td>→</td>
<td>↑</td>
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<tr>
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<td>↑</td>
<td>↑</td>
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<td>↑</td>
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<tr>
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<td>→</td>
<td>↑</td>
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<td>II</td>
<td>F1 + 2</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>→</td>
</tr>
<tr>
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<td>→</td>
<td>→</td>
<td>→</td>
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<td>→</td>
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<tr>
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<tr>
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<td>→</td>
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<td>↑</td>
<td>→</td>
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<td>→</td>
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<td>→</td>
</tr>
</tbody>
</table>

Tabel 5. Overall effects and outcome in patients undergoing CO\textsubscript{2}-PP or gasless LC.

↑: Significantly increased effect of CO\textsubscript{2}-PP compared with that of gasless technique.

→: No difference between CO\textsubscript{2}-PP and gasless technique.

↓: Significantly reduced effect of CO\textsubscript{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 CO₂-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 CO₂-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 CO₂ postoperatively. However, little is known about the clinical, postoperative, pulmonary complications and the CO₂ – homeostasis in patients with obstructive pulmonary disease. Further studies are needed regarding:
  - Per- and postoperative excretion of CO₂ 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 (CO₂-PP) and positional changes of the patients are the general methods of exposing the intraperitoneal organs. Carbonic dioxide (CO₂) 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 CO₂-PP, which may affect the cardiovascular and pulmonary functions. CO₂ 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 CO₂-PP and to evaluate alternative, minimally invasive methods.

Based on a randomized design comparing conventional with gasless laparoscopy the effects of CO₂-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 CO₂-PP compared with gasless technique. However, no difference is registered in postoperative pain or hospital stay
- coagulation and fibrinolysis is not enhanced by CO₂-PP
- endocrine and metabolic response may be activated and the inflammatory response blunted by CO₂-PP
- mean arterial pressure and heart rate is increased during CO₂-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 oploseligt, 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 organssystemer. 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 hjertefunktione
- 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.

31
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 CO₂-pneumoperitoneum blandt patienter med alvorlige hjerte-lunge problemer.
10. Tables

Table 1. Controlled, clinical trials.

<table>
<thead>
<tr>
<th>Operation</th>
<th>author/year References</th>
<th>Intervention</th>
<th>Number</th>
<th>Outcome Perioperative</th>
<th>Outcome Follow-up</th>
<th>Recommendation</th>
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<td>↓ Operative time ↓ Hospital stay → Complications</td>
<td>↓ Readmission → Weight loss</td>
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<td>51</td>
<td>↑ Pain ↓ Hospital stay ↑ Reoperation ↑ Conversion</td>
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<td>↓ Incisional hernia Anastomosis ↑ stricture → Weight loss ↑ Quality of life</td>
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Table 2. Endocrine, metabolic, and inflammatory response.

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: adrenocorticotropic hormone; u: urine

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<td>General anaesthesia vs general + fentanyl</td>
<td>perioperative</td>
<td>↑ cortisol all groups ↑ Cathecholamines group I</td>
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<td>general + epidural</td>
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<td>7 days</td>
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<td>Laparoscopic vs. open</td>
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<td>↑cathecholamines</td>
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<td>Authors &amp; Year</td>
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<td>Time</td>
<td>Changes</td>
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<td>2 days</td>
<td>→ IL-6</td>
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<td>Ninomiya et al 51</td>
<td>Cholecystectomy</td>
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<td>→ IL-6, →CRP, →neutrophil elastase</td>
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<td>?</td>
<td>↓CRP</td>
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<td>Lap. ovarian resection</td>
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Table 3. Haemodynamics, clinical trials.

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11. References for sections 1-4 and 6-10


42. Ido K et al. Femoral vein stasis during laparoscopic cholecystectomy: effects of graded elastic compression leg bandages in preventing thrombus formation. *Gastrointest Endosc* 1995; **42**: 151-5.


12. Appendix