Original Article

Laparoscopic Nissen fundoplication: The effects of high-concentration supplemental perioperative oxygen on the inflammatory and immune response: A randomised controlled trial

Mario Schietroma, Sara Colozzi, Beatrice Pessia, Francesco Carlei, Marino Di Furia, Gianfranco Amicucci

Department of Surgery, University of L'Aquila, L'Aquila, Italy

Abstract

Background: A number of studies have been reported on the effects of high-concentration oxygen (HCO) on cytokine synthesis, with controversial results. We assessed the effect of administration of perioperative HCO on systemic inflammatory and immune response in patients undergoing laparoscopic Nissen fundoplication (LNF).

Materials and Methods: Patients ($n = 117$) were assigned randomly to an oxygen/air mixture with a fraction of inspired oxygen (FiO_2) of 30% ($n = 58$) or 80% ($n = 59$). Administration was commenced after induction of anaesthesia and maintained for 6 h after surgery. White blood cells, peripheral lymphocytes subpopulation, human leucocyte antigen-DR (HLA-DR), neutrophil elastase, interleukin (IL)-1 and IL-6 and C-reactive protein (CRP) were investigated.

Results: A significantly higher concentration of neutrophil elastase, IL-1, IL-6 and CRP was detected post-operatively in the 30% FiO_2 group patients in comparison with the 80% FiO_2 group ($P < 0.05$). A statistically significant change in HLA-DR expression was recorded post-operatively at 24 h, as a reduction of this antigen expressed on monocyte surface in patients from 30% FiO_2 group; no changes were noted in 80% FiO_2 group ($P < 0.05$).

Conclusions: This study demonstrated that perioperative HCO (80%), during LNF, can lead to a reduction in post-operative inflammatory response, and possibly, avoid post-operative immunosuppression.

Keywords: Immune response, laparoscopic Nissen fundoplication, oxygen

Address for correspondence: Dr. Beatrice Pessia, Università Degli Studi Di L'Aquila, Facoltà Di Medicina E Chirurgia, Dipartimento Di Scienze Chirurgiche, Presso Ospedale San Salvatore, Edificio Delta 6, 67100 Coppito (AQ), L'Aquila, Italy.
E-mail: pessiabeatrice87@gmail.com
Received: 08.12.2016, **Accepted:** 14.09.2017

INTRODUCTION

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's oesophagus, and eventually, adenocarcinoma of the oesophagus.[1-3]

Access this article online	
Quick Response Code:	Website: www.journalofmas.com
	DOI: 10.4103/jmas.JMAS_120_16

How to cite this article: Schietroma M, Colozzi S, Pessia B, Carlei F, Di Furia M, Amicucci G. Laparoscopic nissen fundoplication: The effects of high-concentration supplemental perioperative oxygen on the inflammatory and immune response: A randomised controlled trial. J Min Access Surg 2018;14:221-9.

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 these of the open technique[7,8] and is the most frequently performed operation for GERD.[9] Several randomised studies have demonstrated that LNF has similar 5- and 10-years[10,11] 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 hospitalisation period and quicker recovery are undeniable.[6] Although the exact cause for this better clinical outcome is still being investigated, better preservation of systemic inflammatory and immune function might also contribute to this improved recovery.[14-16] During anaesthesia and surgery, oxygen is routinely administered to all patients. Inspired oxygen concentrations, however, vary between 30% and 100% and oxygen is often administered in a seemingly random manner. During the past decade, it has been shown in several randomised trials that perioperative supplemental oxygen administration might improve outcome after certain surgical procedure.[17-19] Some studies have shown that supplemental oxygen also decreases the rate of post-operative nausea and vomiting after laparoscopic and open abdominal surgical procedures.[20,21] Furthermore, 80% inspired oxygen fraction almost doubles subcutaneous tissue oxygen tension and halves the rate of post-operative wound infections.[22-26] A striking conundrum is evident immediately when one review studies on the effects of oxygen on cytokine synthesis. Most investigators have found that hyperoxia enhances proinflammatory cytokine transcription and translation.[27-31] In contrast, hyperbaric oxygen has generally been shown to suppress stimulus-induced pro-inflammatory cytokine production.[32] Other studies have demonstrated that supplemental oxygen improves inflammatory and immune function,[33-36] and it is not associated with clinically important side effects.[37] Surgical procedure may be divided into three groups depending on the degree of trauma: (1) minor surgical trauma (cataract, biopsy, inguinal and femoral herniorrhaphy with local anaesthesia, etc.); (2) moderate surgical trauma (laparoscopic cholecystectomy, LNF, etc.) and (3) major surgical trauma (gastric resection, hemicolectomy, hepatic resection, etc.). Although laparoscopy is thought to be moderate surgical trauma, CO2 insufflation may lead to further pathophysiological changes. The effects of low- and high-intra-abdominal pressures and different anaesthetic agents on immune response have been studied previously,[38,39] but regarding the use of supplemental oxygen in LNF and inflammatory and immune response, there is no information in the literature.

The aim of the present study, prospective randomised, was to assess the effect of administration of high-concentration supplemental perioperative oxygen therapy on systemic inflammatory and immune response in patients undergoing elective LNF.

MATERIALS AND METHODS

From March 2011 to April 2016, we studied, in a prospective randomised study, 117 patients consecutively (66 men, 51 women; mean age: 56.2 years), with documented GERD who underwent an LNF. Criteria for exclusion were endocrine or immune systemic disorders; hematologic disorders; anticoagulant treatment; current or recent (6 months) thromboembolic disorders; renal, hepatic, rheumatic or vascular disorders; pregnancy; recent (6 months) surgery; current or recent (3 years) malignancy; chronic inflammatory disease and marked obesity (body mass index >36 kg/m^2). We also excluded patients taking corticosteroids drugs or other drugs, which may affect their immunologic responses. The patients were classified as Grade I or II according to the American Society of Anesthesiologists grading system.[40]

The LNF was performed by the same team of surgeons in each case, using the same surgical technique and four trocars. CO_2 pneumoperitoneum (12–14 mmHg) was established with open laparoscopy. Most of the patients underwent LNF go home 2 days after operation. Anaesthesia was obtained using the same procedure across all patients. Pre-anaesthesia 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/oxygen (O_2) 2:1. After intubation, anaesthesia was maintained with oxygen in air, sevoflurane and remifentanil (0.25 μg/kg/min). Randomisation to intervention was stratified by study centre. Computer-generated codes were maintained in sequentially numbered opaque envelopes. The randomisation envelopes were opened in the operating department after induction of anaesthesia by the anaesthesiologist. Patients were assigned randomly to an oxygen/air mixture with a fraction of inspired

oxygen (FiO_2) of 30% (Group 1) or 80% (Group 2). The displays of the anaesthesia machine and gas monitors were covered with cardboard shields in both the operating department and post-anaesthesia care unit (PACU) to keep the surgical team blinded to group assigned. Patients were not informed of their group assignments. Furthermore, the surgical team was blinded to the oxygen concentration administered. The Ethical Committee of the University of L'Aquila approved the study protocol. All patients gave informed written consent. As shown in Table 1 data, pre-, intra- and post-operative were comparable in the two groups. Electrocardiogram, heart rate, non-invasive blood pressure, FiO_2, pulse oximetry (SpO_2) and end-tidal concentrations of carbon dioxide and sevoflurane were continuously monitored during the surgery. An arterial blood sample was obtained 1 h after induction of anaesthesia to evaluate partial pressure of oxygen; another sample was obtained 2 h after extubation. When the operation was finished, the inhaled anaesthetic was stopped, and FiO_2 was increased to 100% during extubation. During the first 6 post-operative h, all patients were administered non-rebreathing facemasks with a reservoir (Intersurgical, Wokingham, Berkshire); oxygen was provided at the randomly designated concentration at a total flow of 16 L/min. Subsequently, patients breathed ambient air, although supplemental oxygen was provided as necessary to maintain oxygen saturation as measured by pulse oximetry of at least 92%. An intention-to-treat analysis was performed, and patients who required a transient increase in inspired oxygen concentration were included in the analysis. Furthermore, the patients requiring conversion were included in the analysis. Perioperative normothermia [Table 1] was maintained in all patients with circulating-water mattresses and forced-air heaters. Fluids were administered intraoperatively at a rate of 20 mL/kg/h; blood loss was restored with crystalloids (physiologic saline solution, 0.9% or lactated Ringer's solution) or colloids (hydroxyethyl starch). Blood loss was replaced 1:1 with colloids and blood transfusion was not necessary. Fluid was administered at 5 mL/kg/h during the first 6 post-operative hours and then reduced to 3 mL/kg/h after patients were transferred to the ward. In the PACU, vital signs (blood pressure, pulse, respiration, pulse oximetry and adequate answering) were monitored every 15 min. Patients were discharged from PACU when vital signs were normalised. We used a prophylactic multimodal analgesic technique for treatment of post-operative pain. Thus, patients received incisional local anaesthetics using a total of 20 ml (100 mg) of bupivacaine (0.5% bupivacaine). Intravenous ketorolac tromethamine (30 mg), was given every 6 h on the 2 days after operation, and afterwards on demand. Blood samples were collected from all patients before operation and at days 1, 3 and 6 after operation. Serum concentration of interleukin (IL)-1 and IL-6 and C-reactive protein (CRP) were measured at 0, 30, 60, 90, 120 and 180 min, at 12, 24 h and then daily (8 am) until post-operative day 6. 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 gamma/delta and the T-helper/T-suppressor ratio (CD4/CD8). Human leucocyte antigen-DR (HLA-DR) of peripheral monocytes was measured by cytofluorimetric method. All blood samples (10 ml) were collected with ethylenediaminetetracetic acid (0.5 ml). A monoclonal antibody for the HLA-DR antigen fluorescein isothiocyanate conjugated (10 μl) was added. Whole blood (100 μl) from each patient was then used, and the tubes were stirred with vortex and stored at 4°C for 30 min. Two ml of lysing solution were added to each sample. All samples were stirred and then incubated for 15 min at room temperature. Finally, an orthocytofluorimeter was used for the assay. Elastase concentration was determined photometrically, using an immune-activation immunoassay (Merck, Darmstadt, Germany), as a complex with α1-proteinase inhibitor, according to the method described by Hafner.[41] Serum concentration of IL-1 and IL-6 were measured using a quantitative 'sandwich' enzyme-linked immunosorbent assay (ELISA) kit (R and D System, Minneapolis, USA) according to the manufacturer's description (range IL-1β: 3.9–250 pg/mL; IL-6: 3.13–300 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 h at room temperature,

Table 1: Comparison of patient characteristics in the two group

Parameters	30% FiO_2	80% FiO_2
No of patients	58	59*
Age, Y, mean (range)	55.8 (36-74)	56.9 (40-78)
Sex radio (M: F)	33/25	33/26
ASA grade no (%)		
I	38 (65.5)	39 (66.1)
II	20 (34.4)	20 (33.9)
Respiratory disease	2 (3.4)	1 (1.6)
Cardiovascular disease	2 (3.4)	3 (5)
Core temperature, °C mean (range)	36.2 (35.8-36.6)	36.3 (35.6-36.9)
EBL, mean (range) mL	50 (20-100)	45 (30-90)
Anesthesia, min mean (range)	42.8 (32-60)	43.2 (30-90)
Operative time, min mean (range)	37.1 (20-52)	37.4 (25-55)
Postoperative complications:	2 (3.4)	1 (1.6)
Bronchopneumonia wound	1	1
infention grade I	1	/
Postoperative hospitalization days, mean (range)	2.2 (2-4)	2.8 (2-6)

ASA: American Society of Anesthesiologists, ESL: Estimated blood loss. *One patient (1.6%) was converted to open surgery

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 h 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 min at 37°C. The reaction was terminated with the addition of a stop solution. Absorbance was determined 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. The plasma concentration of CRP was measured using a competitive CRP ELISA Kit.

Statistical analysis

A statistical analysis was performed using Student's *t*-test, and $P < 0.05$ was considered to be significant. The values were expressed as the mean and standard deviation. Areas under the curves [Figures 1-3] in two groups were compared using the Mann–Whitney U-test. The magnitude of changes in each metabolic variable (areas under the curve) was compared by the Pearson's correlation coefficient (*r*). An alpha adjustment according to Bonferroni–Holm was applied when appropriate.

RESULTS

We collected data from 117 patients who were enrolled and randomised: 58 received 30% perioperative oxygen and 59 received 80% perioperative oxygen. In Figure 4, the CONSORT analysis is described in detail.[42] One patient was converted to open surgery, and belonged to 80% FiO_2 group. The condition that required conversion was the inability to reduce a very large hiatal hernia. This patient who required conversion showed no significant difference in immunological and inflammatory data as regards 80% oxygen group. Estimated blood Loss was, in 30% FiO_2 group, mean 50 mL (range 20–100 mL), and in 80% FiO_2 group, mean 45 mL (range 30–90 mL) [Table 1]. Post-operative complications are cited in Table 1. There were no differences between the 30% FiO_2 group and the 80% FiO_2 group (3.4% vs. 1.6%) [Table 1]. Slight leucocytosis (range 10.400–13.600) was observed only in the 30% FiO_2 group, but not in the 80% FiO_2 group, mostly due to an increment of neutrophils [Figure 5] (day 1, $P < 0.05$). This value returned to the normal range within 2–3 days in the 30% FiO_2 group. Other WBC types showed no significant variation. As concern lymphocyte subpopulations, there were no differences between the two groups of patients before and after operation.

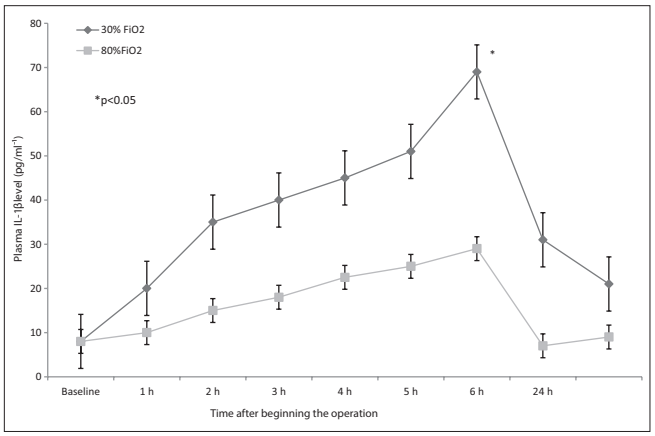

Figure 1: Interleukin-1β levels in patients receiving 30% FiO_2 or 80% FiO_2; $P < 0.05$ for all values compared with baseline (Mann–Whitney U-test). For the 80% FiO_2 group at 6 h, $^*P < 0.05$ compared with 30% FiO_2 group (Mann–Whitney U-test)

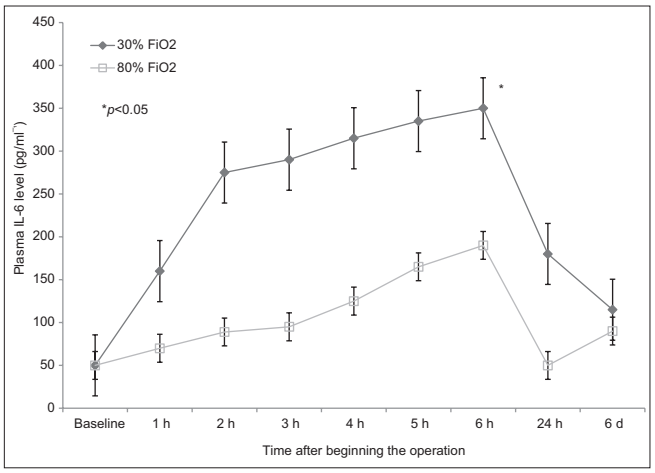

Figure 2: Interleukin-6 levels in patients receiving 30% FiO_2 or 80% FiO_2; $P < 0.05$ for all values compared with baseline (Mann–Whitney U-test). For the 80% FiO_2 group at 6 h, $^*P < 0.05$ compared with 30% FiO_2 group (Mann–Whitney U-test)

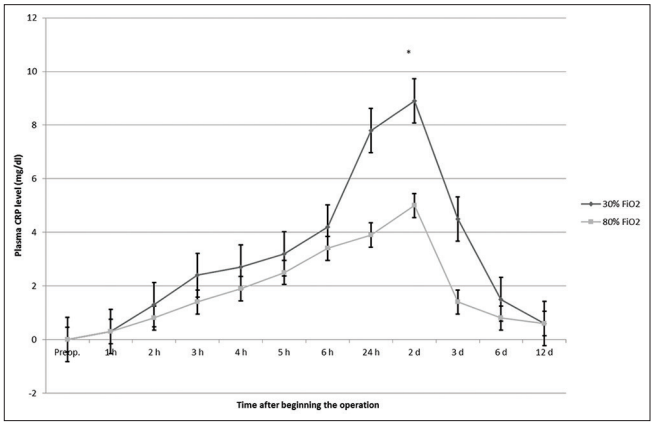

Figure 3: Changes in serum C-reactive protein levels in patients receiving 30% FiO_2 or 80% FiO_2. The increase in C-reactive protein was significantly higher in the 30% FiO_2 group at days 1 and 3 ($^*P < 0.05$)

A statistically significant change in HLA-DR expression was recorded post-operative at day 1 as a reduction of this

antigen expressed on monocyte surface in patients from Group 1 (30% FiO_2); no changes were noted in the 80% FiO_2 group [Figure 6] ($P < 0.05$). In this case, HLA-DR expression returned to normal values within 3 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 post-operative at days 1 and 3 as an increase of this neutral proteinase in patients from Group 1 (30% FiO_2) when compared to 80% FiO_2 group [Figure 7] ($P < 0.05$). In the 30% FiO_2 group, plasma elastase concentration returned to normal values within 6 days after operation. Finally, the ages of the patients did not affect neutrophil elastase concentration in either group. Before the operation, the serum levels of neither IL-1 nor IL-6 were significantly different between these two groups. Figures 1 and 2 show the chronological change in the serum level of IL-1 and IL-6 both after surgery. In the 30% FiO_2 group, the serum IL-1 and IL-6 levels began to significantly increase as early as 1 h from the beginning of the operation revealing a peak at the 6th h (approximately 4 h after the operation), and thereafter, declining to preoperative levels by the 6 days. On the other hand, in the 80% FiO_2 group patients, the increase in the serum IL-1 and IL-6 levels was delayed, and

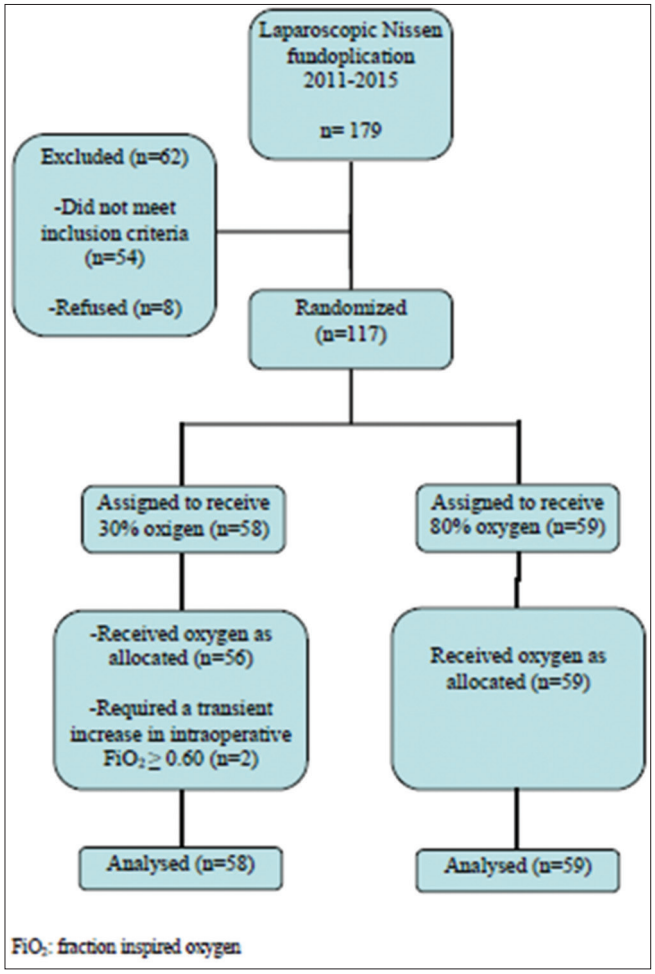

Figure 4: Trial profile: CONSORT analysis

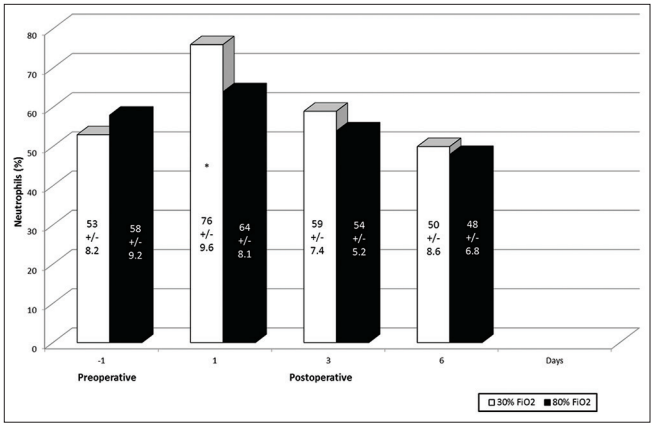

Figure 5: Neutrophil concentration (mean ± standard deviation) in patients receiving 30% FiO_2 or 80% FiO_2. The increase in neutrophils was significantly higher in the 30% FiO_2 group at day 1 (*$P < 0.05$)

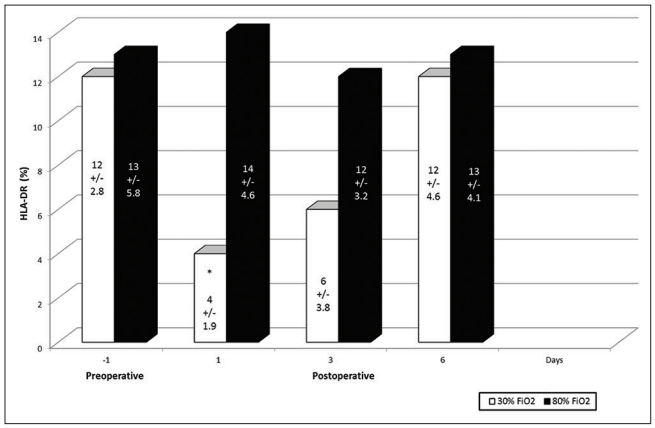

Figure 6: Changes in human leucocyte antigen-DR expression (mean ± standard deviation) in patients receiving 30% FiO_2 or 80% FiO_2. The decrease in human leucocyte antigen-DR was significantly higher in the 30% FiO_2 group at day 1 (*$P < 0.05$)

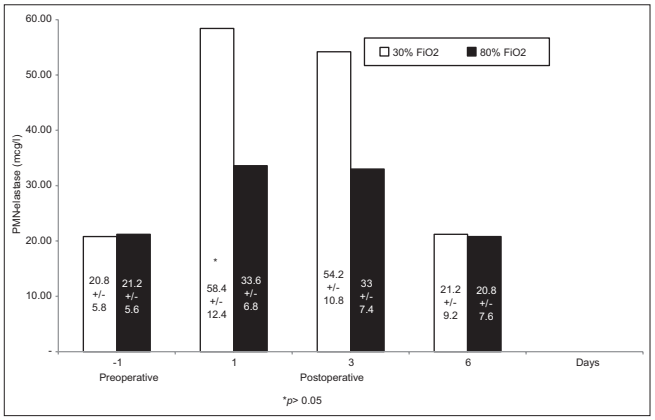

Figure 7: Changes in plasma elastase concentration (mean ± standard deviation) in patients receiving 30% FiO_2 or 80% FiO_2. The increase in plasma elastase was significantly higher in the 30% FiO_2 group at days 1 and 3 (*$P < 0.05$)

the peak values were significantly lower than these in the 30% FiO_2 group ($P < 0.05$).

The average values of the serum CRP on post-operative days 1 and 3 were also significantly lower in the 80% FiO_2 group than those in the 30% FiO_2 group ($P < 0.05$) [Figure 3]. In this case, CRP concentration returned to normal values within 6 days after operation. Two of 58 patients (3.4%) in the 30% oxygen group required a FiO_2 of 0.60 or greater for >1 h to maintain arterial oxygen saturation above 94% in accordance with safety measures in clinical practice. One patient suffered from chronic obstructive pulmonary disease. In any case, these patients who required a transient increase in inspired oxygen concentration showed no significant difference in immunological and inflammatory data as regards 30% oxygen group.

DISCUSSION

LNF is nowadays considered the treatment of choice for symptomatic GERD.[11,43] Performed at first in 1991[44,45] LNF rapidly became the elective surgical procedure in the United States[5,46] and Europe.[47,48] When compared with open Nissen fundoplication, LNF presents several advantages, such as reduced post-operative pain, prompt post-operative bowel activity (6 to 24 h after operation), reduced hospitalisation (1 to 2 days), earlier return to work, better aesthetic results and reduced post-operative infections. The impact of surgical stress on the inflammatory and immune response is a possible predictive factor of patients' clinical outcome.[49-52] Laparoscopic surgery induces less trauma and is, therefore, less aggravating for the immune system.[53,54] The overall immune response to surgery, in general, is reflected mainly in terms of alteration in cytokine function and the cellular messenger system.[55] The acute phase response and cytokines are important and necessary components of immunological function. Although cytokine levels do not indicate immune status directly, they are a good guide in the assessment of the activation of the systemic immune system. However, the overproduction of cytokines, or their production at non-inflammatory sites, may lead to deleterious effects on tissues, so a decrease production of cytokines (reduced inflammatory reaction) might be considered beneficial during the post-operative period. The cytokines IL-1 and IL-6 play a major role in the acute phase response.[14,56] The expression of IL-6 is believed to be directly proportional to the extent of surgical trauma.[57] CRP is also a dependable marker of acute phase response. CRP levels usually rise approximately 4 to 12 h after operation and peak at 24–72 h, thereafter remaining raised for approximately 2 weeks.[58] In the present study, significant increase in IL-1 β, IL-6 and CRP levels were observed in both treatment groups, but these levels increased significantly less in the 80% FiO_2 group compared with 30% FiO_2 group. How does high-concentration supplemental perioperative oxygen inhibit stimulus-induced proinflammatory cytokine production? The inhibitory effect of high-concentration oxygen (HCO) seen in the *ex vivo* and *in vivo* models could be due to changes in the distribution of mononuclear cell subsets.[59,60] In some models, HCO could reduce cytokine production by inducing apoptosis in cytokine-producing cells. For example, HCO stimulates apoptosis in murine thymocytes as well as lymphocytic and granulocytic cell lines.[61] However, in the study of Benson *et al*.[62] the inhibitory effects of HCO on cytokine synthesis were only transient, thereby suggesting that HCO induced a qualitative change in the monocyte-macrophage. This change according to Benson *et al*.[62] is probably mediated by interference or augmentation of an early signaling event. For example, HCO could inhibit cytokine production by downregulating PGE2 production[63] through suppression of cyclooxygenase-2 expression[64] or by inducing the formation of heat shock proteins.[65] Moreover, in 30% FiO_2 group, we observed a statistically significant post-operative decrease of HLA-DR monocyte antigen expression; no changes were noted in the 80% FiO_2 group. The previous studies have demonstrated the crucial role of this antigen in assessing the activity of the immune system.[66,67] The HLA-DR antigen expression on monocytes has an important role in antigen presentation to lymphocytes, particularly T-helper lymphocytes:[67] in fact, these cells require both HLA-DR and exogenic antigens on the macrophage surface to initiate proliferation. Moreover, the previous studies have shown that HLA-DR is related to the severity of the surgical trauma in the pathogenesis of the septic process and in its healing.[50,68-70] Because HLA-DR expression is not significantly affected by age, sex, or race, this antigen can be considered of crucial significance in the post-operative monitoring of surgical patients.[50] Neutrophil elastase (PMN-elastase) is a neutral proteinase (30 kD), consisting of 218 amino acids, present mainly in the neutrophils granules of segmented granulocytes. Its function is to contribute to tissue repair after trauma, inflammation or necrosis and can also cause, by non-specific proteolysis, tissue injuries and breakdown of regulatory proteins, thus sustaining the inflammatory process.[71,72] Ninety percent of the circulating elastase is 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[73] 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 the 30% FiO_2 group, we observed a statistically

significant post-operative increase of plasma elastase concentration. In the 80% FiO_2 group, the patients showed no significant difference in the activity of leucocyte of elastase considering the pre-operative and post-operative values. Does the difference in immune functioning between high and low concentration supplemental perioperative oxygen influence the clinical outcome? The publication on the subject of immune alteration, after high and low concentration supplemental perioperative oxygen, are few and little is known about this difference in post-operative clinical outcomes.[36] 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 high and low concentration supplemental perioperative oxygen. This study also compared clinical results of administration of inspired oxygen of 30% versus 80%. No mortality and no serious adverse events were noted in either group. No difference was seen in the proportion of participants with non-serious adverse events between the two groups. However, our trial has some limitations. First, LNF is a short and relatively less traumatic procedure. Second, we have included low anaesthetic risk patients. Third, the confidence intervals of serious and non-serious adverse events are wide, and significant increases or decreases in complications due to high-concentration supplemental perioperative oxygen cannot ruled out. Therefore, further well-designed trials are required for LNF, and in particularly in people with acute cardiopulmonary disorders who undergo LNF. Even though there is a need for additional studies to prove beneficial effects of high-concentration supplemental perioperative oxygen on cytokines factors concentrations, our observations may be of certain importance in assessing this technique also in 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 high- and low-concentration supplemental perioperative oxygen, as cancer patients may show different cytokine response to the two techniques with different concentration supplemental perioperative oxygen. In contrast, laparoscopic-assisted colorectal resection for cancer requires an incision substantially larger than that typically required for other laparoscopic procedures, such as laparoscopic cholecystectomy. 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.[74] Other variables that may impact the results of cytokine studies include blood transfusions and elevated (≥14 mmHg) 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.[74,75] Laparoscopic-assisted colorectal resections for cancer, performed with high-concentration supplemental perioperative oxygen, may induce the release of minor acute-phase response mediators with the return to mean baseline levels by 48–72 h. Anyway, in these patients, the clinical importance of better preserved immune function post-operatively has yet to be proven.[74,75] 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.[76-78] Even though there is a need for more studies to prove beneficial effects of high-concentration supplemental perioperative oxygen 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 gallstones or GERD but certainly when treating cancer patients. In these cases, post-operative immunosuppression is indicated among factors responsible not only for post-operative infections but also for tumours spread and metastasis.[76] 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 post-operative immune response.

CONCLUSIONS

This study demonstrates that high-concentration (80%) supplemental perioperative oxygen, during LNF, can lead to a reduction in post-operative inflammatory response, and possibly, avoid post-operative immunosuppression. We need detailed studies concerning effects of various degrees of high-concentration supplemental perioperative oxygen on systemic inflammation and immune response in laparoscopic surgeries, especially during and after oncology laparoscopic operations.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Odze RD. Pathology of the gastroesophageal junction. Semin Diagn Pathol 2005;22:256-65.
2. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. Lancet

2006;367:2086-100.
3. Cheng L, Harnett KM, Cao W, Liu F, Behar J, Fiocchi C, *et al*. Hydrogen peroxide reduces lower esophageal sphincter tone in human esophagitis. Gastroenterology 2005;129:1675-85.
4. Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? Gut 2007;56:593-4.
5. Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F, *et al*. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of a randomized controlled trial. JAMA 2001;285:2331-8.
6. Vakil N. Review article: The role of surgery in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2007;25:1365-72.
7. Hinder RA, Filipi CJ, Wetscher G, Neary P, DeMeester TR, Perdikis G, *et al*. Laparoscopic nissen fundoplication is an effective treatment for gastroesophageal reflux disease. Ann Surg 1994;220:472-81.
8. Rantanen TK, Salo JA, Salminen JT, Kellokumpu IH. Functional outcome after laparoscopic or open nissen fundoplication: A follow-up study. Arch Surg 1999;134:240-4.
9. Broeders JA, Mauritz FA, Ahmed Ali U, Draaisma WA, Ruurda JP, Gooszen HG, *et al*. Systematic review and meta-analysis of laparoscopic nissen (posterior total) versus toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 2010;97:1318-30.
10. Draaisma WA, Rijnhart-de Jong HG, Broeders IA, Smout AJ, Furnee EJ, Gooszen HG, *et al*. Five-year subjective and objective results of laparoscopic and conventional nissen fundoplication: A randomized trial. Ann Surg 2006;244:34-41.
11. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG, *et al*. Ten-year outcome of laparoscopic and conventional nissen fundoplication: Randomized clinical trial. Ann Surg 2009;250:698-706.
12. Fuchs KH, Feussner H, Bonavina L, Collard JM, Coosemans W. Current status and trends in laparoscopic antireflux surgery: Results of a consensus meeting. The European Study Group for Antireflux Surgery (ESGARS). Endoscopy 1997;29:298-308.
13. Guidelines for surgical treatment of gastroesophageal reflux disease (GERD). Society of American gastrointestinal endoscopic Surgeons (SAGES). Surg Endosc 1998;12:186-8.
14. Cruickshank AM, Fraser WD, Burns HJ, Van Damme J, Shenkin A. Response of serum interleukin-6 in patients undergoing elective surgery of varying severity. Clin Sci (Lond) 1990;79:161-5.
15. Grace PA, Quereshi A, Coleman J, Keane R, McEntee G, Broe P, *et al*. Reduced postoperative hospitalization after laparoscopic cholecystectomy. Br J Surg 1991;78:160-2.
16. Faist E, Kupper TS, Baker CC, Chaudry IH, Dwyer J, Baue AE, *et al*. Depression of cellular immunity after major injury. Its association with posttraumatic complications and its reversal with immunomodulation. Arch Surg 1986;121:1000-5.
17. Schietroma M, Carlei F, Cecilia EM, Piccione F, Bianchi Z, Amicucci G, *et al*. Colorectal infraperitoneal anastomosis: The effects of perioperative supplemental oxygen administration on the anastomotic dehiscence. J Gastrointest Surg 2012;16:427-34.
18. García-Botello SA, García-Granero E, Lillo R, López-Mozos F, Millán M, Lledó S, *et al*. Randomized clinical trial to evaluate the effects of perioperative supplemental oxygen administration on the colorectal anastomosis. Br J Surg 2006;93:698-706.
19. Schietroma M, Cecilia EM, Carlei F, Sista F, De Santis G, Piccione F, *et al*. Prevention of anastomotic leakage after total gastrectomy with perioperative supplemental oxygen administration: A prospective randomized, double-blind, controlled, single-center trial. Ann Surg Oncol 2013;20:1584-90.
20. Greif R, Laciny S, Rapf B, Hickle RS, Sessler DI. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology 1999;91:1246-52.
21. Goll V, Akça O, Greif R, Freitag H, Arkiliç CF, Scheck T, *et al*. Ondansetron is no more effective than supplemental intraoperative oxygen for prevention of postoperative nausea and vomiting. Anesth Analg 2001;92:112-7.
22. Belda FJ, Aguilera L, García de la Asunción J, Alberti J, Vicente R, Ferrándiz L, *et al*. Supplemental perioperative oxygen and the risk of surgical wound infection: A randomized controlled trial. JAMA 2005;294:2035-42.
23. Greif R, Akça O, Horn EP, Kurz A, Sessler DI, Outcomes Research Group. *et al*. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. N Engl J Med 2000;342:161-7.
24. Chura JC, Boyd A, Argenta PA. Surgical site infections and supplemental perioperative oxygen in colorectal surgery patients: A systematic review. Surg Infect (Larchmt) 2007;8:455-61.
25. Al-Niaimi A, Safdar N. Supplemental perioperative oxygen for reducing surgical site infection: A meta-analysis. J Eval Clin Pract 2009;15:360-5.
26. Qadan M, Akça O, Mahid SS, Hornung CA, Polk HC Jr. Perioperative supplemental oxygen therapy and surgical site infection: A meta-analysis of randomized controlled trials. Arch Surg 2009;144:359-66.
27. Jensen JC, Pogrebniak HW, Pass HI, Buresh C, Merino MJ, Kauffman D, *et al*. Role of tumor necrosis factor in oxygen toxicity. J Appl Physiol (1985) 1992;72:1902-7.
28. Tsan MF, White JE, Michelsen PB, Wong GH. Pulmonary O2 toxicity: Role of endogenous tumor necrosis factor. Exp Lung Res 1995;21:589-97.
29. Barazzone C, Tacchini-Cottier F, Vesin C, Rochat AF, Piguet PF. Hyperoxia induces platelet activation and lung sequestration: An event dependent on tumor necrosis factor-alpha and CD11a. Am J Respir Cell Mol Biol 1996;15:107-14.
30. Johnston CJ, Wright TW, Reed CK, Finkelstein JN. Comparison of adult and newborn pulmonary cytokine mRNA expression after hyperoxia. Exp Lung Res 1997;23:537-52.
31. Piedboeuf B, Horowitz S, Johnston CJ, Gamache M, Bélanger S, Poubelle PE, *et al*. Interleukin-1 expression during hyperoxic lung injury in the mouse. Free Radic Biol Med 1998;24:1446-54.
32. Brenner I, Shephard RJ, Shek PN. Immune function in hyperbaric environments, diving, and decompression. Undersea Hyperb Med 1999;26:27-39.
33. Kotani N, Hashimoto H, Sessler DI, Muraoka M, Hashiba E, Kubota T, *et al*. Supplemental intraoperative oxygen augments antimicrobial and proinflammatory responses of alveolar macrophages. Anesthesiology 2000;93:15-25.
34. Kotani N, Lin CY, Wang JS, Gurley JM, Tolin FP, Michelassi F, *et al*. Loss of alveolar macrophages during anesthesia and operation in humans. Anesth Analg 1995;81:1255-62.
35. Kotani N, Hashimoto H, Sessler DI, Yasuda T, Ebina T, Muraoka M, *et al*. Expression of genes for proinflammatory cytokines in alveolar macrophages during propofol and isoflurane anesthesia. Anesth Analg 1999;89:1250-6.
36. Kabon B, Kurz A. Optimal perioperative oxygen administration. Curr Opin Anaesthesiol 2006;19:11-8.
37. Tinits P. Oxygen therapy and oxygen toxicity. Ann Emerg Med 1983;12:321-8.
38. Gurusamy KS, Vaughan J, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. Cochrane Database Syst Rev 2014;18:CD006930.
39. Helmy SA, Wahby MA, El-Nawaway M. The effect of anaesthesia and surgery on plasma cytokine production. Anaesthesia 1999;54:733-8.
40. American Society of Anesthesiologists. New classification of physiology status. Anesthesiologists 1963;24:111.
41. Hafner G, Dreher M, Lütgehaus M, Ehrenthal W, Heubner A, Swars H, *et al*. Determination of human granulocyte elastase by the immunoactivation method on the Hitachi 717 automated analyser. Eur J Clin Chem Clin Biochem 1991;29:179-83.
42. Moher D, Schulz KF, Altman D. The CONSORT statement: Revised recommendation for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987-91.
43. Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C,

Monami B, *et al*. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc 2006;20:159-65.
44. Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic nissen fundoplication: Preliminary report. Surg Laparosc Endosc 1991;1:138-43.
45. Geagea T. Laparoscopic nissen's fundoplication: Preliminary report on ten cases. Surg Endosc 1991;5:170-3.
46. Oleynikov D, Eubanks TR, Oelschlager BK, Pellegrini CA. Total fundoplication is the operation of choice for patients with gastroesophageal reflux and defective peristalsis. Surg Endosc 2002;16:909-13.
47. Nilsson G, Larsson S, Johnsson F. Randomized clinical trial of laparoscopic versus open fundoplication: Blind evaluation of recovery and discharge period. Br J Surg 2000;87:873-8.
48. Booth MI, Jones L, Stratford J, Dehn TC. Results of laparoscopic nissen fundoplication at 2-8 years after surgery. Br J Surg 2002;89:476-81.
49. Christou NV, Meakins JL, MacLean LD. The predictive role of delayed hypersensitivity in preoperative patients. Surg Gynecol Obstet 1981;152:297-301.
50. Hershman MJ, Cheadle WG, Wellhausen SR, Davidson PF, Polk HC Jr. Monocyte HLA-DR antigen expression characterizes clinical outcome in the trauma patient. Br J Surg 1990;77:204-7.
51. Poenaru D, Christou NV. Clinical outcome of seriously ill surgical patients with intraabdominal infection depends on both physiologic (APACHE II score) and immunologic (DTH score) alterations. Ann Surg 1991;213:130-6.
52. Sietses C, Beelen RH, Meijer S, Cuesta MA. Immunological consequences of laparoscopic surgery, speculations on the cause and clinical implications. Langenbecks Arch Surg 1999;384:250-8.
53. Allendorf JD, Bessler M, Whelan RL, Trokel M, Laird DA, Terry MB, *et al*. Postoperative immune function varies inversely with the degree of surgical trauma in a murine model. Surg Endosc 1997;11:427-30.
54. Redmond HP, Watson RW, Houghton T, Condron C, Watson RG, Bouchier-Hayes D, *et al*. Immune function in patients undergoing open vs. laparoscopic cholecystectomy. Arch Surg 1994;129:1240-6.
55. Gupta A, Watson DI. Effect of laparoscopy on immune function. Br J Surg 2001;88:1296-306.
56. Perlmutter DH, Dinarello CA, Punsal PI, Colten HR. Cachectin/tumor necrosis factor regulates hepatic acute-phase gene expression. J Clin Invest 1986;78:1349-54.
57. Sakamoto K, Arakawa H, Mita S, Ishiko T, Ikei S, Egami H, *et al*. Elevation of circulating interleukin 6 after surgery: Factors influencing the serum level. Cytokine 1994;6:181-6.
58. Ohzato H, Yoshizaki K, Nishimoto N, Ogata A, Tagoh H, Monden M, *et al*. Interleukin-6 as a new indicator of inflammatory status: Detection of serum levels of interleukin-6 and C-reactive protein after surgery. Surgery 1992;111:201-9.
59. Bitterman N, Bitterman H, Kinarty A, Melamed Y, Lahat N. Effect of a single exposure to hyperbaric oxygen on blood mononuclear cells in human subjects. Undersea Hyperb Med 1993;20:197-204.
60. Bitterman N, Lahat N, Rosenwald T, Kinarty A, Melamed Y, Bitterman H, *et al*. Effect of hyperbaric oxygen on tissue distribution of mononuclear cell subsets in the rat. J Appl Physiol (1985) 1994;77:2355-9.
61. Ganguly BJ, Tonomura N, Benson RM, Osborne BA, Granowitz EV. Hyperbaric oxygen enhances apoptosis in hematopoietic cells. Apoptosis 2002;7:499-510.
62. Benson RM, Minter LM, Osborne BA, Granowitz EV. Hyperbaric oxygen inhibits stimulus-induced proinflammatory cytokine synthesis by human blood-derived monocyte-macrophages. Clin Exp Immunol 2003;134:57-62.
63. Inamoto Y, Okuno F, Saito K, Tanaka Y, Watanabe K, Morimoto I, *et al*. Effect of hyperbaric oxygenation on macrophage function in mice. Biochem Biophys Res Commun 1991;179:886-91.
64. Yin W, Badr AE, Mychaskiw G, Zhang JH. Down regulation of COX-2 is involved in hyperbaric oxygen treatment in a rat transient focal cerebral ischemia model. Brain Res 2002;926:165-71.
65. Xie Y, Cahill CM, Asea A, Auron PE, Calderwood SK. Heat shock proteins and regulation of cytokine expression. Infect Dis Obstet Gynecol 1999;7:26-30.
66. Cheadle WG, Hershman MJ, Wellhausen SR, Polk HC Jr. HLA-DR antigen expression on peripheral blood monocytes correlates with surgical infection. Am J Surg 1991;161:639-45.
67. Neefjes JJ, Ploegh HL. Intracellular transport of MHC class II molecules. Immunol Today 1992;13:179-84.
68. Appel SH, Wellhausen SR, Montgomery R, DeWeese RC, Polk HC Jr. Experimental and clinical significance of endotoxin-dependent HLA-DR expression on monocytes. J Surg Res 1989;47:39-44.
69. Browder W, Williams D, Pretus H, Olivero G, Enrichens F, Mao P, *et al*. Beneficial effect of enhanced macrophage function in the trauma patient. Ann Surg 1990;211:605-12.
70. Faist E, Mewes A, Strasser T, Walz A, Alkan S, Baker C, *et al*. Alteration of monocyte function following major injury. Arch Surg 1988;123:287-92.
71. Biffl WL, Moore EE, Zallen G, Johnson JL, Gabriel J, Offner PJ, *et al*. Neutrophils are primed for cytotoxicity and resist apoptosis in injured patients at risk for multiple organ failure. Surgery 1999;126:198-202.
72. Partrick DA, Moore EE, Offner PJ, Barnett CC, Barkin M, Silliman CC, *et al*. Nitric oxide attenuates platelet-activating factor priming for elastase release in human neutrophils via a cyclic guanosine monophosphate-dependent pathway. Surgery 1997;122:196-202.
73. Borregaard N. The human neutrophil. Function and dysfunction. Eur J Haematol 1988;41:401-13.
74. Sylla P, Kirman I, Whelan RL. Immunological advantages of advanced laparoscopy. Surg Clin North Am 2005;85:1-18, vii.
75. Ng CS, Whelan RL, Lacy AM, Yim AP. Is minimal access surgery for cancer associated with immunologic benefits? World J Surg 2005;29:975-81.
76. Eilber FR, Morton DL. Impaired immunologic reactivity and recurrence following cancer surgery. Cancer 1970;25:362-7.
77. Pietsch JB, Meakins JL, MacLean LD. The delayed hypersensitivity response: Application in clinical surgery. Surgery 1977;82:349-55.
78. Lundy J, Lovett EJ 3rd, Wolinsky SM, Conran P. Immune impairment and metastatic tumor growth: The need for an immunorestorative drug as an adjunct to surgery. Cancer 1979;43:945-51.