A Prospective Randomized Study of Systemic Inflammation and Immune Response After Laparoscopic Nissen Fundoplication Performed With Standard and Low-pressure Pneumoperitoneum

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Background: The aim of this study was to compare changes in the systemic inflammation and immune response in the early postoperative (p.o.) period after laparoscopic Nissen fundoplication (LNF) was performed with standard-preassure and low-pressure carbon dioxide pneumoperitoneum.

Materials and Methods: We studied 68 patients with documented gastroesophageal reflux disease and who underwent a LNF: 35 using standard-pressure (12 to 14 mmHg) and 33 low-pressure (6 to 8 mmHg) pneumoperitoneum. White blood cells, peripheral lymphocites subpopulation, human leukocyte antigen-DR, neutrophil elastase, interleukin (IL)-6 and IL-1, and C-reactive protein were investigated.

Results: A significantly higher concentration of neutrophil elastase, IL-6 and IL-1, and C-reactive protein was detected postoperatively in the standard-pressure group of patients in comparison with the low-pressure group ($P < 0.05$). A statistically significant change in human leukocyte antigen-DR expression was recorded p.o. at 24 hours, as a reduction of this antigen expressed on monocyte surface in patients from standard group; no changes were noted in low-pressure group patients ($P < 0.05$).

Conclusions: This study demonstrated that reducing the pressure of the pneumoperitoneum to 6 to 8 mm Hg during LNF is reduced p.o. inflammatory response and avoided p.o. immunosuppression.

Key Words: laparoscopic Nissen fundoplication, standard-pressure/low-pressure pneumoperitoneum, immune response

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Gastroesophageal reflux disease (GERD) is one of the most common disorders. In the western world, it is extremely common; over 30% of the general population suffers from at least monthly reflux episodes. GERD may lead to the development of serious complications, including ulcers, strictures, bleeding, Barrett esophagus, and eventually, adenocarcinoma of the esophagus.[1–3]

Accepted indications for antireflux surgery are persistent regurgitation despite adequate medical therapy, incomplete response to acid-suppressing drugs in patients with proven reflux, and unwillingness to take lifelong medication.[4–6]

Since 1991, the laparoscopic Nissen fundoplication (LNF) has shown physiological results similar to those of the open technique[7–8] and is the most frequently performed operation for GERD.[9] Several randomized studies have demonstrated that LNF has similar 5-[10] and 10-year[11] rates for disease control compared with open fundoplication. LNF has been recommended as the surgical therapy of choice by the European Study Group for Antireflux Surgery[12] and the Society of American Gastrointestinal Endoscopic Surgeons.[13] Its advantages over open Nissen fundoplication, such as lower surgical stress, shorter hospitalization period, and quicker recovery are undeniable.[6] As the technique improved, the number of implications for laparoscopy has grown and the number of contradictions decreased.

Nevertheless, laparoscopy is not devoid of disadvantage, mostly because of carbon dioxide (CO_2) pneumoperitoneum used during standard technique laparoscopic procedures. The CO_2 and higher abdominal pressure adversely affect the patient's homeostasis, causing significant changes in cardiovascular and respiratory systems, decreasing perfusion in abdominal organs and blood flow in inferior vena cava, and causing increased risk of thrombotic disease.[14] It has been also suggested by some authors that CO_2 pneumoperitoneum may have an unfavorable effect on the local immune response.[15–17] Peritoneal macrophages seem to produce fewer cytokines, and their intrinsic function (phagocytosis) diminishes in the presence of CO_2.[18–19] Many studies have evaluated the effect of the degree of surgical trauma and different anesthetic agents on immune response.[15,16,20–24] There have, however, been only few studies conducted that compared standard-pressure and low-pressure CO_2 pneumoperitoneum laparoscopy with respect to immune response.[25,26] Moreover, we could not find any effect of various degree of intra-abdominal pressure during LNF. The aim of this prospective randomized study was to compare changes in the systemic inflammation and immune response in the early postoperative (p.o.) period after LNF was performed with standard-pressure and low-pressure CO_2 pneumoperitoneum.

MATERIALS AND METHODS

From February 2009 to February 2011, we studied, in a prospective randomized manner, 68 patients consecutively

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The authors declare no conflicts of interest.

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TABLE 1. Characteristics of Patients

Parameters	Standard Intra-Abdominal Pressure (12-14 mm Hg)	Low Intra-Abdominal Pressure (6-8 mm Hg)
No. patients	35	33
Age (y), mean (range)	56.2 (39-71)	55.4 (42-70)
Sex (F/M)	19/16	18/15
ASA* grade		
I	23	21
II	12	12
Anesthesia minimum, mean (range)	41.4 (34-66)	42.3 (31-62)
Operative time minimum, mean (range)	40.1 (29-61)	40.8 (27-57)
Postoperative complications	—	—
Postoperative hospitalization (d), mean (range)	2.3 (2-3)	2.4 (2-3)

ASA indicates American Society of Anesthesiology.

(37 men, 31 women; mean age 56 y) with documented GERD who underwent a LNF.

Criteria for exclusion were: endocrine or immune systemic disorders; hematologic disorders; anticoagulant treatment; current or recent (6 mo) thromboembolic disorders; renal, hepatic, rheumatic or vascular disorders; pregnancy; recent (6 mo) surgery; current or recent (3 y) malignancy; chronic inflammatory disease; and marked obesity (body mass index $>36\,kg/m^2$). We also excluded patients taking corticosteroids drugs or others drugs, which may affect their immunologic responses.

Patients were randomly assigned to 2 groups.

Thirty-five patients (19 men, 16 women; mean age 56.2 y) (Table 1) underwent standard LNF (group 1).

The remaining 33 patients (18 men, 15 women; mean age 55.4 y) (Table 1) were operated on using a low-pressure CO_2 pneumoperitoneum laparoscopy technique (group 2).

The LNF was performed by the same team of surgeons in each case, using the same surgical technique and 4 trocars. CO_2 pneumoperitoneum was established with open laparoscopy. In the standard laparoscopy group, intra-abdominal pressure of 12 to 14 mm Hg was maintained throughout the procedure, whereas in patients from the second group, pressure of 6 to 8 mm Hg was applied to perform surgery. There were no differences in total dose (volume) of insufflated CO_2 between the 2 groups.

The study protocol was approved by the Ethics Committee of the Faculty of Medicine of the University of L'Aquila, and informed consent was obtained from every patient. The patients were classified as grade I or II, according to the American Society of Anesthesiologists (ASA) grading system.[27] Anesthesia was obtained in both groups using the same procedure. Preanesthesia was accomplished using atropine (0.01 mg/kg) plus promethazine (0.5 mg/kg); induction using sodium thiopental (5 mg/kg) and atracurium (0.5 mg/kg), and tracheal intubation and assisted ventilation using nitrogen dioxide (NO_2)/oxygen (O_2) (2:1). After intubation, anesthesia was maintained with O_2 in air, sevoflurane, and remifentanil (0.25 μg/kg/min).

No patients were converted to an open procedure. As presented in Table 1, age, sex, ASA grades, time of anesthesia and operation, and p.o. hospitalization stay were comparable in the 2 groups.

Venous blood samples were taken from all patients before the surgery, and 6, 24, and 48 hours from the beginning of the operation. Serum concentration of interleukin (IL)-1 (IL-1) and IL-6 were measured at 0, 30, 60, 90, 120, and 180 minutes and at 4, 6, 12, 24, and 48 hours p.o..

All samples were tested for total white blood cells (WBC) count and WBC population (neutrophils, total lymphocytes), T-helper lymphocytes (CD4), T-suppressor lymphocytes (CD8), natural killer lymphocytes (CD16 and CD56), pan B-cell antigen (CD20), T cell receptor γ/δ, and the T-helper/T-suppressor ratio (CD4/CD8).

Human leukocyte antigen-DR (HLA-DR) of peripheral monocytes were measured by cytofluorimetric method. All blood samples (10 mL) were collected with ethylene diamine tetracetic acid (0.5 mL). A monoclonal antibody for the HLA-DR antigen, coniugated with fluoresceinisothiocyanate (10 μL) was added. Whole blood (100 μL) from each patients was then used, and the tubes were stirred with vortex and stored at 4°C for 30 minutes. Two milliliters of lysing solution were added to each sample. All samples were stirred and then incubated for 15 minutes at room temperature. Finally, an ortho cytofluorimeter was used for the assay.

Elastase concentration was determined photometrically, using an immune-activation immunoassay (Merck, Damstadt, Germany), as a complex with α_1-proteinase inhibitor, according to the method described by Hafner et al.[28]

The plasma concentration of C-reactive protein (CRP) was measured using a competitive CRP enzyme-linked immunosorbent assay (ELISA) kit.

Serum concentration of IL-1 and IL-6 were measured using a quantitative "sandwich" ELISA kit (R&D System, MI), according to the manufacturer's description (range, IL-1 β-3.9 to 250 pg/mL; IL-6-3.13 to 300 pg/mL). Samples of serum (100 μL) were dispensed into wells of 96-well microlitre plates, which had been coated with the relevant monoclonal cytokine antibody. After incubation for 2 hours at room temperature, unbound proteins were washed away from the wells to which subsequently an enzyme-linked antibody was added, directed against the relevant cytokine for another 2 hours at room temperature. After further rinsing to remove unbound antibody, a substrate solution was added to each well and the mixture were incubated for 20 minutes at 37°C. The reaction was terminated with the addition of a stop solution. Adsorbance was determined by using an ELISA plate reading at 450 nm. Serial dilution of the relevant recombinant cytokine provided the standard curve. Assays were performed on duplicate samples. Samples were diluted appropriately with the diluent provided in the kit, if the levels of neat samples were beyond the linear measuring range.

Statistical Analysis

A statistical analysis was performed using Student t test, and P values of <0.05 were considered to be significant. The values were expressed as the mean and SD. Areas under the curves (Figs. 3–5) in 2 groups were compared using the Mann-Whitney U test. The magnitude of

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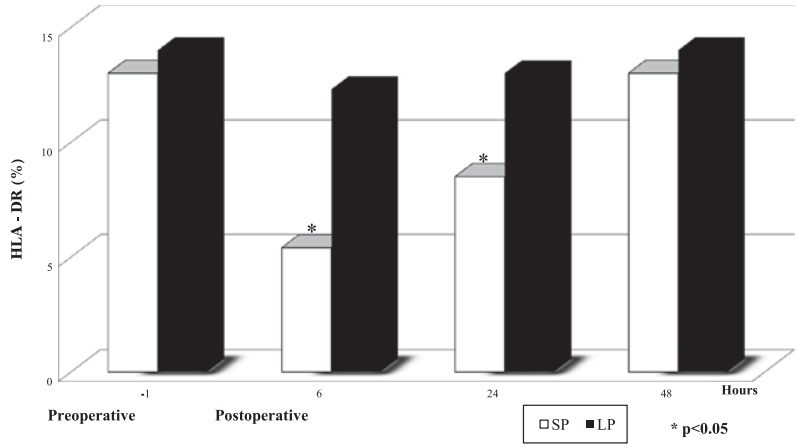

FIGURE 1. Human leukocyte antigen-DR (HLA-DR) expression (mean ± SD) in the standard-pressure (SP) versus low-pressure (LP) pneumoperitoneum laparoscopy. *$P < 0.05$ (6 and 24 h).

changes in each metabolic variable (areas under the curve) were compared by the Pearson correlation coefficient (r). An α-adjustment according to Bonferroni-Holm was applied when appropriate.

RESULTS

P.o. hospitalization, time of anesthesia, and operation were comparable in the 2 groups (Table 1). No complications were present during the surgeries or in the p.o. period. During the p.o. period, no differences in the biochemical or hematological parameters were found.

Median body temperature and WBC was similar in both the groups on the first 2 days of p.o. care. Other WBC types showed no significant variation. With respect to lymphocyte subpopulation, there were no differences between the 2 groups of patients before and after operation.

A statistically significant change in HLA-DR expression was recorded p.o. at 6 and 24 hours, as a reduction of this antigen expressed on monocyte surfaces in patients from standard group when compared with low-pressure CO_2 group (Fig. 1) ($P < 0.05$). In the standard group, HLA-DR expression returned to normal values within 2 days after operation. Finally, the ages of the patients did not affect HLA-DR expression in either group.

A statistically significant change in plasma elastase concentration was recorded p.o. at 6 and 24 hours, as there was an increase of this neutral proteinase in patients from standard group when compared with low-pressure CO_2 group (Fig. 2) ($P < 0.05$). In the standard group, plasma elastase concentration returned to normal values within 48 days after operation. Finally, the age of patients did not affect neutrophil elastase concentration in either group.

Before the operation, the serum levels of IL-1 and IL-6 had no significant difference between the 2 groups. Figures 3 and 4 shows the chronological change in the serum level of IL-1 and IL-6 after surgery. In the standard group, the serum IL-1 and IL-6 levels began to significantly increase as early as 1 hour from the beginning of the operation, revealing a peak at the sixth hour (approximately 4 h after the operation) and, thereafter, declining to preoperative levels by 48 hours. In contrast, in the low-pressure CO_2 group patients, the increase in the serum IL-1 and IL-6 was delayed and the peak values were significantly lower than these in the standard group ($r > 0.75$, $P < 0.05$).

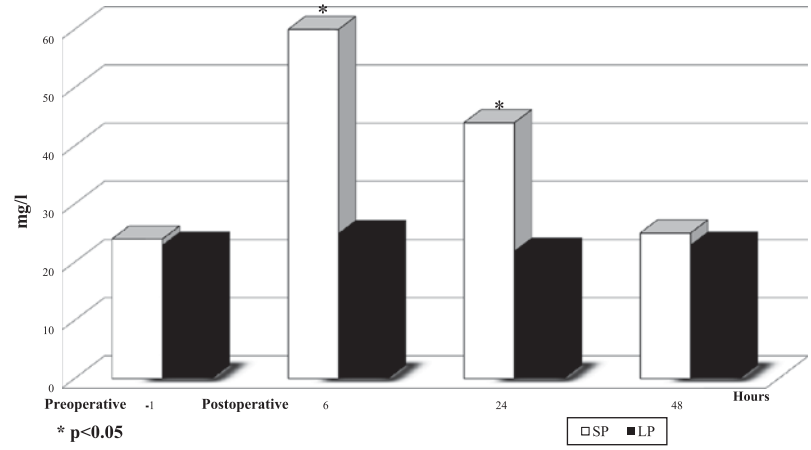

FIGURE 2. Plasma elastase concentration (mean ± SD) in the standard-pressure (SP) versus low-pressure (LP) pneumoperitoneum laparoscopy. *$P < 0.05$ (6 and 24 h).

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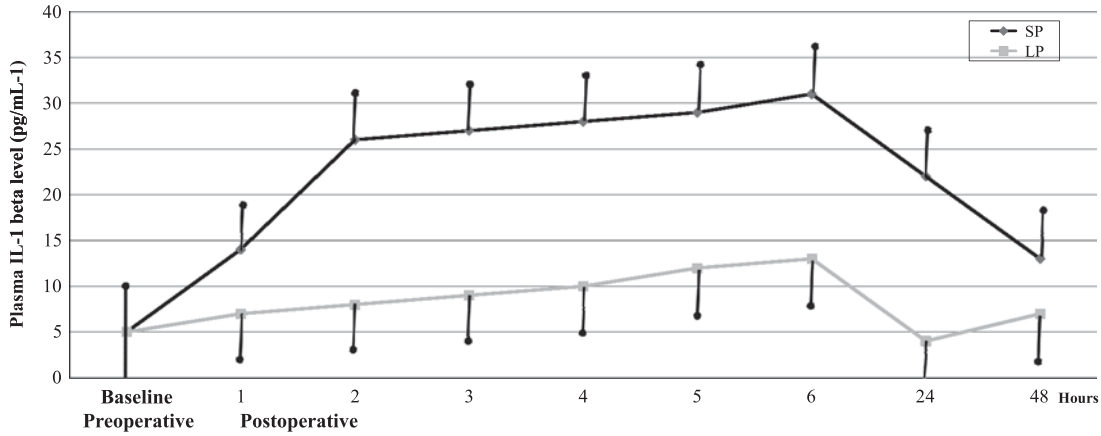

FIGURE 3. Interleukin-1β levels in the standard-pressure (SP) versus low-pressure (LP) pneumoperitoneum laparoscopy. There were significant differences between the 2 groups: $r > 0.75$, $P < 0.05$ (Mann-Whitney *U* tests and Pearson correlation coefficient).

The mean values of the serum CRP on p.o. days were also lower in the low-pressure CO_2 group when compared with those in the standard group ($r > 0.69$, $P < 0.05$) (Fig. 5). In this case, CRP concentration returned to normal values within 48 hours after operation.

Follow-up after 1, 6, and 12 months, a routine procedure for all patients who underwent LNF in our hospital, showed 2 simple infections (grade I) of standard group wound.

DISCUSSION

LNF is nowadays considered the treatment of choice for symptomatic GERD.[11,29] Performed at first in 1991,[30,31] LNF rapidly became the elective surgical procedure in the United States[5,32] and Europe.[33,34]

When compared with open Nissen fundoplication, LNF presents several advantages, such as reduced p.o. pain, prompt p.o. bowel activity (6 to 24 h after operation), reduced hospitalization (1 to 2 d), earlier return to work, better esthetic results, and reduced p.o. infections.

Although laparoscopy is "minimally invasive," systemic immune response is still invariably activated.[21] Overall, responses to surgery in general are reflected in terms of cytokine function and cellular messenger systems, although cytokine levels do not directly reflect immune status, they give us a framework to understand systemic immunity in terms of underlying immune activation. Because alterations are proportional to the extent of injury, the physiological response to minimally invasive surgery may, intuitively, be different than those for traditional open surgery. The acute-phase protein response appears to be 1 example.[35] The cytokines IL-1, tumor necrosis factors, and IL-6 are known to be major mediators of acute-phase response.[36] IL-6 plays a central role in the acute phase of inflammation seen after surgery.[37,38] IL-6 induces the production of acute-phase protein, such as CRP in hepatocytes[35] and also causes fever.[39] It has been reported that surgical stress causes the serum IL-6 level to increase and that the extent of such an increase is closely correlated to the subsequent increase in the serum CRP levels.[38] CRP rise approximately 4 to 12 hours after surgery and peaks at 24 or 72 hours. Subsequently, CRP remains elevated for approximately 2 weeks.[38] The acute-phase response after LNF has been studied in several clinical trials.[40] IL-6 levels have been noted to be reduced in patients undergoing

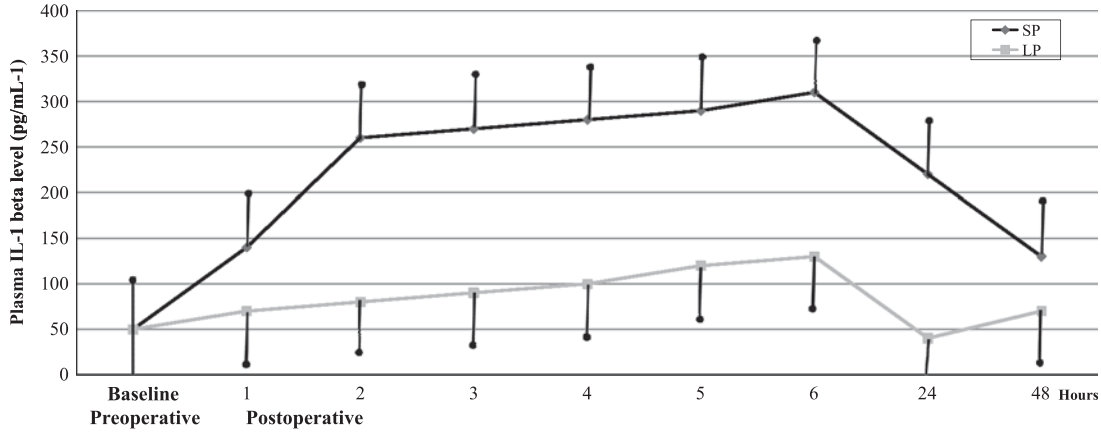

FIGURE 4. Interleukin-6 levels in the standard-pressure (SP) versus low-pressure (LP) pneumoperitoneum laparoscopy. There were significant differences between the 2 groups: $r > 0.75$, $P < 0.05$ (Mann-Whitney *U* tests and Pearson correlation coefficient).

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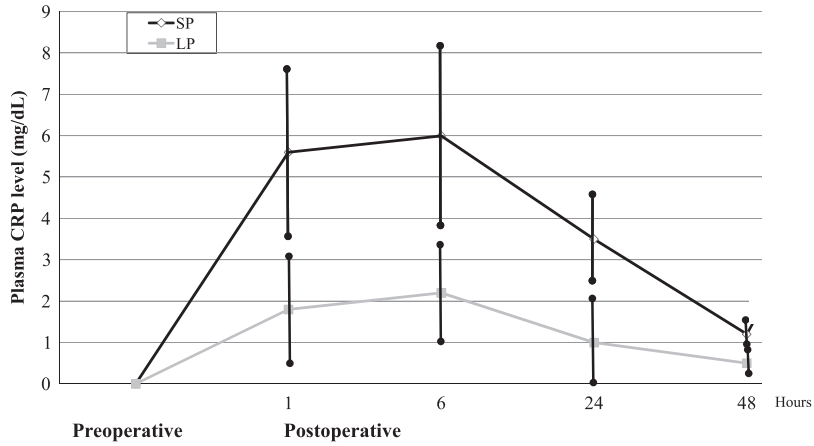

FIGURE 5. Plasma concentration (mean ± SD) of C-reactive protein (CRP) in the standard-pressure (SP) versus low-pressure (LP) pneumoperitoneum laparoscopy. There were significant differences between the 2 groups: $r > 0.69$, $P < 0.05$ (Mann-Whitney *U* tests and Pearson correlation coefficient).

laparoscopic procedures compared with traditional laparotomy.[40–42] In addition, a linear correlation between peak concentrations of IL-6 and CRP has been noted.[40–43]

The advantages of LNF, commonly reported in trials assessing laparoscopic surgery,[44] are believed to be secondary to a reduction in trauma to the abdominal wall with the laparoscopic approach, which results in a reduced inflammatory response.[33,45–47]

CO_2 is the insufflation gas of choice in laparoscopy. It is preferred over air insufflation, which affects the systemic and peritoneal response to a larger degree than CO_2.[48] The usage of CO_2 has some important advantages. It is transparent, noninflammable, and well dissolvable in blood. There are, however, some disadvantages associated with its usage. The increased intra-abdominal pressure increases the absorption of CO_2, causing hypercapnia and acidosis, which has to be avoided by hyperventilation.[49] It also pushes the diaphragm upwards decreasing the pulmonary compliance[49,50] and increases the peak airway pressure.[50,51] Pneumoperitoneum also increases the systemic vascular resistance[51,52] and pulmonary vascular resistance.[51] CO_2 pneumoperitoneum also predisposes to cardiac arrhythmias.[53] During the early phase of pneumoperitoneum, there is a reduction in the cardiac output[50,51] by decreasing the venous return.[54] Although these cardiorespiratory changes maybe tolerated by healthy adults with adequate cardiopulmonary reserve, people with cardiopulmonary diseases may not tolerate these cardiopulmonary changes. About 17% of patients undergoing laparoscopic cholecystectomy and 11% of patients undergoing LNF have an ASA status of III or IV.[27,56] Abdominal wall lift, using a special device (eg, laparolift[53]) or laparotensor[50] introduced through a port in the abdominal wall, has been used to decrease the cardiopulmonary changes.[56] Helium insufflations is an alternative to CO_2 insufflations[57] and has been reported to have little or no effect on pulmonary function in pigs.[58] However, concerns about the solubility of helium in the blood and hence the risk of gas embolism has precluded its routine use in humans.[57]

Randomized clinical trials have shown that using a lower pressure of pneumoperitoneum decreases the cardiac changes,[59] the number of people complaining of shoulder tip pain,[60] the intensity of pain,[61] and the analgesic requirement.[60–68]

Low intra-abdominal pressure has been reported to have a benefit in terms of less catecholamine release in pheochromocytoma[69] and may also prevent mortality due to CO_2 embolism.[70] Moreover, Schwarte et al[71] found that increasing intra-abdominal pressure decreased gastric mucosal O_2 saturation. European Association for Endoscopic Surgery guidelines[54] also recommended use of the lowest intra-abdominal pressure rather than a routine pressure (14 mm Hg), to allow adequate exposure of the operative field. In the study conducted by Torres et al[25] (laparoscopic cholecystectomy performed with standard and low-pressure pneumoperitoneum), no differences were observed between the groups in regards to IL-6, IL-8, and IL-10 levels. Different results were presented by Basgul et al,[26] who revealed IL-6 p.o. levels to increase less in patients operated on with the implementation of low-pressure pneumoperitoneum.

A cochrane review of Gurusami et al[72] has demonstrated that low-pressure pneumoperitoneum appears effective in decreasing pain after laparoscopic cholecystectomy, whereas the incomplete outcome data in 7 trials results in high risk of bias that makes impossible to conclude about the safety of low-pressure pneumoperitoneum.

Therefore, although there are several studies of intra-abdominal pressure and immune functions,[14,25,26,50,73] we could not find any effect of various degree of intra-abdominal pressure during LNF. We aimed to show this effect by measuring the level of serum ILs and preferred to detect IL-1, which is one of the early systemic immune events after surgery,[15] and IL-6, which is one of the mediator of acute-phase response.

In our study IL-1, IL-6, and CRP showed a significant increase perioperatively in the standard intra-abdominal pressure group, whereas the increase in the IL-1, IL-6, and CRP was lower in the low intra-abdominal pressure group.

Neutrophil elastase (PMN-elastase) is a neutral proteinase (30 kD), consisting of 218 amino acids, present mainly in the azurophilic granules of segmented granulocytes. Its function is to contribute to tissue repair after trauma, inflammation, or necrosis and can also cause, by nonspecific proteolysis, tissue injuries, and breakdown of regulatory proteins, thus sustaining the inflammatory process.[74,75] Ninety percent of the circulating elastase is

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bound to an α1-proteinase inhibitor complex. The remaining 10% is bound to α2-macroglobulin, another elastase inhibitor. During the surgical procedures, there is a massive release of elastase from the neutrophils[76] along with other proteinases. Therefore, the measurement of the elastase α1-proteinase inhibitor complex might be a useful indicator of the degree of surgical trauma. In our study, in standard group, we observed a p.o. increase of plasma elastase concentration. In low-pressure CO_2 group, the patients showed no significant difference in the activity of leukocyte of elastase considering the preoperative and postoperative values.

Moreover, in standard group, we observed a p.o. decrease of the HLA-DR of peripheral monocyte. Patients who underwent LNF using a low-pressure CO_2 showed no significant difference in the activity of HLA-DR expression considering the preoperative and postoperative values. Previous studies have demonstrated the crucial role of this antigen in assessing the activity of the immune system.[78] The HLA-DR antigen expression on monocytes has an important role in antigen presentation to lymphocytes, particularly T-helper lymphocytes.[77] In fact, these cells require both HLA-DR and exogenic antigens on the macrophage surface to initiate proliferation. Moreover, studies have shown that HLA-DR is related to the surgical trauma and the occurrence of p.o. sepsis is strongly correlated with less expression of the HLA-DR of peripheral monocytes.[21] Because HLA-DR expression is not significantly affected by age, sex, or race, this antigen can be considered of crucial significance in the p.o. monitoring of surgical patients.[77]

Does the difference in immune functioning between standard-pressure and low-pressure pneumoperitoneum influence clinical outcome? The publications on the subject of immune alterations, after standard and low pneumoperitoneum, are few and little is known about this difference in p.o. clinical outcomes.[72] Sparse information is available on immune function and clinical outcome. Because there still are too little data, no direct correlation could be found between clinical outcome and immunologic changes after standard pneumoperitoneum, as compared with low pneumoperitoneum.

The results obtained in our study did not reveal significant differences between the studied operative procedures with regards to clinical data. Nevertheless, these observations might be a result of the type of surgical procedure that was chosen for this study. LNF is a short and relatively less traumatic procedure. However, the influence of CO_2 pneumoperitoneum might have been strong enough to induce significant cytokine and HLA-DR concentration changes. Lower concentration of IL-1, IL-6, CRP, neutrophils-elastase, and increased levels of HLA-DR observed in the population operated on with low-pressure pneumoperitoneum may suggest that this technique is more favorable with regards to systemic inflammation and immune response. During LNF, the parameter returns to near baseline levels by 48 hours as this intervention causes a moderate surgical trauma. Even though there is a need for additional studies to prove beneficial effects of low-pressure pneumoperitoneum on cytokines factors concentrations, our observations maybe of certain importance in choosing operative technique in case of cancer patients. On the basis of the results obtained by other authors, we think that there is a need for studies comparing changes in the concentration of cytokines factors during and after oncology, laparoscopic operations performed with standard-pressure and low-pressure pneumoperitoneum, as cancer patients may show different cytokine response to the 2 technique with different pressures. In contrast, laparoscopic-assisted colorectal resection for cancer requires an incision substantially larger than that typically required for other advanced laparoscopic procedures, such as antireflux procedure. Further, with respect to colectomy, there is a wide variation in the size of the incision needed to extract the specimen and facilitate the anastomosis, dependent on body habitus, the size of the specimen, and the surgeon.[78] Other variables that may impact the results of cytokine studies include blood transfusions and elevated (≥14 mm Hg) and persistent (≥3 h) intra-abdominal pressure as a result of intraperitoneal insufflation. In these cases, the parameters tested return to near baseline levels on the order of 3 or 6 days.[78,79] Laparoscopic-assisted colorectal resections for cancer, performed with low-pressure pneumoperitoneum, may induce the release of minor acute-phase response mediators with the return to near baseline levels by 48 to 72 hours. The clinical importance of better preserved immune function postoperatively has yet to be proven. Certainly, when one compares operative morbidity and cancer recurrence rates in healthy immunocompetent patients to patients who are immunosuppressed to begin with, the latter group has significantly worse results than the former.[80,81]

Furthermore, as surgeons continue to perform increasingly longer, more complex operations with extensive operative dissection and internal tissue manipulation, the degree of surgical insult attributable to the size of the incision(s) becomes relatively less important. As the magnitude of the operation begins to outweigh the magnitude of the incision, the predominant difference between laparoscopic and open surgery become the unique physiology of CO_2 pneumoperitoneum.

The main criticism of low-pressure pneumoperitoneum is its ability to provide adequate surgical exposure and hence, its safety. The nearly equal operating time and lack of difference in the morbidity or conversion to open fundoplication suggest that we had adequate vision. Future trials must include surgeons' satisfaction as one of the outcome. Sandhu et al[68] affirm that if there is evidence that the operative field is not feasible in the low-pressure group, there should be no hesitation in increasing the pressure to 14 mm Hg, as in their series. In this study, conversion to high-pressure pneumoperitoneum was required in 2 of 70 cases; both of these patients were rather obese. For these reason, we have excluded patients with marked obesity (body mass index $> 36\,kg/m^2$).

Even though there is a need for more studies to prove beneficial effects of low-pressure pneumoperitoneum on inflammatory and immunologic factors concentration, our observation could be of certain importance in choosing operative technique, maybe not so much for the surgical treatment of benign diseases such as GERD or gallstones but certainly when treating cancer patients. In these cases, p.o. immunosuppression is indicated among factors responsible not only for postoperative infections but also for tumor spread and metastasis.[82] In contrast, surgery is almost always the ultimate therapeutic procedure in oncology. Therefore, it is important to avoid in these patients, often already presenting immunologic depression, all the conditions that could further reduce the p.o. immune response.

In conclusion, this study demonstrated that reducing the pressure of the pneumoperitoneum to 6 to 8 mm Hg is

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feasible during LNF. Reduced insufflation pressures can also lead to a reduction in p.o. inflammatory response, and possibly, avoid p.o. immunosuppression. The low-pressure technique could be employed in the majority of patients subjected to LNF with reasonable safety by an experienced surgeon. We need detailed studies concerning effects of various degrees of intra-abdominal pressure on systemic inflammation and immune response in laparoscopic surgeries, especially during and after oncology laparoscopic operations.

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