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REVIEW ARTICLE

Physiological Effects of Pneumoperitoneum

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Since its inception in the early 1980s, laparoscopy has become a widely accepted surgical approach. Smaller incisions impart several clinical benefits such as improved cosmesis, decreased pain, and an earlier return to preoperative activities.[1,2] Laparoscopy, however, requires the establishment of pneumoperitoneum, which alters certain physiologic functions. We will review the physiologic effects of pneumoperitoneum (Fig. 1).

Acid/Base The most commonly used gas for insufflation is carbon dioxide. It is noncombustible, rapidly soluble in the blood, and relatively inexpensive. Because carbon dioxide is the main by-product of cellular metabolism, humans have an efficient mechanism for its elimination. A small portion of CO_2 is dissolved in blood and is delivered directly to the lungs. The majority of CO_2 combines with water in red blood cells to form carbonic acid, which then dissociates into hydrogen and bicarbonate.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3$$

The produced hydrogen ions complex with hemoglobin, and the bicarbonate diffuses into the plasma. Carbon dioxide absorbed through the peritoneum is handled in the same manner and, ultimately, is eliminated by respiratory exchange in the lungs. Insufflation increases the delivery of CO_2 to the lungs by as much as 50%, which necessitates a compensatory increase in minute ventilation to maintain eucapnia. While under general anesthesia, minute ventilation volumes must be increased by up to 16% to maintain normocarbia.[3] Even if the increase in $PaCO_2$ is not fully compensated by hyperventilation, most healthy patients are easily able to adapt to the transient increase in end tidal CO_2 and slight decrease in pH by increasing by maximizing the use of their intracellular and plasma buffering systems and increasing the rate of CO_2 transport. Some patients, however, have less homeostatic reserve and are unable to tolerate the increased CO_2 load during insufflation. Patients particularly at risk are those with decreased pulmonary function (i.e., severe chronic obstructive pulmonary disease), reduced cardiac output, or a high metabolic and cellular respiratory rate (i.e., septic patients).[4] These patients require strict monitoring of end-tidal CO_2 and arterial blood pH to avoid significant hypercarbia and acidemia and subsequent complications.

Pulmonary Abdominal insufflation during laparoscopy affects intraoperative pulmonary mechanics. Increases in intraabdominal pressure and volume impede diaphragmatic movement resulting in decreased functional residual capacity and an increase in alveolar dead space. Postoperative pulmonary function tests reveal a significant reduction in forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF) and forced vital capacity (FVC).[5] Additionally, there is a rise in peak airway pressures, with a concomitant decrease in pulmonary compliance.[3,4,6–8] In patients allowed to breathe spontaneously during laparoscopy, these factors can lead to hypoxemia.[9] Controlled ventilation, especially with large tidal volumes, however, decreases the risk of hypoxemia by minimizing alveolar atelectasis and the resultant ventilation/perfusion mismatch.[10] The recruit-

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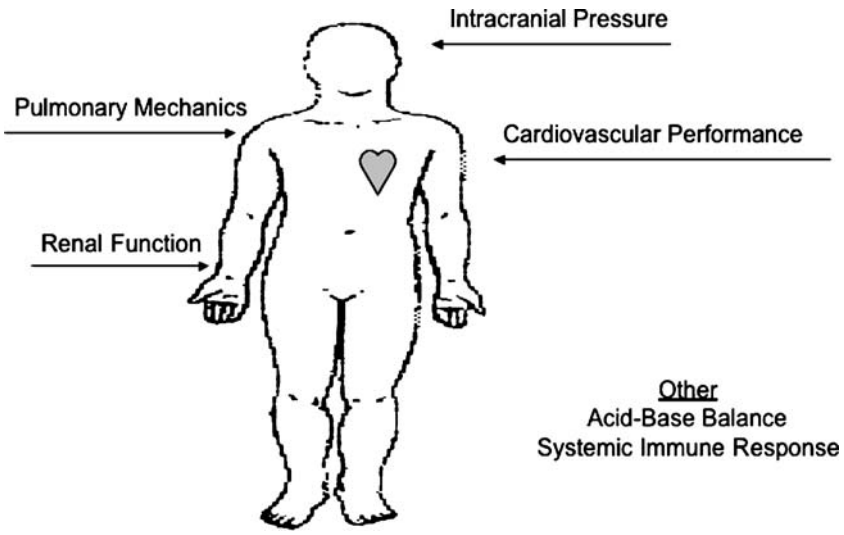

Figure 1 Pneumoperitoneum has effects on multiple organ systems.

ment of alveoli at the lung bases can be further enhanced with the addition of positive end-expiratory pressure (PEEP), though PEEP must be added with caution because of its cardiovascular effects (see below).

Though there are seemingly deleterious effects of laparoscopy to intraoperative pulmonary mechanics, these do not appear to be clinically relevant in most healthy patients.[11] Furthermore, there is abundant literature to suggest that the postoperative pulmonary status of patients is better after laparoscopy compared to after open operation. Schwenk et al.[12] evaluated pulmonary function tests (including FVC, FEV_1, and oxygen saturation) of patients before and after undergoing colon resection; either open or laparoscopically. Though all patients demonstrated depressed pulmonary mechanics postoperatively, those who had an open operation had significantly more impairment than patients in the laparoscopic group, even in light of a shorter operative time for the open operations. These changes in pulmonary function tests translated to worse outcomes. Pneumonia developed in two patients in the open group compared to none in the laparoscopic group, although this difference was not statistically significant.[12] Similar results were obtained by Hasukic et al.[5] in patients undergoing either a laparoscopic or open cholecystectomy. Patients who had an open cholecystectomy had significantly greater reduction in their FEV_1 and FVC from preoperative levels than those who had a laparoscopic cholecystectomy and had significantly more atelectasis (Table 1).[5]

Cardiac/Hemodynamic Insufflation alters cardiovascular performance because of both the effects of hypercarbia as well as the change in intraabdominal pressure. Mild hypercarbia (pCO_2 of 45–50 mmHg) has little effect on hemodynamics, whereas moderate to severe hypercarbia has both direct and indirect effects on cardiac function.[13] At a pCO_2 of 55–70 mmHg, hypercarbia and acidosis cause hemodynamic changes because of carbon dioxide's direct action on the cardiovascular system and because of its indirect effect on the autonomic system. Elevated CO_2 directly causes myocardial depression and vasodilation. These effects are counteracted by a centrally mediated sympathetic stimulation that causes tachycardia and systemic vasoconstriction. This catecholamine release effect predominates, as the overall observed effects of moderate hypercarbia include an increase in heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, cardiac output, and stroke volume.

The hemodynamic effects of chemical hypercarbia are minimal compared to those attributable to the mechanical effect of increased intraperitoneal pressure. The degree to which increased intraabdominal pressure affects hemodynamic function is dependent on several factors, including intravascular volume, level of intraabdominal pressure, and patient position. Data from animal studies demonstrated that an increase in intraabdominal pressure to 5 mmHg increased the cardiac output in all subjects, with mean arterial pressure and caval blood flow increasing only in normovolemic subjects. Further studies showed that in-

Table 1 Changes in Pulmonary Mechanics Because of Insufflation

Respiratory factor	Change
Functional residual capacity	Decrease
Alveolar dead space	Increase
Peak airway pressures	Increase
Pulmonary compliance	Decrease
Forced expiratory volume in 1 second (FEV_1)	Decrease
Forced vital capacity	Decrease
Peak expiratory flow	Decrease

creasing the intraabdominal pressure to 40 mmHg modulates venous resistance and mean systemic pressure, although these changes depend on intravascular volume and cardiac preload.[14,15] At low right atrial pressures, the inferior vena cava compresses, causing a decrease in venous return. At high right atrial pressures, however, the vena cava resists compression, and increased intraabdominal pressures serve to augment venous return.[15,16] Additionally, an increase in intraabdominal pressure results in compression of small capacitance vessels, which also increases venous return. Overall, in hypervolemic animals, cardiac output is augmented by the elevated mean systemic pressure and consequent increase in venous return. In contrast, in hypo- and normovolemic animals, the compression of the vena cava outweighs the increased mean systemic resistance resulting in a decreased cardiac output.

Clinically, the effects of insufflation on hemodynamic function depend on a multitude of patient factors; however, the majority of studies concur that laparoscopy causes a decrease in cardiac index and that this effect appears to be dependent on the level of intraabdominal pressure. Dexter et al.[17] randomized patients to insufflation pressures of either 7 or 15 mmHg during laparoscopic cholecystectomy. Heart rate and mean arterial pressure increased in both groups, but stroke volume and cardiac output were significantly more depressed in the high-pressure group.[17] In a study by McLaughlin et al.,[18] intraabdominal pressure of 15 mmHg caused a 30% decrease in cardiac output (CO) and stroke volume (SV) and a 60% increase in mean arterial pressure (MAP) from pre-insufflation levels, and these changes were determined to be statistically significant.[18] Kraut et al.[19] demonstrated a measurable, but not significant, decrease in cardiac output and stroke volume at insufflation pressures of 15 mmHg. The addition of a 10-cm^2 PEEP, however, exaggerated these reductions to a statistically significant level. The authors, therefore, concluded that humans tolerate an intraabdominal pressure of 15 mmHg or 10 cm^2 of PEEP, but the combination should be avoided.[19]

Patients are often put in the head-up or head-down position to facilitate visualization during laparoscopy. These changes in patient position can also alter hemodynamic function. In a study by Williams and Murr,[20] dogs undergoing laparoscopy had a measurable decrease in cardiac output during insufflation. This reduction was enhanced by placing the dogs in the head-up position. In contrast, at the same level of intraabdominal pressure, dogs positioned in the head-down position had a smaller reduction in cardiac output than those in the horizontal position.[20] Joris et al.[21] measured the hemodynamic changes in patients undergoing laparoscopic cholecystectomy. Positioning the patient in the head-up position reduced the mean arterial pressure by 17% and the cardiac index by 14% compared to the horizontal position. The addition of insufflation to 14 mmHg increased the mean arterial pressure by 37%, but decreased the cardiac output an additional 18%. The combined effect of insufflation and reverse Trendelenburg positioning was a reduction of cardiac index with an unchanged mean arterial pressure. When patients are placed in the Trendelenburg position, cardiac output tends to increase, reflecting an increase in central venous pressure compared to the horizontal position that counteracts the effects on insufflation.[22]

Despite the measurable hemodynamic changes resulting from insufflation and patient position, when the standard 15-mmHg insufflation pressure is employed, these effects do not appear clinically relevant. Indeed, the European Association of Endoscopic Surgeons affirmed, in their clinical practice guidelines from 2001, that when using pressures up to 15 mmHg, the decrease in cardiac output is minimal and without clinical consequence in healthy patients.[23]

Patients with underlying cardiac disease require special consideration when undergoing laparoscopy. Increases in heart rate and afterload, in conjunction with elevated systemic vascular resistance (SVR), have the potential to increase ventricular wall tension, creating a risk of myocardial ischemia. Safran et al.[24] investigated the effects of laparoscopy on patients with severe (American Society of Anesthesiologists class III or IV) heart disease. They indeed noted significant elevations in MAP and SVR and a significant reduction of CO when patients were insufflated to an intraperitoneal pressure of 15 mmHg. In about half of the patients, this increase in intraperitoneal pressure led to a decrease in oxygen delivery accompanied by significant increases in pulmonary artery pressures. The authors concluded that, in these patients, insufflation caused a transient cardiac decompensation because of inadequate left ventricular reserve.[24] In one clinical series, hemodynamic parameters in patients with severe cardiac dysfunction were measured during laparoscopic cholecystectomy. MAP, SVR, and pulmonary artery occlusion pressure increased significantly during insufflation, and three of 17 patients required nitroglycerin to treat blood pressure alterations occurring during pneumoperitoneum.[25] In neither of these studies, however, were there any intraoperative or postoperative long-term cardiac complications, and no patients required conversion to an open procedure. Though laparoscopy does appear to be safe in patients with cardiac disease, these patients require special attention and likely require additional intraoperative monitoring (Table 2).

Renal An increase in intraabdominal pressure has long been known to affect the renal system, specifically, renal blood flow (RBF) and glomerular filtration rate (GFR). Though these effects are certainly influenced by the

Table 2 Changes in Hemodynamics Because of Insufflation with CO_2

Hemodynamic parameter	Change with hypercarbia	Change with increased intraabdominal pressure
Heart rate	Increase	Increase
Mean arterial pressure	Increase	Increase
Central venous pressure	Increase	Increase or decrease[a]
Stroke volume	Increase	Decrease
Cardiac output	Increase	Increase or decrease[a]

[a] Change depends on intravascular volume status

hemodynamic changes caused by an increase in intraperitoneal pressure, they are not entirely dependent on the decrease in cardiac output. Early studies on humans showed that an external compression of the abdomen to an intraabdominal pressure of 20 mmHg reduced both urine production and GFR.[26] Harman et al.[27] studied the effects of intraabdominal pressure by inflating intraperitoneal bags in dogs, thereby increasing their intraabdominal pressure. At a pressure of 20 mmHg, RBF and GFR were reduced to less than 25% of baseline values, with a concomitant decrease in cardiac output. When the cardiac output was returned to baseline with a volume expander, the renal effects persisted, indicating that the renal effects were independent of the hemodynamic changes.[27]

Insufflation during laparoscopy has similar effects. RBF has been evaluated in animal models with many different measurement techniques. The majority of studies indicate that RBF decreases with insufflation. Shuto et al.[28] looked at RBF in pigs undergoing laparoscopy with either helium or carbon dioxide insufflation. They demonstrated a significant decrease in RBF with an insufflation pressure of 20 mmHg, independent of the type of gas used.[28] A similar study using nitrogen as insufflant resulted in a significant decrease in RBF at pressures of 15 or 20 mmHg.[29] Though the effects of insufflation do not depend on the type of gas used, they do appear to correlate with the degree of intraabdominal pressure. Chiu et al.[30] measured the RBF in pigs undergoing insufflation at varying levels of intraabdominal pressure. They observed a gradual reduction in RBF with increasing levels of intraabdominal pressure, with a 75% reduction by 15 mmHg pressure.[30] The exact mechanism by which RBF is affected by pneumoperitoneum has not been elucidated. It does appear to be influenced by volume status, as aggressive fluid hydration can attenuate the reduction in RBF. In a study performed by London et al.,[31] pigs underwent laparoscopy with an intraabdominal pressure of 15 mmHg. They were hydrated with either maintenance fluids, bolus fluids, or hypertonic saline, and RBF was measured using a renal artery flow probe. Those pigs receiving only maintenance fluids had a 30% reduction in their RBF, which was not seen in the pigs more aggressively hydrated.[31]

In addition to decreasing RBF, insufflation affects renal function. GFR is the most accurate measure of renal function, but is difficult to measure in the acute setting.[32] Creatinine clearance, urine output, and serum creatinine have all been used as surrogate markers to assess renal function during laparoscopic procedures. Additionally, urinary *N*-acetyl-B-D-glucosaminidase (U-NAG), a sensitive marker for renal tubulular cell damage, has been measured to assess structural injury to the kidney. The majority of data from animal studies shows a transient decline in renal function during insufflation.[33–35] A study performed by Kirsch et al.,[35] for example, examined the effects on insufflation to a pressure of 5 or 10 mmHg on urine output and serum creatinine in rats. There was a significant decrease in urine output and a significant increase in serum creatinine at an intraabominal pressure of 10 mmHg. These effects, however, were temporary, as urine output returned to baseline by 22 h after desufflation and serum creatinine normalized by 2 h after desufflation.[35] Additionally, examination of kidneys procured after exposure to pneumoperitoneum has, by and large, failed to show any significant histologic damage, in both the short and long term.[36,37] Studies performed in humans corroborate the animal data. There is a measurable decrease in urine output in patients who are exposed to insufflation.[38–40] There is no clear effect on serum creatinine or U-NAG, indicating that the oliguria occurring intraoperatively has little or no postoperative significance.[38,41]

The cause of the decreased renal function seen during insufflation appears to be multifactorial. There is a clear component of vascular and parenchymal compression, but there is also evidence that vasopressin levels are increased during pneumoperitoneum.[42,43] The relative decrease in right atrial volume because of the reduced preload during insufflation induces the release of vasopressin. Vasopressin then acts on the distal tubule and collecting ducts of the kidney to promote reabsorption of water and the formation of more concentrated urine. Indeed, blocking the effects of vasopressin using an antagonist to the vasopressin receptor partially reversed the oliguria seen in rats during insufflation.[44]

RBF and renal function are affected by pneumoperitoneum, but these changes do not appear to be clinically deleterious or have long-term sequelae on kidney function or histology. Knowledge of the effects of insufflation is, however, important to effectively monitor and maintain an appropriate fluid balance for patients during laparoscopy (Table 3).

Table 3 Renal Effects of Insufflation with CO_2

Renal Parameter	Change
Urine output	Decrease
Glomerular filtration rate	Decrease
Renal blood flow	Decrease
Serum creatinine	Increase or No Change
Vasopressin	Increase

Intracranial Pressure Laparoscopy has a well-documented impact on intracranial pressure (ICP). Several animal studies have demonstrated that the induction of pneumoperitoneum provokes a measurable increase in ICP.[45,46] The rise in ICP appears to be independent of arterial pH (and therefore carbon dioxide effects), oxygenation, or mean arterial pressure.[46] The increase in ICP is seen even at low (8 mmHg) abdominal pressures and is especially pronounced in animals with baseline elevated ICP.[47] Trendelenburg position worsens the increase in ICP during insufflation, but reverse Trendelenburg does not eliminate the observed increase.[45] The exact mechanism by which intraabdominal pressure affects ICP has not been elucidated, but it appears to be multifactorial. The Monroe–Kellie doctrine states that the bony skull contains three elements: parenchymal tissue, arterial and venous blood, and cerebrospinal fluid (CSF) in a dynamic equilibrium. With a rapid change in the volume of any of these components, ICP rises. It has been proposed that increased intraabdominal and intrathoracic pressure as well as impaired CSF absorption during insufflation impedes drainage of the lumbar venous plexus and induces an increase in the vascular compartment of the sacral space causing the rise in ICP.[45,48] Additionally, hypercarbia is known to cause cerebral vasodilation, which causes an increased ICP. The peritoneal absorption of carbon dioxide may induce such a vasodilation, exacerbating intracerebral hypertension. In most healthy patients without preexisting intracranial disease, the increase in ICP is without clinical consequence. However, laparoscopy is being considered and used more frequently in critically ill and traumatized patients. Until these effects have been more completely described, caution is in order.

Immune System The trauma of surgery stimulates the systemic immune and inflammatory responses. These responses appear to be different, however, depending on whether the surgical approach is open or laparoscopic. Originally, the immune modification seen with laparoscopy was attributed entirely to the smaller size of the incisions, with a proportionally reduced degree of trauma. There is also compelling data to indicate that insufflation, and, specifically, carbon dioxide insufflation, plays a role.

Acute-Phase Reaction Acute-phase proteins are produced in response to tissue injury. C-reactive protein (CRP) is one of the most thoroughly studied markers of the acute-phase response to surgery. It rises 4 to 12 h after surgery, peaks at 24–72 h, and remains elevated for about 2 weeks.[49] Many studies have shown that the CRP does not reach the same elevated levels after laparoscopic procedures compared to open surgery.[49] Whether this is because of incision size or carbon dioxide insufflation was investigated by Sietses et al.[50] in 2002. They examined patients undergoing cholecystectomy, either with carbon dioxide insufflation, helium insufflation, or with an abdominal wall lifting technique. They noted that CRP levels were significantly higher in the helium and abdominal wall lifting groups, indicating that incision size alone was not responsible for the altered CRP response.[50] Similar findings were seen in an animal model when the rat acute-phase proteins α2-macroglobulin and β-fibrinogen were evaluated in response to abdominal sepsis.[51] Rats underwent cecal ligation and puncture either open or laparoscopically using either carbon dioxide or helium insufflation. The expression of the genes for α2-macroglobulin and β-fibrinogen were significantly lower in the rats with carbon dioxide insufflation compared to those with laparotomy or helium insufflation. These and other studies demonstrate that carbon dioxide insufflation is a key component to the attenuated inflammatory response after laparoscopy.

Cytokines The cytokine response to laparoscopy has been thoroughly investigated. Interleukin 6 (IL-6) is the major cytokine responsible for the acute-phase protein response. It is an early marker of tissue damage and its levels rise in proportion to tissue trauma. Like CRP, IL-6 levels do not reach levels as high in patients undergoing laparoscopic procedures compared to open procedures.[49] In a prospective trial, patients undergoing laparoscopic cholecystectomy had significantly lower IL-6 response than those who had a conventional, open cholecystectomy up to 2 days postoperatively.[52] Similar responses were seen after colon resection, with patients undergoing laparoscopic colectomy exhibiting a significantly reduced IL-6 release when compared with those undergoing an open colectomy.[27] The reduction in IL-6 response appears to be influenced specifically by CO_2 insufflation. Ure et al.[53] showed that pigs insufflated with carbon dioxide had a significantly lower release of IL-6 compared to those insufflated with air.

Further studies have shown that other cytokines are also influenced by the carbon dioxide environment of laparoscopy. West et al.,[54] investigated the release of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and IL-1 in macrophages incubated in different environments and stimulated with lipopolysaccharide (LPS). The release of these cytokines was significantly

lower in those cells incubated in carbon dioxide as compared to helium or air.[54] Similar results were seen in an in vivo experiment in which rats stimulated with intravenous LPS were either not insufflated or insufflated with helium or carbon dioxide. Those animals exposed to CO_2 pneumoperitoneum had a significantly lower level of TNF-α than the control animals. Furthermore, those animals insufflated with carbon dioxide had an even lower level of TNF-α than those insufflated with helium.[55] These results all suggest that there is a modulation of the pro-inflammatory response with carbon dioxide insufflation.

Bacterial Clearance There is continued debate over whether there is an increased occurrence of infectious complications and tumor spread with laparoscopic procedures compared to open laparotomy. Because of this debate, there has been active investigation of the phagocytic capability and immune response of intraperitoneal cells to carbon dioxide pneumoperitoneum with no clear consensus yet reached. Watson et al.[56] examined the phagocytic activity of murine peritoneal macrophages during laparotomy or laparoscopy with either air or carbon dioxide and found the macrophages from mice insufflated with carbon dioxide had significantly better phagocytic capacity than the other groups.[56] Gutt et al.,[57] however, had different results. They studied the function of the mononuclear phagocyte system (MPS) during open fundoplication, laparoscopic fundoplication using carbon dioxide, or gasless laparoscopic fundoplication in rats. They evaluated the MPS function using a carbon clearance test and noted the best carbon clearance in the gasless laparoscopy group and the worst carbon clearance in the carbon dioxide laparoscopy group.[57] Finally, in a randomized trial in human patients undergoing upper gastrointestinal laparoscopic surgery with either helium or air, type of insufflation gas did not affect macrophage phagocytosis.[58] Thus, this is still an important open question.

Overall, the effects of carbon dioxide insufflation on the stress response continue to be discovered. It seems to be one of a blunted inflammatory response compared to open procedures. There are divergent data on the effect of carbon dioxide on other peritoneal macrophage immune functions and no convincing evidence that insufflation increases the incidence of or protects from postoperative infections. The clinical consequences of the immune alterations seen during laparoscopy continue to be investigated (Fig. 2).

Conclusion

As surgeons, we are exposing millions of patients each year to operations that involve the placement of gas (usually CO_2) under pressure in various, and sometimes multiple, body cavities. General clinical experience suggests that there are no obvious dire or hugely beneficial effects of this. However, we owe it to our patients to understand the biology of this dramatic change in our mode of surgery. This is particularly true, as laparoscopic operations become longer, more complex, and take place in less healthy patients. We have reviewed some of the key laboratory findings to date in this important emerging field.

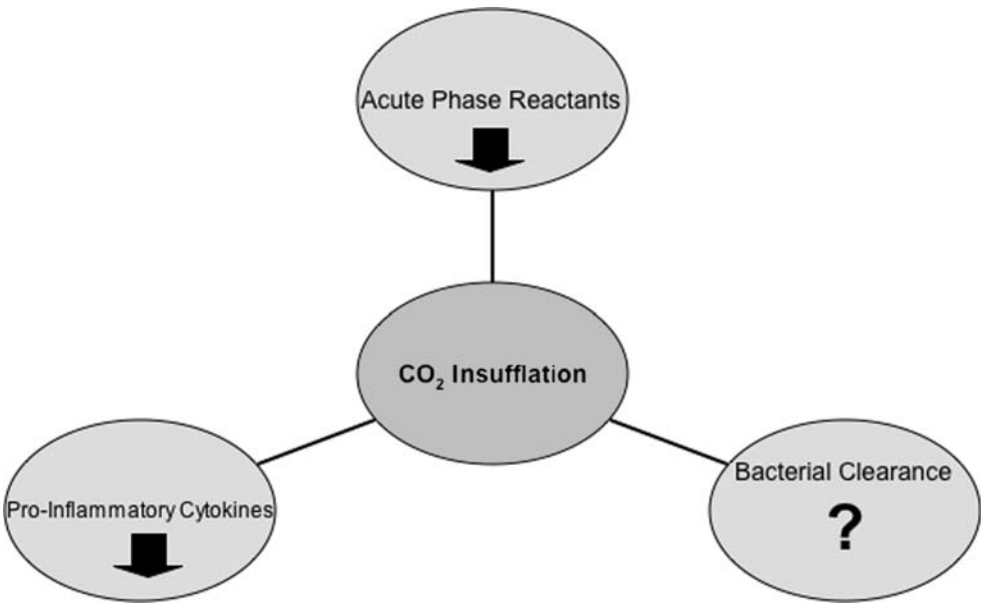

Figure 2 The proposed effect of carbon dioxide insufflation on the systemic inflammatory response compared to either open operation or laparoscopy using helium, air, or abdominal wall lifting technique.

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