

Systematic review of oxidative stress associated with pneumoperitoneum

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Background: There have been several reports of ischaemic complications after routine laparoscopy. The aim of this review was to investigate the relationship between this oxidative stress and pneumoperitoneum.

Methods: Medline, Medline in-process, The Cochrane Library, PubMed and EMBASE were searched for papers on oxidative stress and pneumoperitoneum, from 1947 to March 2008 with no language restriction or restriction on trial design. Papers that did not investigate pneumoperitoneum as a causative factor, or did not report outcome measures related to oxidative stress, were excluded.

Results: A total of 73 relevant papers were identified: 36 animal studies, 21 human clinical trials, nine case reports, five review articles and two comments. Pneumoperitoneum causes a reduction in splanchnic blood flow, resulting in biochemical evidence of oxidative stress in a pressure- and time-dependent manner. There is evidence that the use of carbon dioxide for insufflation is contributory. Several measures proposed to minimize the oxidative stress have shown promise in animal studies, but few have been evaluated in the clinical setting.

Conclusion: There is an increasing body of evidence, mainly from animal studies, that pneumoperitoneum decreases splanchnic perfusion with resulting oxidative stress. It is now appropriate to investigate the clinical significance of pneumoperitoneum-associated oxidative stress.

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Introduction

Laparoscopy was first described in 1901 by Kelling¹. In 1960 Kurt Semm, a German gynaecologist, developed an automatic insufflator to establish pneumoperitoneum, and in 1985 Erich Muhe reported the first successful laparoscopic cholecystectomy². Although laparoscopic surgery is now commonplace³ and generally considered safe, there have been several reports of mesenteric ischaemia and bowel infarction after routine laparoscopic procedures^{4–12}. Most have occurred in patients with evidence of preoperative cardiovascular, hepatic or renal compromise^{6,9,10}; however, there have also been rare reports of complications in healthy young patients^{7,8,11,12}.

These findings have led to the hypothesis that abdominal insufflation and the consequently raised intra-abdominal pressure may produce significant organ ischaemia, followed by reperfusion injury upon deflation of the abdomen¹³. One of the main consequences of this ischaemia–reperfusion is an imbalance between oxidants, such as reactive oxygen species (ROS), and antioxidants¹⁴. This imbalance is defined as oxidative stress, and may result from enhanced ROS formation, or from the malfunction of the scavenging systems. Several enzymatic antioxidant defence systems have been described and characterized, including the superoxide dismutases, catalases and a number of glutathione peroxidases¹⁵. There are also endogenous and exogenous compounds that act as antioxidants¹⁵. The surplus ROS that result in oxidative stress can oxidize macromolecular constituents of cells, such as membrane phospholipids, proteins and DNA, causing cellular injury and organ dysfunction¹⁶.

The Editors are satisfied that all authors have contributed significantly to this publication

Given the increasing complexity and length of laparoscopic procedures, organ ischaemia–reperfusion injury and oxidative stress associated with pneumoperitoneum may become a more significant problem. The aim of this review was to answer four questions. What is the evidence for a reduction in splanchnic blood flow during pneumoperitoneum? What is the nature of the oxidative stress that ensues? What is the relationship between this oxidative stress and insufflation pressure and nature of the gas used? What measures have been shown to reduce the oxidative stress associated with pneumoperitoneum?

Methods

Search

Medline, Medline in-process and other non-indexed citations, The Cochrane Library, PubMed and EMBASE 1947+ were searched independently by two of the authors (T.S., A.M.) for papers on oxidative stress and pneumoperitoneum, using the search terms outlined in *Table 1*. Papers spanning the years from 1947 (earliest EMBASE records) to March 2008 were searched, with no language restriction. Reference lists were then reviewed and an online search of scientific meeting abstracts was performed by a third author (A.K.) to identify further papers. The results were pooled into a single database, and duplicate entries removed.

Inclusion and exclusion criteria

All laboratory studies, clinical trials, reviews and comments were identified. There was no restriction on study design, with randomized controlled trials (RCTs), non-RCTs, case–control studies, case series and case reports all included. Exclusion criteria were any papers that did not investigate pneumoperitoneum as a causative factor, or did not report outcome measures related to oxidative stress, specifically splanchnic blood flow, oxidant/antioxidant marker levels, gastric/intestinal pH or histology scores.

These criteria were applied by two authors (T.S., A.M.) and any disagreement was resolved by consultation with the senior authors (A.R.J.P., J.A.W., A.G.H.).

Data analysis

All results were reviewed by one of the authors (T.S.), and entered into data tables designed before data abstraction. Data were reported only if stated in the text, tables, graphs or figures of the articles, although a critical review of the results is also presented. The data were grouped into animal and human studies, and further categorized by outcome measure. No meta-analyses were possible, and study quality was not assessed owing to the heterogeneity of study design and outcome measures.

Results

Five hundred and sixty-one papers were identified in the initial database search (*Fig. 1*). Fifty-seven of these met the search criteria, and a review of their reference lists and meeting abstracts led to the identification of a further 16 papers. Thus, a total of 73 publications were retrieved for review. Thirty-six of these were animal studies, 21 human clinical trials, nine case reports, five review articles and two comments.

Reduction in splanchnic venous and arterial blood flow

Animal studies

Increased intra-abdominal pressure, from any cause, leads to increased systemic vascular resistance and afterload, and a decrease in cardiac output¹⁷. Early canine studies with high insufflation pressures (20–40 mmHg) demonstrated this, with an associated marked blood flow reduction in all viscera, with the exception of the adrenal gland^{17,18}. In another canine model, within 30 min of establishing pneumoperitoneum at a pressure of 16 mmHg a reduction

Table 1 Search terms used in different databases

Database	Search terms
Medline® and Medline in-process, and other non-indexed citations The Cochrane Library	(Laparoscop\$ OR Endoscop\$ OR Coelioscop\$ OR Celioscop\$ OR Pneumoperitoneum) AND (ischaemi\$ OR ischemi\$ OR precondition\$ OR sequential OR oxida\$).m_titl.
PubMed	(Laparoscop* OR Endoscop* OR Coelioscop* OR Celioscop* OR Pneumoperitoneum [Title]) AND (ischaemi* [Title] OR ischemi* [Title] OR precondition* [Title] OR sequen* [Title] OR oxida* [Title])
EMBASE 1947+	(Laparoscop\$ OR Endoscop\$ OR Coelioscop\$ OR Celioscop\$ OR Pneumoperitoneum) AND (ischaemi\$ OR ischemi\$ OR precondition\$ OR sequential OR oxida\$).m_titl.

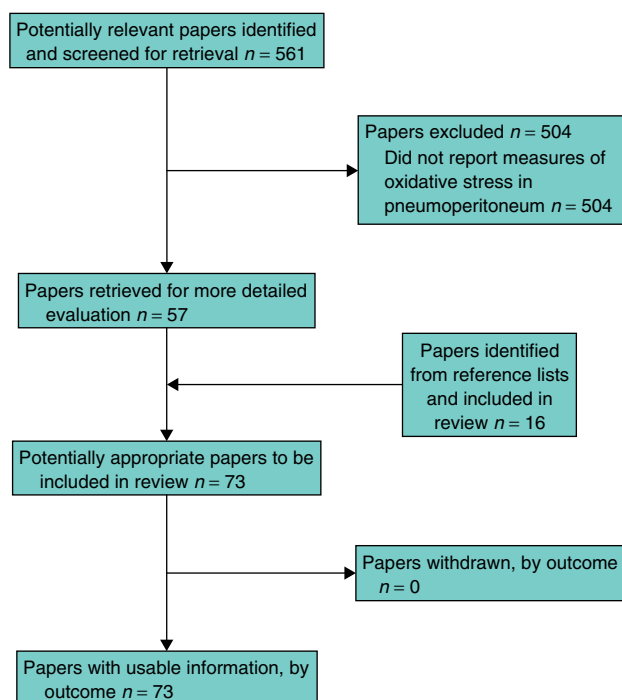


Fig. 1 QUOROM diagram

in blood flow of up to 30 per cent was seen in the superior mesenteric artery and portal vein^{18,19}. This effect can be partially explained by the intra-abdominal pressure exceeding the usual portal venous pressure of 7–10 mmHg¹⁴, but the reduction was also noted to be gradual, progressive with time, and beyond that attributable to the decrease in cardiac output alone²⁰, suggesting that autoregulatory vasoconstriction makes a significant contribution²¹.

Splanchnic vasoconstriction (predominantly at the arteriolar level) is due to several different mechanisms. Vaso-pressin, produced by a central nervous system pathway in response to increased intra-abdominal pressure, constricts renal, superior mesenteric and coeliac vasculature^{17,19,22,23}. Levels of renin and angiotensin (both potent vasoconstrictors) are increased in the renal vein after laparoscopy in a rabbit model²⁴. Furthermore, splanchnic vessels possess a well developed intrinsic myogenic mechanism for local control of vascular tone, and compression of the venous outflow triggers this, causing vasoconstriction¹⁹.

The type of gas used can also influence the mesenteric vascular response. Blobner and colleagues²⁵ compared abdominal insufflation in pigs with air and carbon dioxide at sequentially increasing pressures using direct arterial and venous measurements, and demonstrated a relative mesenteric hyperperfusion in the carbon dioxide group at

lower insufflation pressures. The increase in mesenteric artery and portal venous blood flow was, however, reversed between 8 and 12 mmHg, corresponding to an increase in mesenteric artery resistance and a reduction in cardiac output and inferior vena cava flow. This suggests that hyperaemic effects of carbon dioxide at lower pressures are more than counteracted by the vascular compression effects at 12 mmHg and above.

Human studies

Similar haemodynamic changes have been demonstrated in human laparoscopy studies^{17,26–28}. Insufflation pressure is generally set at 12–15 mmHg, which raises the intra-abdominal pressure above that of the normal portal circulation pressure³. The reduction in cardiac output and accompanying mesenteric vasoconstriction has been reported to cause a significant reduction in organ perfusion and reduced portal venous flow during routine laparoscopic procedures such as cholecystectomy^{26–28}. Although the raised intra-abdominal pressure is contributory, it should be noted that, in the clinical setting, cardiac output and splanchnic perfusion changes are the result of a complex interaction between anaesthesia, the surgical insult, patient position and the nature of the gas used (see below)^{3,29}. A detailed description of the physiology of the laparoscopic procedure is, however, beyond the scope of this article.

Oxidative stress associated with pneumoperitoneum

Various animal^{13,30–37} and human^{38–48} studies have investigated the ischaemia–reperfusion injury that occurs as a result of pneumoperitoneum. These studies used a wide range of outcome measures of oxidative stress, including endogenous antioxidant levels, peroxidation markers, derived gastric intramucosal pH, cytokine levels and histological findings. A simplified schematic representation of the rationale behind these measurements is presented in Fig. 2. It should be noted at this point that the large variation in oxidative stress measures weakens interstudy comparisons. Furthermore, there is no consensus on which peroxidation markers or methods of detection are most valid¹⁵. However, measurements of lipid peroxidation marker levels, specifically malondialdehyde (MDA) and F2-isoprostanes, are generally regarded to be the most reliable and reproducible markers in the clinical setting^{15,49,50}.

Animal studies

There is clear evidence from animal studies that pneumoperitoneum results directly in end-organ ischaemia and injury. A recent study by Nickkholgh *et al.*¹³ demonstrated that pneumoperitoneum at 12 mmHg for

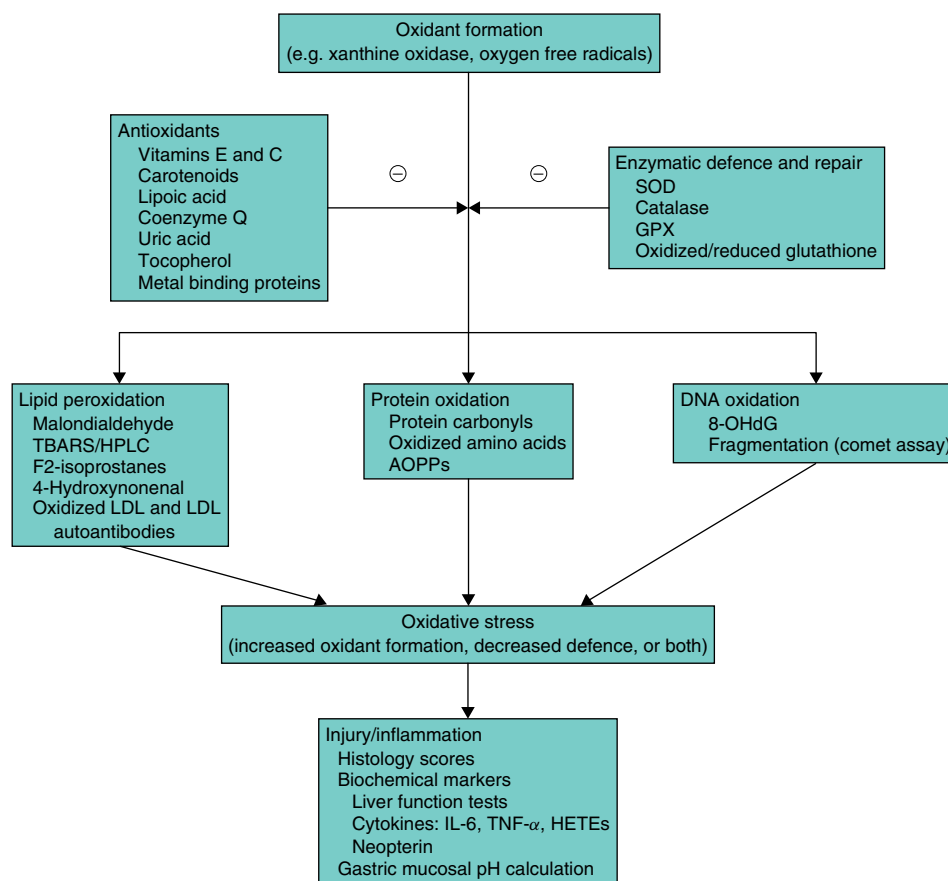


Fig. 2 Simplified diagram of oxidants *versus* endogenous antioxidants, and enzymatic defence and repair mechanisms (modified from Grune and Berger¹⁵). Levels of these compounds can be measured, as can markers of injury that result from their imbalance (oxidative stress). SOD, superoxide dismutase; GPX, glutathione peroxidase; TBARS, thiobarbituric acid-reactive substances; HPLC, high-performance liquid chromatography; LDL, low-density lipoprotein; AOPP, plasma advanced oxidation protein product; 8-OHdG, 8-hydroxydesoxyguanosine; IL, interleukin; TNF, tumour necrosis factor; HETEs, hydroxyeicosatetraenoic acids

90 min induced histological (*in vivo* light microscopy) and biochemical (plasma liver function enzyme levels) evidence of liver reperfusion injury in rats. A significant increase in kidney markers of oxidative stress (MDA, protein carbonyls) was also observed in a rat model of laparoscopic donor nephrectomy compared with controls that underwent a sham operation and were not subjected to pneumoperitoneum^{30,31}. Levels of these markers were shown to rise in a time-dependent manner, with increased protein carbonyls and decreased protein sulphhydryls and tissue superoxide dismutase activities after 240 min of pneumoperitoneum compared with 120 min³⁰. Increased xanthine oxidase activity was observed in rabbit colonic tissue after only 20 min of laparoscopic insufflation³⁴. Other studies have shown similar patterns of tissue oxidative stress in open and retroperitoneoscopic donor nephrectomy³².

Extra-abdominal organs also demonstrate oxidative stress in the context of pneumoperitoneum, with significantly increased MDA levels in rat lungs at 2 and 6 h after deflation³⁵.

Human studies

Thirteen of the 37 human studies identified in the search examined oxidative stress in patients undergoing laparoscopic surgery; details of these are summarized in Table 2.

Three randomized clinical trials^{39,41,48} and two case-control studies^{43,44} compared plasma markers of lipid peroxidation between laparoscopic and open cholecystectomy, and found these to be raised in both groups but significantly higher in open surgery (Table 2). The difference was demonstrable up to day 7 in one of the case-control studies when plasma oxidized low-density

Table 2 Summary of human trials of laparoscopic oxidative stress

Reference	Year	Methods	Exposure*	Comparison*	Insufflation pressure (mmHg)	Marker measured	Timing of measure	Significant result summary
Eleftheriadis <i>et al.</i> ²⁶	1996	Not randomized, uncontrolled	LC (8)	OC (8)	12	Gastric mucosal pH	Intraop.; immediately after deflation in LC group	Lower intraop. pH in LC group, returned to normal after deflation
Gál <i>et al.</i> ³⁹	1997	Randomized, uncontrolled	LC (21)	OC (21)	NS	Plasma: MDA, GPX, myeloperoxidase	Preop.; postop. for up to 5 days (unclear how frequently)	Lower levels of all three measures in LC compared with OC group
Windsor <i>et al.</i> ⁴⁵	1997	Not randomized, uncontrolled	LC (5)	NA	4–8, then 12–15 [†]	Gastric mucosal pH	After induction of anaesthesia before insufflation; after insufflation; after surgery	Intraop. pH reduced; pressure dependent
Seven <i>et al.</i> ⁴³	1999	Case–control; two exposure arms	OC (14), LC (17)	Control: healthy volunteers who did not have surgery (15) OC (20)	NS	Plasma: lipid peroxidation index	Immediately postop.	OC > LC > control
Giantzounis <i>et al.</i> ⁴⁰	2001	Not randomized, uncontrolled	LC (30)	OC (30)	13	Plasma: TBARS, TAS, uric acid	Preop.; 5 min after deflation/end of operation; 24 h postop.	OC versus baseline: TAS and uric acid higher at 24 h LC versus baseline: TBARS higher at 5 min. TAS and uric acid higher at 24 h OC versus LC: TBARS higher in LC group at 5 min, TAS and uric acid higher in OC group at 24 h Plasma MDA higher in LC than in OC group mid-operation only; no other differences found
Ozmen <i>et al.</i> ⁴²	2002	Randomized, uncontrolled	LC (20)	OC (20)	12	Plasma: MDA, NO Tissue: gastric mucosal pH	Plasma samples preop., mid-operation, immediately postop. Gastric pH preop., after anaesthesia induction, 15 min into operation, after deflation/closure of abdomen, 1 and 24 h postop.	

Table 2 (Continued)

Reference	Year	Methods	Exposure*	Comparison*	Insufflation pressure (mmHg)	Marker measured	Timing of measure	Significant result summary
Zulfikaroglu <i>et al.</i> ⁴⁸	2002	Randomized, uncontrolled	LC (25)	OC (25)	12	Plasma: MDA, TAS, NO Tissue: gallbladder MDA	Plasma: intraop after 30 min of insufflation, 30 min postincision, 24 h postop. Tissue: gallbladder tissue immediately after removal from abdomen	OC versus intraop: NO lower, MDA higher at 24 h LC versus intraop.: MDA higher at 24 h OC versus LC: MDA higher in OC intraop., TAS higher in OC at 24 h, gallbladder MDA higher in LC because more manipulation Open (sample 1 versus 2): 15-HETE lower in sample 2 Laparoscopy (sample 1 versus 2): 8-isoprostane, 5-HETE higher in sample 2; correlated with insufflation time and volume of carbon dioxide used Open versus laparoscopy: MDA higher in open group; 8-isoprostane, 5-HETE and 15-HETE higher in laparoscopic group
Bentes de Souza <i>et al.</i> ³⁸	2003	Not randomized, uncontrolled	Laparoscopic excision of uterine myoma or ovarian cyst (14)	Open excision of uterine myoma (14)	15	Tissue: 8-isoprostane, HETEs, MDA	1 × 1-cm peritoneal square removed on breaching peritoneum (sample 1) and at end of procedure (sample 2)	
Polat <i>et al.</i> ⁵¹	2003	Randomized, uncontrolled	LC at 15 mmHg (12)	LC at 10 mmHg (12)	15 and 10	Plasma: TBARS, carbonyl and sulphhydryl levels	Preop., immediately postop., 6 and 24 h postop.	Significant increase versus baseline for both groups; carbonyl levels higher in 15 than 10 mmHg group immediately postop.
Bukan <i>et al.</i> ⁴¹	2004	Randomized, uncontrolled	LC (21)	OC (21)	NS	Plasma: MDA, nitrite + nitrate	1 day preop., 45 min after incision, 1 day postop.	OC versus baseline: MDA and nitrite higher intraop.; back to normal on day 1 LC versus baseline: MDA lower day 1 postop.; nitrite higher intraop., back to normal on day 1 OC versus LC: OC higher nitrite on day 1 postop.

Zhang <i>et al.</i> ⁴⁶	2004	Not randomized, uncontrolled	Laparoscopic enucleation of uterine myoma (20)	Open enucleation of uterine myoma (20)	NS	Plasma: MDA, AOA, GPX	Preop., 5 min after deflation/end of operation, 24 h postop.	Open versus baseline: MDA higher, GPX and AOA lower at 24 h Laparoscopic versus baseline: MDA higher, GPX and AOA lower immediately postop.; back to normal at 24 h Open versus laparoscopic: open higher MDA and lower GPX at 24 h
Stipancic <i>et al.</i> ⁴⁴	2005	Case-control, two exposure arms	LC (21), OC (22)	Control: healthy volunteers who did not have surgery (20)	13	Plasma: POX, oxidized LDL Ab, neopterin, TAS, SOD	24 h preop., 1, 2 and 3 days postop.	OC versus baseline: POX lower on day 1, higher on day 7; oxidized LDL Ab and neopterin higher on day 7 LC versus baseline: POX higher on day 7; oxidized LDL Ab and neopterin no change OC versus LC: POX lower in OC group on day 1; oxidized LDL Ab and neopterin higher in OC group on day 7 No change for TAS or SOD in either group
Zhang <i>et al.</i> ⁴⁷	2005	Randomized, uncontrolled	Laparoscopic enucleation of uterine myoma (20)	Open enucleation of uterine myoma (20)	NS	Plasma: MDA, AOPPs, AOA, GPX	Preop., 5 min after deflation/end of operation, 24 h postop.	Open versus baseline: AOPP and MDA higher, GPX and AOA lower at 24 h Laparoscopic versus baseline: AOPP and MDA higher, GPX and AOA lower immediately postop.; all except AOA back to normal at 24 h Open versus laparoscopic: open higher AOPP and MDA, lower GPX at 24 h

*Values in parentheses are numbers of patients. †All patients subjected to a period of low pressure, then normal pressure insufflation. LC, laparoscopic cholecystectomy; OC, open cholecystectomy; NS, not stated; MDA, malondialdehyde; GPX, glutathione peroxidase; NA, not applicable; TBARS, thiobarbituric acid-reactive substances; TAS, total antioxidant status; NO, nitric oxide; HETE, hydroxyecosatetraenoic acid; AOA, antioxidant activity; POX, endogenous peroxide level; LDL Ab, low-density lipoprotein autoantibodies; SOD, superoxide dismutase; AOPP, plasma advanced oxidation protein product.

lipoprotein autoantibodies and neopterin were utilized as markers⁴⁴. One non-randomized trial found a significantly higher level of thiobarbituric acid-reactive substances in laparoscopic *versus* open cholecystectomy; this was seen only at 5 min postdeflation, with no significant difference at 24 h⁴⁰.

Studies conducted in China on women undergoing laparoscopic and open enucleation of uterine myomas demonstrated consistently higher levels of MDA and advanced oxidation protein products, and lower levels of glutathione peroxidase and antioxidant activity, immediately after laparoscopic surgery^{46,47}. This picture reversed at 24 h, with deterioration in patients having open surgery at this time point, whereas levels in the laparoscopic group had essentially normalized. Another gynaecological study, which included both uterine myomas and ovarian cysts, showed a greater increase in MDA levels in the open group, but a higher level of isoprostanes and hydroxy eicosatetranoic acids in the laparoscopic group³⁸. The authors hypothesized that the oxidative stress was occurring through different pathways (thromboxane synthesis with open surgery, and lipid peroxidation with laparoscopic surgery). However, the comparison was weakened by the significant difference in baseline uterine pathology between groups. Interestingly, the extent of the oxidative stress in the laparoscopic group appeared to correlate significantly with the volume of gas used, as well as the duration of insufflation³⁸.

Gastric mucosal pH has also been used as a measure of tissue oxygenation in human studies^{52,53}. This technique assumes equilibrium across the superficial gastric mucosa between the partial pressure of carbon dioxide (PCO_2) in the gut lumen and the bicarbonate concentration in the blood. It is inherently limited by these assumptions, but serves as an indirect measure of splanchnic perfusion⁵⁴. In 1997, Windsor and co-workers⁴⁵ published a preliminary study showing that there was a measurable and continuous reduction in gastric mucosal pH during laparoscopic cholecystectomy. It is not known whether this reduction is more pronounced compared with that for open cholecystectomy. In an early study, Eleftheriadis and colleagues²⁶ performed a non-randomized comparison of laparoscopic and open cholecystectomy using a single intraoperative gastric mucosal pH measurement, and demonstrated a significantly lower pH in the laparoscopic group. However, this result has been challenged by a larger randomized trial conducted by Ozmen *et al.*⁴² that did not show a significant difference in gastric mucosal pH between laparoscopic and open cholecystectomy when this was measured at multiple points during and after surgery (Table 2)⁵⁵. In addition to study design, another possible

reason for the different outcomes of these two studies is that Ozmen and colleagues excluded all patients with significant co-morbidity and therefore the study patients may have been better able to tolerate pneumoperitoneum than the general patient population. Both studies used similar insufflation pressures of approximately 12 mmHg.

The presented data suggest that pneumoperitoneum causes oxidative stress, with significantly increased levels of local and plasma markers in the laparoscopy groups in most studies, even for relatively minor surgery. It is notable that the increase in biochemical markers after laparoscopy is not necessarily higher than for corresponding open procedures. This is to be expected, however, given that laparoscopy as a less invasive operative approach is known to be associated with a lesser postsurgical systemic stress response compared with open surgery^{56–58}. The finding that laparoscopic surgery is associated with oxidative stress requires some explanation, and it is reasonable to ask whether the raised intra-abdominal pressure alone might be responsible, or whether other factors such as the nature of the gas used for insufflation may also contribute.

Impact of insufflation pressure

Animal studies

Pneumoperitoneum applied in rats with pressure of 5, 10 or 15 mmHg resulted in an incremental increase in the formation of free oxygen radicals in lung and liver tissues⁵⁹. Similar increases were seen in MDA levels in the small intestine of rabbit subjected to pneumoperitoneum at 0, 15 and 25 mmHg³⁶, and in the kidneys of rats in the laparoscopic donor nephrectomy model mentioned above³¹. In the study by Nickkholgh and colleagues¹³, histological and biochemical evidence of liver reperfusion injury was demonstrable at 12 mmHg but not at 8 mmHg. In a pig model, Windberger *et al.*⁶⁰ observed a significantly reduced portal venous flow and hepatic tissue pH when pneumoperitoneum of 14 mmHg was performed, compared with 7 mmHg, at 60 min postinsufflation.

Human studies

Laplace's law describes the effect of pneumoperitoneum on pressure across the abdominal wall (the higher the tension on the abdominal wall, the higher the intra-abdominal pressure for a given fixed radius at maximal abdominal expansion)⁶¹. This pressure reduces peritoneal microcirculation during laparoscopy, in addition to the systemic haemodynamic effect discussed above^{38,62}. Schilling and co-workers²⁸ demonstrated that this reduction in organ perfusion is pressure dependent by studying the effect of different insufflation pressures in laparoscopic cholecystectomy using a laser Doppler flow probe to measure

organ perfusion. Increasing pressure from 10 to 15 mmHg significantly decreased the blood flow in the stomach by 40 per cent, duodenum by 11 per cent, jejunum by 32 per cent, colon by 44 per cent, liver by 39 per cent and the parietal peritoneum by 60 per cent. Splanchnic blood flow also decreased significantly with operating time at a constant intra-arterial pressure²⁸. In addition, there was a significant reduction in gastric mucosal pH in patients undergoing laparoscopic cholecystectomy when an insufflation pressure of 12–15 mmHg was used compared with 4–8 mmHg⁴⁵. Polat *et al.*⁵¹ showed a trend towards increased oxidative markers when laparoscopic cholecystectomy was performed in patients at 15 mmHg rather than 10 mmHg, but this was statistically significant only for carbonyl levels immediately after surgery (Table 2). It is interesting to draw an analogy with abdominal compartment syndrome, where the detrimental effects of increased intra-abdominal pressure are frequently observed, usually in surgical intensive care units. In this setting, intra-abdominal hypertension is usually defined as an intra-abdominal pressure of 12 mmHg or more⁶³.

Impact of the nature of gas used

Type of gas

An ideal gas for establishing pneumoperitoneum is neutral (so as not to support combustion), easily absorbed and completely non-toxic to the peritoneal environment. The most widely used gas, carbon dioxide, is not ideal, but does have the advantage of being readily available, quickly absorbed and excreted, inexpensive and non-flammable^{64,65}. When insufflated into the abdominal cavity, carbon dioxide normally diffuses across the peritoneum, and is carried by the circulation to the lung, where it is expired^{59,66}. However, adverse effects have been associated with the increased systemic carbon dioxide load manifested by recordable increases in arterial PCO_2 after laparoscopy^{18,19,48}. This increased PCO_2 results in a reduced tissue pH^{67,68}, causing vasoconstriction and reducing mesenteric and hepatic blood flow^{18,19}. Furthermore, local acidity caused by the carbon dioxide being converted to carbonic acid in the peritoneal fluid results in microscopically visible histological damage to the mesothelial ultrastructure, which is more pronounced than when peritoneum is exposed to room air^{64,69–71}. There is also evidence that carbon dioxide directly blunts peritoneal macrophage function *in vivo*⁷².

Non-reactive gases such as helium and argon have been considered as alternatives. Yilmaz and colleagues¹⁴ showed a significantly greater increase in oxidative stress markers when carbon dioxide was used compared

with helium for a given insufflation pressure in a rat model. Helium pneumoperitoneum did not produce any significant increase in MDA and carbonyl levels, even at 15 mmHg, compared with controls, but carbon dioxide pneumoperitoneum caused a significant increase, even at pressures as low as 10 mmHg¹⁴. Despite these apparent advantages it is likely that carbon dioxide will remain the preferred gas for pneumoperitoneum, largely owing to concerns that non-absorbable gases might be at greater risk of contributing to potentially fatal gas emboli and pneumothoraces^{64,73}.

Nitrous oxide was commonly used in the 1970s. Although it may offer some advantages in terms of patient tolerance⁶⁴, its combustibility makes it unsafe for use with electrocautery. Its use as an insufflation agent has declined dramatically in parallel with the increased use of electrocautery, and its relative effects on pneumoperitoneum-associated oxidative stress have not been studied.

Gas temperature and humidity

The gas used in laparoscopy is typically cold and dry, at 21°C and 0 per cent relative humidity⁷⁴. Large volumes of gas may be required for a single patient (up to 500 litres), owing to the imperfect seal of the laparoscopic ports and peritoneal carbon dioxide absorption. The effect of this cold, dry gas flow on the peritoneal environment is significant⁷⁴, with the desiccating and cooling effect producing visible structural, morphological and biochemical changes (increased cytokine response) in the peritoneal mesothelial surface layer^{64,72,75,76}. This includes bulging of mesothelial cells, widening of intercellular junctions and exposure of the basement membrane underneath⁷².

Warming of the insufflated carbon dioxide is associated with a reduced peritoneal cytokine response after laparoscopic cholecystectomy in humans⁷⁷, but, to the authors' knowledge, there have not been any animal or human studies investigating whether this contributes directly to oxidative stress during pneumoperitoneum.

Measures to reduce oxidative stress associated with pneumoperitoneum

Practical measures

Routine laparoscopy is well tolerated in fit patients, but the clinical significance of the oxidative stress caused by pneumoperitoneum in those with significant co-morbidity needs further investigation. Several authors have recommended simple measures that might reduce its impact in situations where physiological reserves are compromised, such as in patients with significant co-morbidity,

particularly those with cardiovascular compromise. In order to reduce haemodynamic compromise, it is recommended that the lowest possible inflation pressure is used, with insufflation started at a standard pressure (12–15 mmHg) and then gradually lowered as much as possible without compromising visibility ('dial-down' approach)^{78,79}. Some have also advocated releasing gas intermittently during the procedure^{19,80}. Gasless surgery using various abdominal wall lifting devices has also been employed, although this may not provide uniform exposure and increases operating time^{78,81}. From a haemodynamic point of view, the head-up position should be avoided, as this reduces venous return^{29,82,83}. Intravascular volume expansion with intravenous fluids before commencement of pneumoperitoneum can enhance renal perfusion and reduce the extent of renal injury⁸⁴. The evidence for this is limited, however, and there are no guidelines on which subset of patients would benefit most. Indeed, in certain patients with severe cardiovascular or renal function compromise, volume expansion can be detrimental to end-organ perfusion, as the extra fluid cannot be distributed or excreted adequately. This has led to the concept of individually tailored fluid replacement, where the volume given during surgery is goal directed (based on direct measures of cardiac output)^{85,86}. These protocols have been shown to result in improved short-term postoperative outcomes, although their relationship with oxidative stress has not been investigated^{84,86}.

A mechanical solution raised by Bickel involves using an intermittent sequential pneumatic compression device to improve venous return⁸⁷. This device compresses the lower limb veins, using two sleeves wrapped around the patient's legs from ankle to groin. This has been shown to reduce venous stasis and deep venous thrombosis^{88–92}, to improve haemodynamic parameters during operation^{87,93,94} and to reduce plasma levels of total lipid peroxides during the reperfusion phase in laparoscopic cholecystectomy^{95,96}. Peroneal nerve compression has been reported as a rare complication of this system of lower leg compression^{97,98}.

Ischaemic preconditioning

Ischaemic preconditioning is a concept that has been employed to avoid the harmful effects of ischaemia–reperfusion injury in cardiac⁹⁹, liver^{100,101} and reconstructive surgery¹⁰². It consists of short cycles of ischaemia–reperfusion, performed before the main insult. These cycles can be followed by increased resistance to exacerbated cellular reoxygenation injury¹⁰³. This theory has been tested in rats using various protocols of short periods of inflation and deflation upon establishment of pneumoperitoneum. The results consistently demonstrate a

reduction in oxidative stress as measured by various plasma and tissue markers^{65,103–106}. Furthermore, a reduction in peritoneal and plasma cytokine levels, and an improvement in small bowel, kidney and liver histological injury scores, were seen in preconditioned animals compared with those that were not preconditioned^{65,103–107}. Cevrioglu *et al.*¹⁰⁴ also included a low-pressure group in their study (insufflated at 10 mmHg). Although this improved oxidative stress compared with insufflation at 15 mmHg, preconditioning (with 10 min of 15 mmHg followed by deflation for 10 min) before the usual 15 mmHg of insufflation resulted in significantly reduced levels of oxidative stress markers compared with levels in the low-pressure group. The authors concluded that preconditioning 'can be more effective than low-pressure pneumoperitoneum in reducing the oxidative stress and inflammatory cytokine response associated with laparoscopy'. Despite this success in animals, no human studies on preconditioning in pneumoperitoneum have been conducted to the authors' knowledge, and preconditioning has not found a definite place in clinical practice. This may be because experimental protocols of preconditioning are conceived by some to be too lengthy for practical use^{103,104}.

Pharmacological agents

Various pharmacological agents have been tested to combat oxidative stress, and some antioxidants and vasodilators have been shown to be successful in animal models^{78,108,109}. Administration of dopamine and endothelin 1 antagonists greatly improved the portal circulation in rats subjected to carbon dioxide and helium insufflation, but oxidative stress markers were not measured¹⁰⁹. Pretreatment with the calcium channel antagonist verapamil significantly reduced oxidant levels and increased antioxidant levels in a rabbit model of retroperitoneoscopy¹⁶. This was based on previous studies of verapamil showing a reduction in renal and hepatic ischaemia–reperfusion injury by acting on calcium influx, although a specific molecular interaction between calcium channel antagonists and ROS was not evident^{110,111}.

Erythropoietin is a hypoxia-inducible growth factor expressed mainly in the kidney. It has multiple protective effects against oxidants and apoptosis¹⁰⁶. Administration of erythropoietin in a rat model at a dose of 1000 units/kg before laparoscopy significantly decreased plasma MDA levels compared with those in controls¹⁰⁶. Similarly, melatonin (10 mg/kg) administered 5 min before insufflation and immediately before desufflation in a rat model significantly reduced mean MDA levels in liver, small intestine and kidney, and improved small bowel histological parameters¹¹².

Other endogenous antioxidants, such as tocopherol, glutathione and superoxide dismutase, and various synthetic antioxidant drugs, such as xanthine oxidase inhibitors²¹, provide possible avenues to minimize tissue injury in laparoscopic surgery, and also in open surgery⁵⁹. Clinical trials are needed before these can be accepted into general use.

Conclusion

This review has examined the relationship between pneumoperitoneum and oxidative stress. It is clear that pneumoperitoneum causes a reduction in splanchnic blood flow as a result of both systemic and local effects, in a pressure- and time-dependent manner, resulting in biochemical evidence of oxidative stress and histological evidence of tissue injury. It is important to note that corresponding open abdominal procedures are also associated with a similar oxidative stress response, indicating that this phenomenon is not simply due to increased intra-abdominal pressure. There is some evidence that the use of carbon dioxide as the insufflation gas may be contributory, although the impact of other factors such as the temperature and humidity of the gas have not been elucidated.

A number of measures have been proposed to reduce oxidative stress caused by pneumoperitoneum; although some of these measures have shown promise in animal studies, few have been evaluated in the clinical setting. It is now appropriate to investigate the clinical significance of pneumoperitoneum-associated oxidative stress and the impact of its reduction on defined clinical endpoints in laparoscopic surgery, particularly in patients with multiple co-morbidities.

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References

- Kelling G. Ueber die Besichtigung der Speiseröhre und des Magens mit biegsamen Instrumenten. In *Verhandlungen der Gesellschaft Deutscher Naturforscher und Aerzte*, 73. Vogel: Leipzig, 1901; 117–119.
- Reynolds W Jr. The first laparoscopic cholecystectomy. *JSL* 2001; **5**: 89–94.
- Hulka JF, Reich H. *Textbook of Laparoscopy* (3rd edn). Philadelphia: WB Saunders, 1998.
- Richmond BK. Re: *JSL* 2006; **10**: 236–238 Intestinal ischemia after laparoscopic cholecystectomy. *JSL* 2006; **10**: 546.
- Leduc LJ, Mitchell A. Intestinal ischemia after laparoscopic cholecystectomy. *JSL* 2006; **10**: 236–238.
- Bandyopadhyay D, Kapadia CR. Large bowel ischemia following laparoscopic inguinal hernioplasty. *Surg Endosc* 2003; **17**: 520–521.
- Wassenaar EB, Raymakers JT, Rakic S. Fatal intestinal ischemia after laparoscopic correction of incisional hernia. *JSL* 2007; **11**: 389–393.
- Johnson PR. Re: *JSL* 2007; **11**: 389–393 Fatal intestinal ischemia after laparoscopic correction of incisional hernia. *JSL* 2008; **12**: 217.
- Paul A, Troidl H, Peters S, Stuttmann R. Fatal intestinal ischaemia following laparoscopic cholecystectomy. *Br J Surg* 1994; **81**: 1207.
- Talbot D, Miller IT, Miller IA. Fatal intestinal ischaemia following laparoscopic cholecystectomy. *Br J Surg* 1995; **82**: 1143.
- Hasson HM, Galanopoulos C, Langerman A. Ischemic necrosis of small bowel following laparoscopic surgery. *JSL* 2004; **8**: 159–163.
- Dwerryhouse SJ, Melsom DS, Burton PA, Thompson MH. Acute intestinal ischaemia after laparoscopic cholecystectomy. *Br J Surg* 1995; **82**: 1413.
- Nickkholgh A, Barro-Bejarano M, Liang R, Zorn M, Mehrabi A, Gebhard MM *et al.* Signs of reperfusion injury following CO₂ pneumoperitoneum: an *in vivo* microscopy study. *Surg Endosc* 2008; **22**: 122–128.
- Yilmaz S, Polat C, Kahraman A, Koken T, Arıkan Y, Dilek ON *et al.* The comparison of the oxidative stress effects of different gases and intra-abdominal pressures in an experimental rat model. *J Laparoendosc Adv Surg Tech A* 2004; **14**: 165–168.
- Grune T, Berger MM. Markers of oxidative stress in ICU clinical settings: present and future. *Curr Opin Clin Nutr Metab Care* 2007; **10**: 712–717.
- Guler C, Samli M, Aksoy Y, Demirbas M, Kiliç A, Ellidokuz E *et al.* Effects of carbon dioxide pneumoperitoneum on free radical formation in remote organs and use of verapamil as an antioxidant. *J Endourol* 2004; **18**: 245–249.
- Ben-Haim M, Rosenthal RJ. Causes of arterial hypertension and splanchnic ischemia during acute elevations in intra-abdominal pressure with CO₂ pneumoperitoneum: a complex central nervous system mediated response. *Int J Colorectal Dis* 1999; **14**: 227–236.
- Ivankovich AD, Miletich DJ, Albrecht RF, Heyman HJ, Bonnet RF. Cardiovascular effects of intraperitoneal insufflation with carbon dioxide and nitrous oxide in the dog. *Anesthesiology* 1975; **42**: 281–287.
- Ishizaki Y, Bandai Y, Shimomura K, Abe H, Ohtomo Y, Idezuki Y. Changes in splanchnic blood flow and cardiovascular effects following peritoneal insufflation of carbon dioxide. *Surg Endosc* 1993; **7**: 420–423.

- 20 Caldwell CB, Ricotta JJ. Changes in visceral blood flow with elevated intraabdominal pressure. *J Surg Res* 1987; **43**: 14–20.
- 21 Mittal A, Phillips AR, Loveday B, Windsor JA. The potential role for xanthine oxidase inhibition in major intra-abdominal surgery. *World J Surg* 2008; **32**: 288–295.
- 22 Melville RJ, Frizis HI, Forsling ML, LeQuesne LP. The stimulus for vasopressin release during laparoscopy. *Surg Gynecol Obstet* 1985; **161**: 253–256.
- 23 Viinamki O, Punnonen R. Vasopressin release during laparoscopy: role of increase intra-abdominal pressure. *Lancet* 1982; **1**: 175–176.
- 24 Altintas F, Tunali Y, Bozkurt P, Kaya G, Uygun N, Aricioglu F *et al*. An experimental study on the relationship of intra-abdominal pressure and renal ischemia. *Middle East J Anesthesiol* 2001; **16**: 55–66.
- 25 Blobner M, Bogdanski R, Kochs E, Henke J, Findeis A, Jelen-Esselborn S. Effects of intraabdominally insufflated carbon dioxide and elevated intraabdominal pressure on splanchnic circulation: an experimental study in pigs. *Anesthesiology* 1998; **89**: 475–482.
- 26 Eleftheriadis E, Kotzampassi K, Botsios D, Tzartinoglou E, Farmakis H, Dadoukis J. Splanchnic ischemia during laparoscopic cholecystectomy. *Surg Endosc* 1996; **10**: 324–326.
- 27 Jakimowicz J, Stultiens G, Smulders F. Laparoscopic insufflation of the abdomen reduces portal venous flow. *Surg Endosc* 1998; **12**: 129–132.
- 28 Schilling MK, Redaelli C, Krähenbühl L, Signer C, Büchler MW. Splanchnic microcirculatory changes during CO₂ laparoscopy. *J Am Coll Surg* 1997; **184**: 378–382.
- 29 Kotake Y, Takeda J, Matsumoto M, Tagawa M, Kikuchi H. Subclinical hepatic dysfunction in laparoscopic cholecystectomy and laparoscopic colectomy. *Br J Anaesth* 2001; **87**: 774–777.
- 30 Akbulut G, Polat C, Aktepe F, Yilmaz S, Kahraman A, Serteser M *et al*. The oxidative effect of prolonged CO₂ pneumoperitoneum on renal tissue of rats. *Surg Endosc* 2004; **18**: 1384–1388.
- 31 Akbulut G, Serteser M, Polat C, Köken T, Aktepe F, Yilmaz S *et al*. Changes in tissue-oxidative stress markers in an experimental model of laparoscopic donor nephrectomy. *Transplantation* 2002; **74**: 1768–1772.
- 32 Demirbas M, Samli M, Aksoy Y, Guler C, Kilinc A, Dincel C. Comparison of changes in tissue oxidative-stress markers in experimental model of open, laparoscopic, and retroperitoneoscopic donor nephrectomy. *J Endourol* 2004; **18**: 105–108.
- 33 Diebel LN, Dulchavsky SA, Wilson RF. Effect of increased intra-abdominal pressure on mesenteric arterial and intestinal mucosal blood flow. *J Trauma* 1992; **33**: 45–48.
- 34 Emir H, Akman M, Belce A, Gümüştaş K, Soylet Y. Is intestinal ischemia a risk of laparoscopy? An experimental study in rabbits. *Eur J Pediatr Surg* 2001; **11**: 158–162.
- 35 Pross M, Schulz HU, Flechsig A, Manger T, Halangk W, Augustin W *et al*. Oxidative stress in lung tissue induced by CO₂ pneumoperitoneum in the rat. *Surg Endosc* 2000; **14**: 1180–1184.
- 36 Kaya Y, Coskun T, Demir MA, Var A, Ozsoy Y, Aydemir EO. Abdominal insufflation–deflation injury in small intestine in rabbits. *Eur J Surg* 2002; **168**: 410–417.
- 37 Eleftheriadis E, Kotzampassi K, Papanotas K, Heliadis N, Sarris K. Gut ischemia, oxidative stress, and bacterial translocation in elevated abdominal pressure in rats. *World J Surg* 1996; **20**: 11–16.
- 38 Bentes de Souza AM, Rogers MS, Wang CC, Yuen PM, Ng PS. Comparison of peritoneal oxidative stress during laparoscopy and laparotomy. *J Am Assoc Gynecol Laparosc* 2003; **10**: 65–74.
- 39 Gál I, Róth E, Lantos J, Varga G, Jaberansari MT. Inflammatory mediators and surgical trauma regarding laparoscopic access: free radical mediated reactions. *Acta Chir Hung* 1997; **36**: 97–99.
- 40 Glantzounis GK, Tselepis AD, Tambaki AP, Trikalinos TA, Manataki AD, Galaris DA *et al*. Laparoscopic surgery-induced changes in oxidative stress markers in human plasma. *Surg Endosc* 2001; **15**: 1315–1319.
- 41 Bukan MH, Bukan N, Kaymakcioglu N, Tufan T. Effects of open *vs* laparoscopic cholecystectomy on oxidative stress. *Toboku J Exp Med* 2004; **202**: 51–56.
- 42 Ozmen MM, Kessaf Aslar A, Besler HT, Cinel I. Does splanchnic ischemia occur during laparoscopic cholecystectomy? *Surg Endosc* 2002; **16**: 468–471.
- 43 Seven R, Seven A, Erbil Y, Mercan S, Burçak G. Lipid peroxidation and antioxidant state after laparoscopic and open cholecystectomy. *Eur J Surg* 1999; **165**: 871–874.
- 44 Stipancic I, Zarkovic N, Servis D, Sabolović S, Tatzber F, Busic Z. Oxidative stress markers after laparoscopic and open cholecystectomy. *J Laparoendosc Adv Surg Tech A* 2005; **15**: 347–352.
- 45 Windsor MA, Bonham MJ, Rumball M. Splanchnic mucosal ischemia: an unrecognized consequence of routine pneumoperitoneum. *Surg Laparosc Endosc* 1997; **7**: 480–482.
- 46 Zhang GL, Liu GB, Huang QL, Xing FQ. [Comparative study of the impacts of laparoscopic and open laparotomic surgeries on oxidative stress in patients with uterine myomas.] *Di Yi Jun Yi Da Xue Xue Bao* 2004; **24**: 907–909.
- 47 Zhang GL, Wen WQ, Xing FQ. [Effect of enucleation of hysteromyoma by laparoscopic surgery on protein oxidation and lipid hyperoxidation.] *Zhonghua Yi Xue Za Zhi* 2005; **85**: 177–180.
- 48 Zulfikaroglu B, Koc M, Soran A, Isman FK, Cinel I. Evaluation of oxidative stress in laparoscopic cholecystectomy. *Surg Today* 2002; **32**: 869–874.
- 49 Del Rio D, Stewart AJ, Pellegrini N. A review of recent studies on malondialdehyde as toxic molecule and biological marker of oxidative stress. *Nutr Metab Cardiovasc Dis* 2005; **15**: 316–328.
- 50 Comporti M, Signorini C, Arezzini B, Vecchio D, Monaco B, Gardi C. F₂-isoprostanes are not just markers of oxidative stress. *Free Radic Biol Med* 2008; **44**: 247–256.

- 51 Polat C, Yilmaz S, Serteser M, Koken T, Kahraman A, Dilek ON. The effect of different intraabdominal pressures on lipid peroxidation and protein oxidation status during laparoscopic cholecystectomy. *Surg Endosc* 2003; **17**: 1719–1722.
- 52 Fiddian-Green RG. Gastric intramucosal pH, tissue oxygenation and acid–base balance. *Br J Anaesth* 1995; **74**: 591–606.
- 53 Clark CH, Gutierrez G. Gastric intramucosal pH: a noninvasive method for the indirect measurement of tissue oxygenation. *Am J Crit Care* 1992; **1**: 53–60.
- 54 Cerny V, Cvachovec K. Gastric tonometry and intramucosal pH – theoretical principles and clinical application. *Physiol Res* 2000; **49**: 289–297.
- 55 Polat C, Yilmaz S, Gökçe O. Does ischemia occur during laparoscopic cholecystectomy? *Surg Endosc* 2003; **17**: 1337.
- 56 Novitsky YW, Litwin DE, Callery MP. The net immunologic advantage of laparoscopic surgery. *Surg Endosc* 2004; **18**: 1411–1419.
- 57 Gupta A, Watson DI. Effect of laparoscopy on immune function. *Br J Surg* 2001; **88**: 1296–1306.
- 58 Glaser F, Sannwald GA, Buhr HJ, Kuntz C, Mayer H, Klee F *et al.* General stress response to conventional and laparoscopic cholecystectomy. *Ann Surg* 1995; **221**: 372–380.
- 59 Sare M, Hamamci D, Yilmaz I, Birincioglu M, Menten BB, Ozmen M *et al.* Effects of carbon dioxide pneumoperitoneum on free radical formation in lung and liver tissues. *Surg Endosc* 2002; **16**: 188–192.
- 60 Windberger UB, Auer R, Keplinger F, Längle F, Heinze G, Schindl M *et al.* The role of intra-abdominal pressure on splanchnic and pulmonary hemodynamic and metabolic changes during carbon dioxide pneumoperitoneum. *Gastrointest Endosc* 1999; **49**: 84–91.
- 61 Online Medical Dictionary. <http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=laplace%27s+law> [accessed 20 June 2008].
- 62 Ishizaki Y, Bandai Y, Shimomura K, Abe H, Ohtomo Y, Idezuki Y. Safe intraabdominal pressure of carbon dioxide pneumoperitoneum during laparoscopic surgery. *Surgery* 1993; **114**: 549–554.
- 63 An G, West MA. Abdominal compartment syndrome: a concise clinical review. *Crit Care Med* 2008; **36**: 1304–1310.
- 64 Neuhaus SJ, Gupta A, Watson DI. Helium and other alternative insufflation gases for laparoscopy. *Surg Endosc* 2001; **15**: 553–560.
- 65 Yilmaz S, Ates E, Polat C, Koken T, Tokyol C, Akbulut G *et al.* Ischemic preconditioning decreases laparoscopy-induced oxidative stress in small intestine. *Hepatogastroenterology* 2003; **50**: 979–982.
- 66 Kazama T, Ikeda K, Sanjo Y. Comparative carbon dioxide output through injured and noninjured peritoneum during laparoscopic procedures. *J Clin Monit Comput* 1998; **14**: 171–176.
- 67 Wong YT, Shah PC, Birkett DH, Brams DM. Peritoneal pH during laparoscopy is dependent on ambient gas environment: helium and nitrous oxide do not cause peritoneal acidosis. *Surg Endosc* 2005; **19**: 60–64.
- 68 Taura P, Lopez A, Lacy AM, Anglada T, Beltran J, Fernandez-Cruz L *et al.* Prolonged pneumoperitoneum at 15 mmHg causes lactic acidosis. *Surg Endosc* 1998; **12**: 198–201.
- 69 Rosário MT, Ribeiro U Jr, Corbett CE, Ozaki AC, Bresciani CC, Zilberstein B *et al.* Does CO₂ pneumoperitoneum alter the ultra-structure of the mesothelium? *J Surg Res* 2006; **133**: 84–88.
- 70 Tahara K, Fujii K, Yamaguchi K, Suematsu T, Shiraishi N, Kitano S. Increased expression of P-cadherin mRNA in the mouse peritoneum after carbon dioxide insufflation. *Surg Endosc* 2001; **15**: 946–949.
- 71 Suematsu T, Hirabayashi Y, Shiraishi N, Adachi Y, Kitamura H, Kitano S. Morphology of the murine peritoneum after pneumoperitoneum *vs* laparotomy. *Surg Endosc* 2001; **15**: 954–958.
- 72 Neuhaus SJ, Watson DI. Pneumoperitoneum and peritoneal surface changes: a review. *Surg Endosc* 2004; **18**: 1316–1322.
- 73 Wolf JS Jr, Carrier S, Stoller ML. Gas embolism: helium is more lethal than carbon dioxide. *J Laparoendosc Surg* 1994; **4**: 173–177.
- 74 Sammour T, Kahokehr A, Hill AG. Meta-analysis of the effect of warm humidified insufflation on pain after laparoscopy. *Br J Surg* 2008; **95**: 950–956.
- 75 Koster S, Spacek Z, Paweletz N, Volz J. [A scanning microscopy study of the peritoneum in mice after application of a CO₂-pneumoperitoneum.] *Zentralbl Gynakol* 1999; **121**: 244–247.
- 76 Erikoglu M, Yol S, Avunduk MC, Erdemli E, Can A. Electron-microscopic alterations of the peritoneum after both cold and heated carbon dioxide pneumoperitoneum. *J Surg Res* 2005; **125**: 73–77.
- 77 Puttick MI, Scott-Coombes DM, Dye J, Nduka CC, Menzies-Gow NM, Mansfield AO *et al.* Comparison of immunologic and physiologic effects of CO₂ pneumoperitoneum at room and body temperatures. *Surg Endosc* 1999; **13**: 572–575.
- 78 Cuschieri A. Adverse cardiovascular changes induced by positive pressure pneumoperitoneum. Possible solutions to a problem. *Surg Endosc* 1998; **12**: 93–94.
- 79 Andrei VE, Schein M, Wise L. Small bowel ischemia following laparoscopic cholecystectomy. *Dig Surg* 1999; **16**: 522–524.
- 80 Jaffe V, Russell RC. Fatal intestinal ischaemia following laparoscopic cholecystectomy. *Br J Surg* 1994; **81**: 1827–1828.
- 81 Gurusamy KS, Samraj K, Davidson BR. Abdominal lift for laparoscopic cholecystectomy. *Cochrane Database Syst Rev* 2008; (2)CD006574.
- 82 Junghans T, Böhm B, Gründel K, Schwenk W, Müller JM. Does pneumoperitoneum with different gases, body positions, and intraperitoneal pressures influence renal and hepatic blood flow? *Surgery* 1997; **121**: 206–211.

- 83 Glantzounis GK, Tsimaris I, Tselepis AD, Thomas C, Galaris DA, Tsimoyiannis EC. Alterations in plasma oxidative stress markers after laparoscopic operations of the upper and lower abdomen. *Angiology* 2005; **56**: 459–465.
- 84 London ET, Ho HS, Neuhaus AM, Wolfe BM, Rudich SM, Perez RV. Effect of intravascular volume expansion on renal function during prolonged CO₂ pneumoperitoneum. *Ann Surg* 2000; **231**: 195–201.
- 85 Lassen K. Intravenous fluid therapy. *Br J Surg* 2009; **96**: 123–124.
- 86 Abbas SM, Hill AG. Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. *Anaesthesia* 2008; **63**: 44–51.
- 87 Alishahi S, Francis N, Crofts S, Duncan L, Bickel A, Cuschieri A. Central and peripheral adverse hemodynamic changes during laparoscopic surgery and their reversal with a novel intermittent sequential pneumatic compression device. *Ann Surg* 2001; **233**: 176–182.
- 88 Schwenk W, Böhm B, Junghans T, Hofmann H, Müller JM. Intermittent sequential compression of the lower limbs prevents venous stasis in laparoscopic and conventional colorectal surgery. *Dis Colon Rectum* 1997; **40**: 1056–1062.
- 89 Millard JA, Hill BB, Cook PS, Fenoglio ME, Stahlgren LH. Intermittent sequential pneumatic compression in prevention of venous stasis associated with pneumoperitoneum during laparoscopic cholecystectomy. *Arch Surg* 1993; **128**: 914–918.
- 90 Isoda N, Suzuki T, Ido K, Kawamoto C, Nagamine N, Sohara H *et al.* Femoral vein stasis during laparoscopic cholecystectomy: effect of an intermittent sequential pneumatic compression device. *Digest Endosc* 2000; **12**: 225–228.
- 91 Schwenk W, Böhm B, Fügner A, Müller JM. Intermittent pneumatic sequential compression (ISC) of the lower extremities prevents venous stasis during laparoscopic cholecystectomy. A prospective randomized study. *Surg Endosc* 1998; **12**: 7–11.
- 92 Nicolaides AN, Miles C, Hoare M, Jury P, Helmis E, Venniker R. Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. *Surgery* 1983; **94**: 21–25.
- 93 Schwenk W, Haase O, Junghans T. Perspectives in sequential pneumatic compression of the lower extremities (SCD) for laparoscopic surgery. *Acta Chir Belg* 2002; **102**: 83–91.
- 94 Kurukahvecioglu O, Sare M, Karamercan A, Gunaydin B, Anadol Z, Tezel E. Intermittent pneumatic sequential compression of the lower extremities restores the cerebral oxygen saturation during laparoscopic cholecystectomy. *Surg Endosc* 2008; **22**: 907–911.
- 95 Bickel A, Drobot A, Aviram M, Eitan A. Validation and reduction of the oxidative stress following laparoscopic operations: a prospective randomized controlled study. *Ann Surg* 2007; **246**: 31–35.
- 96 Bickel A, Yahalom M, Roguin N, Ivry S, Breslava J, Frankel R *et al.* Improving the adverse changes in cardiac autonomic nervous control during laparoscopic surgery, using an intermittent sequential pneumatic compression device. *Am J Surg* 2004; **187**: 124–127.
- 97 Cisek LJ, Walsh PC. Thromboembolic complications following radical retropubic prostatectomy. Influence of external sequential pneumatic compression devices. *Urology* 1993; **42**: 406–408.
- 98 McGrory BJ, Burke DW. Peroneal nerve palsy following intermittent sequential pneumatic compression. *Orthopedics* 2000; **23**: 1103–1105.
- 99 Eisen A, Fisman EZ, Rubenfire M, Freimark D, McKechnie R, Tenenbaum A *et al.* Ischemic preconditioning: nearly two decades of research. A comprehensive review. *Atherosclerosis* 2004; **172**: 201–210.
- 100 Koti RS, Seifalian AM, Davidson BR. Protection of the liver by ischemic preconditioning: a review of mechanisms and clinical applications. *Dig Surg* 2003; **20**: 383–396.
- 101 Peralta C, Prats N, Xaus C, Gelpi E, Roselló-Catafau J. Protective effect of liver ischemic preconditioning on liver and lung injury induced by hepatic ischemia–reperfusion in the rat. *Hepatology* 1999; **30**: 1481–1489.
- 102 Künthscher MV, Hartmann B, Germann G. Remote ischemic preconditioning of flaps: a review. *Microsurgery* 2005; **25**: 346–352.
- 103 Sahin DA, Haliloglu B, Sahin FK, Akbulut G, Fidan H, Koken G *et al.* Stepwise rising CO₂ insufflation as an ischemic preconditioning method. *J Laparoendosc Adv Surg Tech A* 2007; **17**: 723–729.
- 104 Cevrioglu AS, Yilmaz S, Koken T, Tokyol C, Yilmazer M, Fenkci IV. Comparison of the effects of low intra-abdominal pressure and ischaemic preconditioning on the generation of oxidative stress markers and inflammatory cytokines during laparoscopy in rats. *Hum Reprod* 2004; **19**: 2144–2151.
- 105 Yilmaz S, Koken T, Tokyol C, Kahraman A, Akbulut G, Serteser M *et al.* Can preconditioning reduce laparoscopy-induced tissue injury? *Surg Endosc* 2003; **17**: 819–824.
- 106 Ates E, Yilmaz S, Ihtiyar E, Yasar B, Karahuseyinoglu E. Preconditioning-like amelioration of erythropoietin against laparoscopy-induced oxidative injury. *Surg Endosc* 2006; **20**: 815–819.
- 107 Altindis M, Yilmaz S, Polat C, Serteser M. Sequential periods of preconditioning decrease laparoscopy-related elevations in hepatic TNF-alpha and IL-6 levels in rats. *J Laparoendosc Adv Surg Tech A* 2004; **14**: 380–383.
- 108 Gudmundsson FF, Viste A, Myking OL, Grong K, Svanes K. Effects of the aldosterone receptor antagonist potassium canrenoate on renal blood flow and urinary output during prolonged increased intraabdominal pressure (IAP) in pigs. *Surg Endosc* 2004; **18**: 1528–1534.

- 109 Kim ZG, Sanli E, Brinkmann L, Lorenz M, Gutt CN. Impact of dopamine and endothelin-1 antagonism on portal venous blood flow during laparoscopic surgery. *Surg Endosc* 2002; **16**: 1292–1296.
- 110 Döslüoğlu HH, Aktan AO, Yeğen C, Okboy N, Yalçın AS, Yahn R *et al.* The cytoprotective effects of verapamil and iloprost (ZK 36374) on ischemia/reperfusion injury of kidneys. *Transpl Int* 1993; **6**: 138–142.
- 111 Karwinski W, Garcia R, Helton WS. Protective effects of the calcium channel blocker verapamil on hepatic function following warm ischemia. *J Surg Res* 1996; **64**: 150–155.
- 112 Cay A, Imamodlu M, Unsal MA, Aydin S, Alver A, Akyol A *et al.* Does anti-oxidant prophylaxis with melatonin prevent adverse outcomes related to increased oxidative stress caused by laparoscopy in experimental rat model? *J Surg Res* 2006; **135**: 2–8.