Review Article

Influence of gas type, pressure, and temperature in laparoscopy—a systematic review

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Background: Laparoscopy is the favoured access to a lot of abdominal operations. The first step to laparoscopy is to establish a pneumoperitoneum which elevates the abdominal wall and provides for the surgeon's field of view. Different types of gas, temperatures, and pressures can be applied. This review aims to explain the rationale behind these topics, summarise the current knowledge, and demonstrate open questions.

Methods: For each topic gas type, temperature, and pressure, separate systematic literature research on MEDLINE was performed. Randomized controlled trials (RCT) on adults, published between 2011 and March 2021 were considered. Cochrane Reviews summarizing older data were respected. Data extraction and analysis followed the PICO process.

Results: Gas type—10 RCTs compared nitrous oxide (N_2O, laughing gas), helium (He), or room air to carbon dioxide (CO_2). Helium and N_2O did not exhibit more cardiopulmonary complications than CO_2. N_2O has an anaesthetic effect. CO_2 causes hypercapnia. Temperature—23 RCTs were found. Warm humidified CO_2 was not advantageous over cold dry gas. Pressure—47 RCTs were included. Low intraabdominal pressure reduces postoperative shoulder pain but decreases the surgeon's comfort. Conclusions on the safety of low pressure for cardiopulmonary diseased patients cannot be inferred.

Discussion: CO_2 is the preferred gas to establish a pneumoperitoneum. Alternatives are not sufficiently evaluated. Room air is ubiquitously available and cheap and is therefore of interest to low-income countries. Warm humidified gas is not advantageous over cold dry CO_2 but associated with higher costs. There is no benefit from using low instead of standard pressure. The safety of low-pressure pneumoperitoneum needs to be evaluated for multimorbid patients.

Keywords: Laparoscopy; gas; temperature; pressure

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Introduction

Laparoscopy is the favoured access to a lot of abdominal operations; for many indications, it is associated with less trauma, faster recovery, reduced costs, similar or better safety, and similar radicality and long-term prognosis in the case of oncologic surgery.

The first step to laparoscopy is to establish a pneumoperitoneum which elevates the abdominal wall and provides for the surgeon's field of view. This is so natural, that probably most young surgeons do not give a second thought. However, there are reasons for every step of pneumoperitoneum: Why do we use carbon dioxide (CO_2)? Why do not we use simple air or some other gas?

Will the patient's body cool down by the gas? Where does it go? How much pressure do we need? Why do we need pressure? Does it do any damage?

Although laparoscopy was invented more than a hundred years ago and has been, depending on the operation, a routine procedure since the 1980s and 1990s, these questions are not trivial and not completely answered, yet. Following a systematic approach, most questions can be summarised within three categories: gas type, temperature, and pressure. This article aims to explain the rationale behind these topics, summarise the current knowledge, and demonstrate open questions. We present the following article in accordance with the PRISMA reporting checklist (available at https://ales.amegroups.com/article/view/10.21037/ales-21-24/rc).

Methods

For each topic gas type, temperature, and pressure, we give a rationale, why it is important, and which are the theoretical considerations, we declare the specific search string, summarise the results and discuss them.

Separate systematic literature research on MEDLINE for randomized controlled trials (RCT) was performed for each topic as a double-search by both authors. Trials on adults, published between 2011 and March 2021 were considered. The following data were extracted: author, publishing year, trial registry ID, study type, patients, type of surgery, intervention (gas type, temperature, or pressure), comparator, sample size, primary outcomes, secondary outcomes. If the trial did not declare a primary outcome, all outcomes were considered secondary. For each trial we summarise, which comparator was favoured. Current Cochrane reviews with older data were included in the qualitative analysis.

Gas type

Rationale

The ideal gas for a pneumoperitoneum must be cheap, colourless, incombustible, easily removed from the body, non-toxic, and harmless to the patient and the personnel.

Gases that are or have been used, are CO_2, nitrous oxide (N_2O, laughing gas), air, oxygen, nitrogen (N_2), and the inert gases helium (He) and argon (Ar).

CO_2 is the most common and fulfills most of the aforementioned criteria. It is absorbed by the peritoneum, delivered to the lungs via blood, and exhaled. Being a soluble acid, it causes hypercarbia and acidosis, which must be compensated by the anaesthetist by hyperventilation. Hypercarbia can directly decrease cardiac contractility and sensitize the myocardium to arrhythmogenic effects of catecholamines, and indirectly lead to sympathetic stimulation with tachycardia (1). Peritoneal irritation with postoperative pain is reported.

N_2O is rather inert, cheap, and non-flammable, however, it can support combustion (2). In the early days of colonoscopy, there were explosions when electrocautery was used in an unprepared colon. Later, bowel preparation formulas contained mannitol, a substrate for hydrogen-producing bacteria. The fear of flammable colonic gases (methane and hydrogen) mixing up with N_2O during laparoscopy and two case reports of intraoperative explosions from the 1970s lead to the abandonment of N_2O and the recommendation to use CO_2 (3-8). The assumed hemodynamic advantages of N_2O were not evident in the Cochrane reviews. There was low evidence of lower pain scores compared to CO_2, as nitrous oxide is an anaesthetic agent.

CO_2, and—to a lesser extent—nitrous oxide and helium can increase intracranial pressure (9). There is no information on the other gases.

Helium is the least soluble gas for a pneumoperitoneum, potentially increasing the risk of gas embolism. It requires special insufflators.

Ar is another inert gas, more soluble than N_2 and nearly as soluble as air (2).

The generation of trocar metastasis and the influence of the gas are under discussion. Trocar metastases are reported for CO_2 and air pneumoperitoneum, again there is insufficient information for other gases (10). As tumour manipulation by the surgeon, aggressivity of the tumour, and a gas spray effect by the intraabdominal pressure are supposed reasons, port-site metastasis cannot be attributed to the gas type (2).

Gas embolism can occur due to misplacement of a Verres needle into a vein, but also by direct absorption of the gas. Therefore, gases with high solubility are safer. In this respect, CO_2 is superior to N_2O, and both are more soluble than air, oxygen, N_2, and the inert gases He and Ar (1).

All gases can affect the cardiocirculatory, respiratory, and neurohumoral systems by their intraabdominal pressure. These effects are less gas-specific and are discussed in the pressure section.

Methods

MEDLINE was searched through pubmed.gov with the search string: "((((((((((((((((((laparoscop*) OR (video-assisted

surgery)) OR (minimally invasive)) OR (coelioscop*)) OR (celioscop*)) OR (peritoneoscop*)) AND (gas type)) OR (carbon dioxide)) OR (CO_2)) OR (nitrous oxide)) OR (laughing gas)) OR (N_2O)) OR (nitrogen)) OR (N_2)) OR (helium)) OR (argon)) AND (pneumoperitoneum)) OR (peritoneum)". RCTs on adults, published between 2011 and March 2021 were eligible.

Results

We found nine RCTs, of which six had to be excluded because they did not compare CO_2 with another gas, and two because they studied animals or cadavers (*Table 1*).

The only remaining trial compared CO_2 laparoscopy in general anaesthesia (GC group) with gasless laparoscopy in general anaesthesia (GG group) and gasless laparoscopy in epidural anaesthesia (GE group) (11). The gasless laparoscopy was established with an abdominal lift apparatus. The authors focussed on the stress response, measuring plasma levels of cortisol, TNF-α, IL-6, IL-10, and Hsp70 before, during, and after the operation. Starting with similar baseline levels in all three groups, the cytokine levels increased most in the GC group, followed by the GG and GE groups. The authors assume that CO_2-laparoscopy induces a larger stress response than gasless techniques, and that general anaesthesia contributes more to stress response than epidural anaesthesia.

The current Cochrane review identified nine RCTs comparing nitrous oxide, helium, and room air to CO_2 with regards to cardiopulmonary complications, surgical morbidity, pneumoperitoneum related serious adverse events (primary endpoints), mortality, quality of life, pain scores, analgesic requirements, costs, and cardiopulmonary changes (secondary outcomes) (12). One trial overlapped with our research. Nitrous oxide was analysed by three trials and exhibited more cardiopulmonary complications (5.7% *vs.* 2.9%, relative risk ratio 2.0), but the difference was not significant, the trials were heterogeneous and the level of evidence was very low. There were no differences in the other outcomes, either, except for pain levels and analgesia requirements, which were lower with nitrous oxide.

Helium was examined in three trials and exhibited non-significant higher rates of cardiopulmonary complications (4.4% *vs.* 3.0%) and subcutaneous emphysema (4.9% *vs.* 0%), and more morphine requirements, but not higher pain scores. The partial blood pressure of CO_2 was lower with helium (–13 mmHg). For room air, only one RCT was found, which did not reveal differences regarding complications and mortality. Costs and pain scores were lower with room air. However, the study quality and consequently the level of evidence were very low.

Discussion

There are many requirements for the ideal gas for a pneumoperitoneum, and none of the gases used are perfect in every aspect. CO_2 has become the standard because it is safe, non-combustible, non-explosive, and cheap. It has some effects on hypercapnia, which is not relevant in cardiopulmonary healthy people, and which the anaesthesiologists have broad experience with and know how to treat.

As the first and only reason to take gas is to improve the surgeon's field of view, one approach is to completely abandon gas and use mechanical abdominal wall lifting techniques. It is unclear, whether the "no-gas"-study of Han *et al.* should be attributed to the use of air instead of CO_2 or to the lower intraabdominal pressure by an abdominal wall lifting technique. The influence of pressure is discussed in the next section. Furthermore, abdominal wall lifting is a quite invasive tool to be combined with minimally invasive surgery.

No recent data is expanding the results of the Cochrane reviews of 2013 and 2017 (12,13). There is a lack of effort in testing inert gases like He or Ar against the standard, especially with regards to safety. One risk is gas embolism. CO_2 is safer than oxygen, nitrous oxide, and room air in animal studies, because of its solubility. However, as venous gas embolism is rare, larger scaled meta-analyses will be necessary to provide better safety evidence. Cardiopulmonary changes due to CO_2 that we discussed in the rationale are only relevant in patients with pre-existing diseases. As there is broad experience with the properties of CO_2 and the handling of its disadvantages, it seems, at first sight, that there is no need for alternatives to CO_2. To establish another gas, more high-quality RCTs and meta-analyses are necessary. For which gas should we take these efforts?

For low-income countries, the use of filtered room air promises lower costs. The higher cost-effectiveness of air has been shown (14). However, room air has the narrowest data basis of all gases. From the author's point of view, perhaps more academic efforts should be directed towards room air.

Temperature

Rationale

CO_2 is stored in a compressed and liquid state at about

Table 1 Current randomized trials testing different gas types

Author	Year	Trial registry	Study type	P	I	C	n	Primary outcome	Secondary outcomes	Favours
Han (11)	2012	–	RCT	Women	Gynecologic	CO_2/general anaesthesia *vs.* gasless/ general anaesthesia *vs.* gasless/ epidural	75	n.a.	Stress response: serum cortisol, tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-6, IL-10, and Hsp70 levels at four time points: Before anesthesia (T1), at 30 minutes after the beginning of the operation (T2), at 10 minutes after the end of surgery (T3), and at 8:00 a.m. on the following day (T4)	Gasless/ epidural anaesthesia over gasless/ general anaesthesia over CO_2/ general anaesthesia

–90 ℃. When released, it expands rapidly and enters the patient's body at room temperature with no humidity. Cold CO_2 is therefore supposed to cool the body and expose the patient to hypothermia which can cause coagulopathies and alter drug metabolism. However, calorimetric calculations have demonstrated that hundreds of litres of cold dry CO_2 will have hardly any impact on the patient's core temperature (far below 0.5 ℃) (15).

Dry CO_2 is discussed to damage mesothelial cells (16), leading to peritoneal inflammation, which is assumed to contribute to postoperative pain and the long-time forming of peritoneal adhesions. More adhesions were found in animal models (17).

Methods

MEDLINE was searched via pubmed.gov with the search string: "(((((((laparoscop*) OR (coelioscop*)) OR (celioscop*)) OR (peritoneoscop*)) OR (minimally invasive)) OR (video assisted surgery)) AND (temperature OR therm*)) AND (pneumoperitoneum)". RCTs on adults, published from 2011 to March 2021 were eligible.

Results

We identified only four RCTs, one of which with only the abstract, as the full text was in the Russian language (*Table 2*). We, therefore, decided to include one RCT on children (age 8–14 years) with appendectomies. All studies compared warm humidified (WH; 37 ℃ and 95–98% humidity) with cool dry (CD; 20 ℃, 0%) CO_2.

Agaev *et al.* found fewer pain scores and the need for analgesics in the WH in 150 laparoscopic operations (cholecystectomies and fundoplications); however, we could not access the full text since it was published in the Russian language (18).

Jiang *et al.* compared WH with two CD-groups; one had external warming with electric (CE) and one with forced heated air blankets (CF). They included only elderly patients with colorectal surgery. Pain scores were similar in WH and CE, but higher in CF. The same constellation was found for intraoperative hypothermia, coagulation dysfunction, early postoperative cough pain, sufentanil consumption, days to first flatus and solid food intake, and length of hospital stay. The authors attribute the differences to insufficient maintenance of normothermia in the group with electric blankets and emphasize the necessity of normothermia. WH and CD with forced heated air blankets were equivalent in this trial (19).

Sammour *et al.* published a five-year follow-up of a randomized trial of 2010 (23), focussing on the long-term effects of small bowel obstruction as representative of adhesions, local tumour recurrence, overall and cancer-specific survival (20). There were no differences between WH and CD. Small bowel obstruction occurred in 5.6% of WH and 0% of CD patients (P=0.2). One should consider that on one hand, small bowel obstruction is not the only surrogate of adhesions, on the other hand, it can have other reasons than adhesions, for example, anastomotic stenosis.

Sutton *et al.* combined clinical and experimental outcomes (21). In a subgroup of 42 of 101 patients, they took peritoneal samples at the start and at the end of the operation, which were compared histologically. They found fewer histologic alterations in the end-of-operation specimens in the WH group compared to the CD group, but the difference was not statistically significant. Postoperative plasma levels of cytokines did not differ between WH and CD, either. The WH group needed fewer narcotics and early

Table 2 Current randomized trials testing different temperatures

Author	Year	Trial registry	Study type	P	I	C	n	Primary outcome	Secondary outcomes	Favours
Agaev* (18)	2013	–	RCT (blinding unclear)	n.a.	Cholecystectomy and fundoplication	WH *vs.* Standard	150	–	WH: less pain scores, less need for analgesics	WH
Jiang (19)	2019	ChiCTR-IOR-17010915	RCT (blinding unclear)	Adults 65–75 years	Colorectal	37 ℃/98% *vs.* 20 ℃ /0%/ electric blankets *vs.* 20 ℃ /0%/bear hugger	150	Pain: reduced in WH and CB compared to CE	WH and CB are better concerning intraoperative hypothermia, dysfunction of coagulation, early postoperative cough pain, sufentanil consumption, days to first flatus, solid food intake, length of hospital stay, patients' satisfaction, surgeons' satisfaction	WH and CB
Sammour (20)	2015	NCT00642005	Double-blind RCT	Adults	Colorectal	37 ℃/98% *vs.* 19 ℃/0%	82	–	No difference in small bowel obstruction, local recurrence, overall survival, cancer specific survival	–
Sutton (21)	2017	–	Single-blind RCT	Adults	Colorectal	36.7 ℃ /95% *vs.* room temp./0 ℃	101	Cytokines (IL-6, TIMP-1, sVEGF-R1, and HSP-70), no difference	WH needed less narcotics and pain medication, pain scores were similar. No differences in length of stay, complication rates, time of flatus, time of diet. WH had less histological changes in peritoneal biopsies at the start and at the end of operation (n=42, not significant)	WH
Yu (22)	2013	NCT01027455	Double-blind RCT	Children 8–14 years	Appendectomy	37 ℃/98% *vs.* 20 ℃/0%	190	Opioid consumption: no difference	Pain scores, intraoperative core body temp., postop. recovery and return to normal activities: no difference	–

*, only abstract available, full text in Russian language. CD, cold dry gas; CE, cold dry gas and electric blankets; CF, cold dry gas and bear hugger; WH, warm humidified gas.

postoperative analgetic medication, although the pain scores were similar. The authors state not to draw "firm conclusions … regarding the use of pain medications". There were no differences in clinical outcome parameters length of stay, complication rates, time of flatus, and time of diet.

Yu *et al.* performed a large-scaled RCT on appendectomies in children, revealing no differences in postoperative opioid consumption, pain scores, intraoperative core body temperature, postoperative recovery, and return to normal activities (22).

A current Cochrane analysis summarises the current knowledge up to 2016 (24): the authors found 22 randomized trials, four of which overlapped with our search. The intraoperative body core temperature was 0.31 ℃ higher in the warm, humidified CO_2 group; however, when studies with a moderate or high risk of bias were excluded, this difference was not statistically significant. Postoperative pain scores did not differ between the warm and cold groups. Morphine use at the first and second postoperative days was similar in the cold and warm, humidified groups, but higher in the warm, not humidified CO_2 group. The postoperative recovery time did not differ when the only high risk of bias study was excluded from the analysis. Length of hospital stay and recovery time were similar in all groups.

Discussion

Since up to several hundred litres of gas flow through the abdomen during the operation, it is reasonable to assume that the gas should have a relevant influence on core body temperature and the body's moisture homeostasis. However, the clinical studies demonstrate that the body temperature is not impaired by CD in a clinically relevant manner. The

clinical trials recording the core temperature found only minimal changes which fit very well to the theoretical calorimetric calculations of Roth *et al.* (15). The Cochrane analysis did not find significant differences in postoperative pain scores and the need for analgesic medication, and the few recent trials published after the Cochrane review are heterogeneous, not favouring WH gas. Short-time clinical outcomes are not influenced by WH or CD, either.

There is hardly any evidence of the formation of adhesions due to the use of WH or CD gas. It is always difficult to measure the effectiveness of an intervention on the forming of adhesions within a human clinical trial, as the generation of adhesions is multifactorial and difficult to quantify. Even animal autopsy trials do not allow to conclude from the morphologic evidence of adhesions on their clinical relevance. Thus, although there is a clinical long-term follow-up RCT, the data are insufficient to judge the impact of WH and CD on adhesions.

In conclusion, there is no evidence for the use of WH gas. The decision to use WH should be drawn based on the local availability, since warming and humidifying CO_2 is related to additional costs.

Pressure

Rationale

A pneumoperitoneum, and therefore pressure, is necessary to elevate the abdominal wall from the organs to provide for the surgeon's field of view. Even abdominal wall lifting techniques which avoid a classic pneumoperitoneum, aim to establish the field of view.

The pressure on the peritoneum, however, reduces the blood flow in the low-pressure vessels, capillaries, and veins, which could contribute to inflammatory or stress response. It also affects the vasopressin and renin-angiotensin-aldosterone-system (25). The pressure on the liver (veins), diaphragm, and lung can reduce the cardiac preload, the lung volume by about one-third, provoke atelectasis, shunt, and ventilation-perfusion-mismatch.

Thus, it seems desirable to reduce the pressure to minimize cardiopulmonary complications, and simultaneously find the balance to still provide a good field of view.

Methods

MEDLINE was searched through pubmed.gov with the string: "(((((((laparoscop*) OR (coelioscop*)) OR (celioscop*)) OR (peritoneoscop*)) OR (minimally invasive)) OR (video assisted surgery)) AND (pressure)) AND (pneumoperitoneum)". The search was limited to randomised clinical trials from 2010 to March 2021. Trials on children, animals, or cadavers were excluded. In contrast to the Cochrane review, all kinds of laparoscopic operations were considered.

Results

Thirty-eight RCTs were identified (*Table 3*). Nine trials were excluded: three were study protocols, three were not randomised trials, three were trials on children. Most RCTs compared low pressure (LP, about 8 mmHg) with standard (SP, about 12 mmHg) or high pressure (HP, >15 mmHg); these categories were quite homogenous.

Six trials focussed on the effect of deep compared to standard neuromuscular blockade (NMB) to facilitate a lower intraabdominal pressure (37,38,41,47,53,54). The outcomes of these NMB-studies focussed on the surgeon's conditions (space, field of view, surgeon's satisfaction) in four trials, all favouring deep NMB (41,47,53,54), intraocular pressure, and intraabdominal contractions (38,53), both favouring deep NMB. General and patient-related outcomes (pain, emesis, opioid consumption, length of stay, etc.) did not differ between deep and normal NMB combined with low-pressure peritoneum.

All eight trials focussing on postoperative pain or analgesic consumption favoured LP (28,34,37,46,49-52). Experimental or biochemical studies revealed an improved peritoneal perfusion in the LP group (27,32), less histological damage in renal tubules (26), partially less elevation of liver enzymes (30,33,40), less inflammatory blood markers (26,31,39). The impact on coagulation was heterogeneous in two studies [(44), no difference; (48), impaired thrombelastography in HP; (49), more haemorrhage in HP]. The femoral vein diameter and blood flow were better in LP group (44).

Only two trials measured respiratory parameters: maximal values of peak airway pressure, end-tidal CO_2, and systolic blood pressure were lower in the LP group at Sroussi *et al.* (46), base excess and bicarbonate were higher with HP, but within normal limits at Hypolito *et al.* (35). The LP group had higher urine output, but no difference in creatinine serum levels (52).

Quality of recovery as a patient-related outcome was assessed by two RCTs with no landmark results (XX).

The Cochrane review of 2014 identified 21 RCTs comparing low with standard pressure in patients with

Table 3 Current randomized trials testing different intraabdominal pressures

First author	Year	Trial registry	Study type	P	I	C	n	Primary outcome	Secondary outcomes	Favours
Aditianingsih (26)	2020	NCT03219398	RCT	Adults 18–65	Living donor nephrectomy	8 *vs.* 12 mmHg	44	n.a.	LP: lower intra- and postop. HR, intraop. blood levels of IL-6, sVEGFR-2, syndecan-1; higher proximal tubule syndecan-1 expression; intact EM renal tubule and peritubular histology compared to cell damage in SP group	LP
Albers (27)	2020	NCT03928171	Observer blinded RCT	Adults	Robot colorectal surgery	8 *vs.* 12 *vs.* 16 mmHg	30	Peritoneal perfusion: improved in LP group		LP
Ali (28)	2016	–	RCT	Adults	ChE	10 *vs.* >10 mmHg	160	Shoulder pain: LP with less pain and less administration of analgesics		LP
Barrio (29)	2017	–	Blinded RCT	Adults	ChE	8 mmHg/ moderate NMB *vs.* 8 mmHg/ deep NMB *vs.* 12 mmHg	90	n.a.	Surgeon's reported satisfaction with (I) surgical field exposure, (II) dissection of the gallbladder, (III) extraction/closure: SP was superior to both LP groups.	SP
Chang-Sheng (30)	2012	–	RCT	Adults	ChE	9 *vs.* 12 *vs.* 15 mmHg	90	Liver enzymes preoperative *vs.* day 1, 3, and 7 postoperative: significant changes of serum ALT, AST, TBIL and DBIL in SP and HP groups.		LP
Díaz-Cambronero (31)	2020	NCT02773173	RCT	Adults	colorectal surgery	Lowest acceptable pressure *vs.* 12 mmHg	166	Postoperative Quality of Recovery Scale: higher in LP	Emotional and overall recovery, intraoperative complications and lymphocyte-neutrophil ratio on postoperative day 3 lower in LP group; no influence on postoperative complications, duration of hospital stay.	LP
Eryılmaz (32)	2012	–	RCT	Adults	ChE	10 *vs.* 14 mmHg	43	Plasma disappearance rate of indocyanine green intraoperatively: decreased in SP	Blood levels of AST, ALAT and bilirubin 1 and 24 hours after surgery: no differences between LP and SP	LP

Table 3 (*continued*)

Table 3 (*continued*)

First author	Year	Trial registry	Study type	P	I	C	n	Primary outcome	Secondary outcomes	Favours
Gupta (33)	2013	–	RCT	Adults	ChE	8 *vs.* 14 mmHg	101	n.a.	Total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase on day 1 and 7 postoperatively: Bilirubin, AST and ALAT were higher in SP on day 1, no differences on day 7.	LP
Hsu (34)	2019	–	RCT	Adults	ChE	12 mmHg, low flow rate induction (1 L/min) *vs.* continuous high flow rate (10L/min)	140	Shoulder pain: less pain in low flow rate group, same incidence in both groups	Length of hospital stay, bradycardia, operative time: no differences	Low flow rate insufflation
Hypolito (35)	2014	–	RCT	Adults		12 *vs.* 20 mmHg	67	n.a.	Mean arterial pressure, pH, HCO3 and base excess differed significantly in HP, but within normal limits	-
Ko-Iam (36)	2016	TCTR20140213001	RCT	Adults 18-75	ChE	etoricoxib/ 7 mmHg *vs.* placebo/ 14 mmHg	120	n.a.	Pain and length of hospital stay: less in the treatment group	n.a. (effects may rise from medication)
Madsen (37)	2016	–	Double-blind RCT	Adults	ChE	8 mmHg/ deep NMB *vs.* 12 mmHg/ moderate NMB	99	Incidence of shoulder pain: less in LP/deep NMB group	No differences in: area under curve VAS scores for shoulder, abdominal, incisional and overall pain during 4 and 14 postoperative days; opioid consumption; incidence of nausea and vomiting; antiemetic consumption; time to recovery of activities of daily living; length of hospital stay; and duration of surgery	LP with deep NMB
Madsen (38)	2017	–	RCT	Adults	Hysterectomy	8 mmHg/ deep NMB *vs.* 12 mmHg/ moderate NMB	110	n.a.	LP/deep NMB: less sudden abdominal contractions	LP with deep NMB

Table 3 (*continued*)

Table 3 (*continued*)

First author	Year	Trial registry	Study type	P	I	C	n	Primary outcome	Secondary outcomes	Favours
Matsuzaki (39)	2017	NCT01887028	Single-blind RCT	Adults	Hysterectomy	8 mmHg/ humidified warm CO_2 *vs.* 8 mmHg/ standard CO_2 *vs.* 12 mmHg/ humidified warm CO_2 *vs.* 12 mmHg/ standard CO_2	82	n.a.	LP and/or warm humidified gas significantly lowered expression of inflammation-related genes in peritoneal tissues and postoperative pain scales	LP +/– warm humidified carbon dioxide
Neogi (40)	2020	–	Double-blind RCT	Adults		7 *vs.* 14 mmHg	82		Surgeon comfort: better in SP; GGT, GPT, GOT and LDH lower in LP	Liver function: LP; surgeon's comfort: SP
Özdemir-van Brunschot (41)	2018	NCT02602964	RCT	Adults	Living donor nephrectomy	Moderate *vs.* deep NMB with 6 mmHg; surgeon was allowed to increase pressure	34	Surgical conditions (Leiden Surgical Rating Scale): better in deep NMB group	Pain scales: not different; postoperative opiate consumption: less in deep NMB group	Deep NMB
Özdemir-van Brunschot (42)	2017	NCT02146417			Living donor nephrectomy	6 mmHg/ deep NMB *vs.* 12 mmHg/deep NMB	64	Quality of Recovery-40-questionnaire on the first postoperative day: no significant difference	Surgical conditions (Leiden Surgical Rating Scale): no differences	–
Schietroma (43)	2013	–	RCT	Adults	Nissen fundoplication	≤8 *vs.* ≥12 mmHg	68		White blood cells, peripheral lymphocytes subpopulation, human leukocyte antigen-DR, neutrophil elastase, interleukin (IL)-6 and IL-1, and C-reactive protein: reduced postoperative inflammatory response and immunosuppression in the LP group; hospitalization, time of anesthesia, and operation: similar	–
Sharma (44)	2016	–	RCT	Adults	ChE	8 *vs.* 14 mmHg	50	Femoral vein diameter and blood flow: better in LP group	Coagulation profile (prothrombin time, prothrombin index, activated plasma thromboplastin time and international normalized ratio): no significant differences	LP

Table 3 (*continued*)

Table 3 (*continued*)

First author	Year	Trial registry	Study type	P	I	C	n	Primary outcome	Secondary outcomes	Favours
Shoar (45)	2016	IRCT201110072982N5	Double-blind RCT	Adults	ChE	8 *vs.* 12 mmHg	50	n.a.	Stress response: mean HR, mean arterial pressure, serum levels of cortisol, glucose, adrenaline, C-reactive protein: no significant differences	–
Sroussi (46)	2017	–	Single-blind RCT	Adults	Gynecologic laparoscopy for benign disorders	7 *vs.* 15 mmHg	60	Incidence of shoulder pain: less in LP	Maximal values of peak airway pressure, end tidal CO_2 and systolic blood pressure: lower in LP group; length of hospital stay: shorter in LP.	LP
Staehr-Rye (47)	2014	NCT01523886	Double-blind RCT	Adults	ChE	8 mmHg/ deep NMB *vs.* 8 mmHg/ moderate NMB	48	Surgical space conditions: "marginally better" in deep NMB group		Deep NMB
Topal (48)	2011	–				10 *vs.* 13 *vs.* 16 mmHg	60	Thrombelastography: impaired in HP group		
Topçu (49)	2014	–	RCT	Adults	gynecologic laparoscopy	8 *vs.* 12 *vs.* 15 mmHg	150	Pain: less in LP	Operation time, hemorrhage: higher in LP	
Vijayaraghavan (50)	2014	–	RCT	Adults	ChE	8 *vs.* 12 mmHg	43	n.a.	Postoperative pain and analgetic medication: less in LP; liver function, peak expiration flow rate: no differences; intraoperative surgeon comfort better in LP.	LP
Warlé (51)	2013	–	RCT	Adults	Living donor nephrectomy	7 *vs.* 14 mmHg	20		LP: longer operation time, higher urine output during pneumoperitoneum, lower pain scores; no differences in creatinine levels, complications, SF-36 quality of life domains	LP
Yasir (52)	2012	–	RCT	Adults	ChE	8 *vs.* 14 mmHg	50	Shoulder pain: less in LP	Analgetic medication, length of hospital stay: less in LP	LP
Yoo (53)	2015	NCT02109133	RCT	Adults	Robotic radical prostatectomy	Deep *vs.* moderate NMB, 8 mmHg, surgeon was allowed to increase up to 20 mmHg	67	Intraocular pressure: lower in deep NMB	Surgeon's comfort: better with deep NMB; lower intraabdominal pressures needed with deep NMB	Deep NMB

ChE, cholecystectomy; NMB, neuromuscular blockade; RCT, randomized controlled trial; HP, high pressure; LP, low pressure; SP, standard pressure.

laparoscopic cholecystectomy. Nineteen of these trials were older than 2011 and did not overlap with our search. Primary outcomes were mortality, serious adverse events, and quality of life, secondary outcomes were conversion to open cholecystectomy, hospital stay, return to normal activity, return to work, operating time. There was no mortality, no differences in serious adverse events. Quality of life and return to work or normal activities were not reported in any of the trials. Length of stay was not significantly different, operating time was 2 minutes longer in the LP group.

Discussion

The reason to use gas is to form a space between abdominal wall and organs to provide for the surgeon's field of view and action. This space enables the operation and also ensures the safety of the patient. However, pressure on the organs is inevitable. The potential effects of pressure are numerous: Capillary and venous blood flow, gut motility, autonomous nerve system, etc.

While the Cochrane review focussed on clinical outcomes of one specific, ubiquitous surgical procedure, i.e., cholecystectomy, our search involved all laparoscopic operations and non-clinical outcomes, too. These trials confirmed differences, which have been deducted from the theoretical considerations: peritoneal perfusion and inflammatory responses are better in the LP group because the low pressure impairs the capillary and venous blood flow less. Following the same logic, urine output and liver enzymes are impaired by higher intraabdominal pressure. Unfortunately, the impact on the organs "beyond the diaphragm", circulation and respiration, is hardly reflected by most of the trials.

However, these statistically significant differences do not translate into clinical relevance, as shown by the Cochrane review. The only clinical difference which has been confirmed is reduced shoulder pain after cholecystectomy. In contrast to this advantage for the patient, there is the surgeon's discomfort with LP. Although this discomfort did not translate into an increased rate of morbidity for the patient, the surgical field of view should not only be considered as the surgeon's comfort but also as a relevant factor for the patient's safety. Furthermore, the low morbidity reported by the Cochrane review corresponds with a rather healthy patient population. Consequently, the authors state that the data do not allow inferences on the impact of LP on a patient with cardiopulmonary comorbidities and that information on the safety of LP is lacking. Recent trials demonstrated that a deeper neuromuscular blockade can facilitate laparoscopy with low pressure. Future trials should focus on patients with comorbidities and high anaesthetical risk and specifically analyse the clinical impact on circulation and respiration.

Summary

CO_2 is the preferred gas to establish a pneumoperitoneum. Although it has some drawbacks like hypercapnia and acidosis especially in cardiorespiratory diseased patients, there is a broad experience in anaesthesiologic techniques which compensate for its disadvantages. Nitrous oxide has a desirable anaesthetic effect, is also cheap and available, but it does not suffocate combustion. The necessity of this suffocating effect is under discussion. Other gases like He, Ar, N_2, and room air are not sufficiently tested for their safety. Room air could be desirable for low-income countries as it is the most cost-effective gas, so more efforts to investigate air for pneumoperitoneum are needed.

The use of warm humidified instead of cold dry CO_2 has no benefit but is associated with higher costs.

The potential benefit of low-pressure peritoneum on possible cardiovascular and respiratory complications could not be demonstrated as most trials focus on low-risk patients. It decreases shoulder pain after cholecystectomy. However, low-pressure peritoneum impairs the surgical field of view. At the moment, there is no benefit from using low instead of standard pressure.

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Footnote

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