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The degree of oxidative stress is associated with major adverse effects after lung resection: A prospective study

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Abstract

Objective: This prospective randomized study was conducted in order to define the contribution of the generated oxygen and nitrogen reactive species on postlobectomy morbidity and mortality. **Patients and methods:** Between 2001 and 2003, 132 patients with non-small cell lung cancer (NSCLC) were prospectively studied. The patients were grouped according to one-lung ventilation (OLV) use or not and to the duration of lung's atelectasis. Group A included 50 patients with confirmed non-small cell lung cancer who were subjected to lobectomy without one-lung ventilation. Group B included 30 patients subjected to 60 min OLV. Group C included 30 patients subjected to 90 min OLV. Group D included 22 patients subjected to 120 min OLV. Preoperative, intraoperative and postoperative strict blood sampling protocol was followed. Malondialdehyde (MDA) plasma levels were measured. The groups were statistically compared for the occurrence of postoperative complications. OLV (groups B—D) along with other clinical parameters were entered in multivariate analysis as risk factors for complication development. **Measurements and results:** Comparison of group A with groups B—D (OLV) documented significant increase ($p < 0.001$) of MDA levels during lung reexpansion. The magnitude of oxidative stress was related to OLV duration (group D > group C > group B, all $p < 0.001$). Univariate analysis disclosed a higher incidence of acute respiratory failure, cardiac arrhythmias and pulmonary hypertension in group D. Multivariate analysis revealed OLV as an independent risk factor for postoperative development of cardiac arrhythmias and pulmonary hypertension. **Conclusion:** Protracted (>1 h) OLV should be considered a potential cause for cardiovascular complications through the generation of severe oxidative stress due to lung reexpansion.

Keywords: Oxidative stress; Lung reexpansion; Postresectional complications

1. Introduction

One-lung ventilation (OLV) is widely used in thoracic surgery. In our previous report, the generation of oxidative stress after OLV was demonstrated [1]. There is still much controversy for the role of free radicals on the development of acute lung injury postoperatively [2,3]. However, there is lack of evidence concerning the role of oxidative stress on minor or major complications, which develop after lung resection with OLV.

This prospective study was conducted in order to define the contribution of the generated oxygen and nitrogen reactive species on postlobectomy morbidity and mortality.

2. Materials and methods

Between July 2001 and July 2003, 132 patients with non-small cell lung cancer (NSCLC) were prospectively studied for reexpansion/reperfusion lung injury.

The population studied in this paper is part of the one studied in our previous publication [1]. The study group included 90 men (68.2%) and 42 women. Their age ranged from 44 to 76 years (mean, 62.1 years). The side of the lesions was to the right in 83 cases (62.8%) and 49 to the left. All were ex-smokers, suffering from non-small cell lung cancer. Chemotherapy, radiation, mechanical ventilation, and infection are widely considered as free oxygen radical generators [4—7]. Twelve patients that needed mechanical ventilation or were septic within the first 48 h postoperatively were excluded from the study along with patients that have been subjected to induction chemotherapy and/or radiotherapy.

The patients were classified into four groups to be analyzed (according to the use and the duration of one-lung ventilation). The patients who would be operated without

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one-lung ventilation (group A) and the ones who would be operated with OLV were randomly allocated in a prospective manner. The population managed with OLV was further classified into three groups (B, C, and D) according to intraoperative procedural criteria (OLV duration). There were no predetermined selection criteria in order to classify a certain patient into a certain group. The comparison was between OLV and non-OLV patients in order to define the impact of oxidative stress.

Group A included 50 patients with confirmed non-small cell lung cancer, who were subjected to lobectomy without one-lung ventilation. Groups B–D were the actual study groups and included 82 patients who were subjected to OLV lobectomy for lung cancer. These patients were grouped according to the duration of OLV subjected. Group B included 30 patients subjected to 60 min OLV. Group C included 30 patients subjected to 90 min OLV. Group D included 22 patients subjected to 120 min OLV.

The direct measurement of free radicals in plasma is very difficult, as biologic half-lives of these molecules range from nanoseconds to milliseconds. Modified proteins and lipids can be measured as an indirect measurement of oxidative stress. As an index of lipid peroxidation by free radicals, plasma malondialdehyde (MDA) levels were measured using high-performance liquid chromatography. A sensitive and easily reproduced method was used that was developed by Fukunaga et al. [8]. Plasma MDA levels were recorded in every patient following a strict blood sampling protocol. Peripheral venous blood was aspirated to an amount of 5 cm^3 each time. The timing of blood sampling was the following: (a) one sample 24 h preoperatively, (b) one sample 30 min after the onset of operation for group A or 30 min after the OLV onset for the study groups B–D, (c) one sample 5 min after lung reoxygenation (groups B–D) and after non-OLV lobectomy performed (group A), and (d) one sample at 1, 6, 12, 24, and 48 h postoperatively for all patients.

Age, gender, primary tumor location, histology, T status, and pathologic staging were recorded. Patients were classified according to postresectional complications. Analytically, the incidence of bronchopleural fistula, postoperative pleural empyema, pneumonia, atelectasis, acute respiratory failure, bronchospasm, ARDS, cardiac arrhythmias, myocardial ischemia, heart failure, pulmonary hypertension, renal failure, liver dysfunction, and 30-day mortality were recorded. The results were subjected to univariate analysis between non-OLV and OLV cases (i.e., A vs B, A vs C, and A vs D).

The patients were followed for several risk factors of postoperative morbidity and mortality. Cases with hemoglobin less than 9 mg/l, albumin less than 2.5 mg/dl, diabetes mellitus, serum creatinine more than 1.5 mg/l, preoperative FEV1 < 2 l, $PaO_2 < 70$ mmHg, preoperative $PaCO_2 > 45$ mmHg, history of coronary artery disease, concurrent thoracic wall excision, intraoperative blood loss more than 300 ml, duration from entrance into the pleura space until lobectomy completion more than 1 h, and need for intensive care unit postoperatively were recorded. These factors along with other clinical characteristics, such as age >65 years, gender, side of the lesion, and pathologic staging, were subjected to multivariate analysis with independent variables set by the results of the univariate analysis about the most common complications in OLV groups B–D in order to evaluate the role of oxidative stress as independent risk factor.

Univariate statistical analysis was performed using Student's *t*-test (otherwise the Wilcoxon rank-sum test) and chi-square (Fisher's exact test when needed) test where appropriate. Multiple logistic regression was used for multivariate analysis (forward method).

3. Results

Clinical characteristics and sampling results are fully described in Tables 1 and 2, respectively. In group A where no OLV was used the manipulations performed in order to accomplish lobectomy and thoracotomy's surgical stress per se generated a medium-size oxidative stress which in contrast to all other groups showed a gradual return to lower levels. When OLV was used the oxidative stress proved to be the most intense. Groups B–D disclosed the same tendency(Table 2). Characteristically the raise of MDA serum levels was relevant to the duration of lung atelectasis. D3 was significantly higher than C3 ($p < 0.001$) and C3 than B3 ($p < 0.001$). The more prolonged OLV the more strengthful

Table 1
Clinical characteristics

	Group			
	A	B	C	D
Number	50	30	30	22
Age (mean) (years)	62.9	64.4	59.8	60.3
Gender				
Male	31 (62%)	21 (70%)	23 (76.6%)	15 (68.2%)
Female	19 (38%)	9 (30%)	7 (23.4%)	7 (27.8%)
Side				
Right	31 (62%)	19 (63.3%)	19 (63.3%)	14 (63.6%)
Left	19 (38%)	11 (36.7%)	11 (36.7%)	8 (36.4%)
Primary tumor location				
RU	19 (38%)	10 (33%)	11 (37%)	9 (41.2%)
RL	2 (4%)	1 (3.3%)	2 (6.4%)	0
RM	10 (20%)	8 (26.9%)	6 (20%)	5 (22.5%)
LU	11 (22%)	4 (13.3%)	8 (26.7%)	6 (27.3%)
LL	8 (16%)	7 (23.5%)	3 (9.9%)	2 (9%)
Histology				
Adeno Ca	22 (44%)	15 (50%)	16 (54%)	10 (45.5%)
Squamous Ca	26 (52%)	12 (40%)	11 (36%)	9 (41%)
Sarcoma	0	0	0	1 (4.5%)
Bronchoalveolar	1 (2%)	0	1 (3.3%)	0
Giant cell	0	1 (3.3%)	0	1 (4.5%)
Other	1 (2%)	2 (6.7%)	2 (6.7%)	1 (4.5%)
Grade				
High	12 (24%)	11 (37%)	7 (23%)	5 (22.5%)
Moderate	29 (58%)	15 (50%)	14 (47%)	1 (50%)
Low	9 (18%)	4 (13%)	9 (30%)	6 (27.5%)
T status				
T1	8 (16%)	5 (16.5%)	4 (13%)	3 (13.6%)
T2	31 (62%)	20 (67%)	18 (60%)	12 (54.4%)
T3	11 (22%)	5 (16.5%)	8 (27%)	7 (32%)
Stage				
I	7 (14%)	4 (13%)	0	0
II	33 (66%)	17 (57%)	19 (63%)	16 (73%)
III	10 (20%)	9 (30%)	11 (37%)	6 (27%)

Table 2
Comparative results of MDA plasma levels (nmol/ml)

Time	Group			
	A	B	C	D
1	5.89 ± 4.7	5.89 ± 4.3	5.89 ± 3.6	5.90 ± 3.4
2	6.44 ± 3.0	6.44 ± 3.6	6.44 ± 3.2	6.35 ± 0.4
3	6.43 ± 3.4	14.48 ± 5.8	15.7 ± 4.0	18.31 ± 3.9
4	6.43 ± 3.3	14.70 ± 3.1	15.68 ± 3.4	18.74 ± 2.9
5	6.44 ± 4.1	9.80 ± 4.2	8.80 ± 3.9	9.75 ± 3.0
6	5.76 ± 5.1	4.90 ± 2.0	3.87 ± 2.8	4.10 ± 0.6
7	3.80 ± 3.3	3.69 ± 2.8	3.94 ± 2.7	4.04 ± 3.7
8	3.12 ± 2.9	3.13 ± 2.5	3.11 ± 2.5	3.11 ± 2.8

Time definitions: 1: 24 h preoperatively; 2: intraoperatively; 3: reventilation or time of lobe/lung removal; 4, 5, 6, 7, and 8: 1, 6, 12, 24, and 48 h postoperatively, respectively.

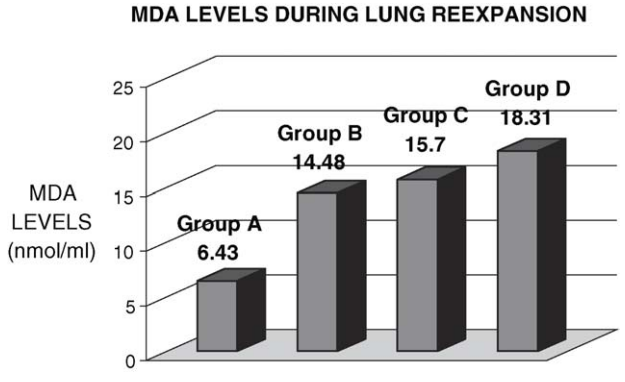

Fig. 1. MDA levels in non-one-lung ventilation lobectomy group (A) and in one-lung ventilation lobectomy groups (B–D) during lung reventilation.

oxidative stress was developed (Fig. 1). These high values were noted up to 1 h postoperatively. After that a gradual decrease was detected to lower than preoperative levels (B1 vs B8, C1 vs C8, and D1 vs D8 were all statistically significant, $p < 0.001$).

Postoperative complications of patients in groups B–D are summarized in Table 3. Statistical comparison of ratios between group B (non-OLV) and groups C and D (OLV) disclosed significant differences only with group D (120 min OLV), concerning higher incidence of acute respiratory failure ($p < 0.05$), cardiac arrhythmias ($p < 0.05$), and of pulmonary hypertension ($p < 0.05$) in the latter group. Non-cardiogenic pulmonary edema was not recorded among the patients of this study.

Table 4
Clinical parameters

	Group			
	A	B	C	D
Hb < 9 mg/l	7 (14%)	3 (6%)	3 (6%)	1 (4.5%)
Albumin < 2.5 mg/l	18 (36%)	7 (23%)	8 (26.4%)	8 (36%)
Diabetes mellitus	9 (18%)	5 (16.5%)	5 (16.5%)	4 (18%)
Creatinine > 1.5 mg/dl	2 (4%)	2 (6.6%)	1 (3.3%)	0
FEV1 < 2 l	7 (14%)	3 (10%)	3 (10%)	1 (4.5%)
PaO_2 < 70 mmHg	2 (4%)	1 (3.3%)	1 (3.3%)	1 (4.5%)
$PaCO_2$ > 50 mmHg	2 (4%)	1 (3.3%)	0	1 (4.5%)
Coronary artery disease	5 (10%)	3 (10%)	2 (6.6%)	1 (4.5%)
Thoracic wall excision	4 (8%)	2 (6.6%)	2 (6.6%)	1 (4.5%)
Duration of lobectomy > 1 h	12 (24%)	0	30 (100%)	22 (100%)
Blood loss > 300 ml	6 (12%)	2 (4%)	2 (4%)	1 (4.5%)
ICU	3 (6%)	3 (10%)	3 (10%)	5 (22.5%)

Risk factors for postoperative complications are presented in Table 4. Using as independent variables, the occurrence of acute respiratory failure, cardiac arrhythmias and pulmonary hypertension, multivariate analysis was conducted. For acute respiratory failure, no independent risk factor was revealed by multivariate analysis. On the contrary, for cardiac arrhythmias significant risk factors proved to be group C ($p = 0.001$, odds ratio 0.099, 95% CI 0.02–0.40) and D ($p = 0.007$, odds ratio 22.53, 95% CI 2.31–219.67), primary tumor location at the right side ($p = 0.012$, odds ratio 4.37, 95% CI 1.37–13.92), age older than 65 years ($p < 0.001$, odds ratio 7.92, 95% CI 2.52–24.89), tumor's stage IIIA ($p = 0.001$, odds ratio 12.01, 95% CI 2.70–53.37), preoperative hemoglobin level less than 9 mg/l ($p < 0.001$, odds ratio 0.03, 95% CI 0.005–0.21) and duration of lobectomy more than 60 min ($p = 0.02$, odds ratio 0.294, 95% CI 0.10–0.86). Group D proved to be the only significant risk factor for pulmonary hypertension development postoperatively ($p = 0.03$, odds ratio 14.80, 95% CI 1.28–170.72).

Mortality rates range from 2% to 4.5% (Table 5). Statistical analysis failed to reveal any significant difference between groups.

Table 3
Postoperative complications

Complications	Group A ($N = 50$)	Group B ($N = 30$)	Group C ($N = 30$)	Group D ($N = 22$)
Bronchopleural fistula	2 (4%)	1 (3.3%)	0 (0%)	1 (4.5%)
Postresectional empyema	3 (6%)	2 (6.6%)	1 (3.3%)	2 (9%)
Pneumonia	0 (0%)	0 (0%)	1 (3.3%)	0 (0%)
Atelectasis	2 (4%)	2 (6.6%)	1 (3.3%)	2 (9%)
Acute respiratory failure	2 (4%)	1 (3.3%)	1 (3.3%)	2 (9%)*
Bronchospasm	2 (4%)	2 (6.6%)	1 (3.3%)	3 (13.6%)
ARDS/ALI	0 (0%)	0 (0%)		1 (4.5%)
Cardiac arrhythmias	16 (32%)	8 (27%)	11 (37%)	13 (59%)*
Myocardial ischemia	1 (2%)	1 (3.3%)	2 (6.6%)	2 (9%)
Heart failure	1 (2%)	0 (0%)	0 (0%)	2 (9%)
Pulmonary hypertension	0 (0%)	0 (0%)	0 (0%)	2 (9%)*
Renal failure	1 (2%)	1 (3.3%)	0 (0%)	0 (0%)
Hepatic failure	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)

* $p < 0.05$.

Table 5
Postoperative mortality

Group A	1 (2%)
Group B	1 (3.3%)
Group C	1 (3.3%)
Group D	1 (4.5%)
Total	4 (3%)

4. Discussion

One-lung ventilation is a powerful free radical generator due to atelectasis reexpansion syndrome and was fully analyzed in our previous study [1]. Cellular damage following a hypoxic insult is biphasic, initiating with the lack of oxygen per se and exacerbating during reoxygenation. There is now abundant evidence that reoxygenation injury is the structural damage caused by the overwhelming generation of free radicals. They interact with cellular structural molecules provoking dysfunction mostly to endothelial cells. In case the oxidant burden is sufficiently powerful, the free radicals overwhelm the inherent antioxidant defense mechanisms, resulting in tissue dysfunction. Neutrophils play a pivotal role in regional and systemic effects of oxidative stress [4].

Previous reports have focused on the effects of oxygen free radicals on lung parenchyma [2,3]. In our study, complications concerning different systems were recorded and analyzed in order to study the impact of OLV oxidative stress on several organs postoperatively. Furthermore, the study was prospectively conducted in a clinical setting. The only affected organs were the heart and the lung. In the former, oxidative stress acted as an arrhythmogenic factor, while in the latter provoked a higher incidence of pulmonary hypertension and of acute respiratory failure. All of them could be attributed to oxygen radical species activity through well-studied mechanisms. An objection to this suggestion might be the fact that these complications were significantly noted only in group D. The duration of operation in this group was the most prolonged one (OLV 120 min). This parameter is another cause of increased complication rates.

In order to define the role of oxidation stress as an independent risk factor for complication development multivariate analysis was performed. The latter disclosed group C as an independent risk factor for cardiac arrhythmias while group D as one for cardiac arrhythmias and pulmonary hypertension development.

There are sufficient data to describe the pathophysiologic routes through which free radicals provoke the above-mentioned complications. In the case of cardiac arrhythmias, the generated hydroxyl radical ($OH^{\bullet}$) during oxidative stress along with hyperoxynitrate are considered the main factors that alter histology and biochemical function of cardiomyocytes through protein nitrotyrosine formation [9,10]. In addition, the propagation of inflammatory procedures further promotes the arrhythmiogenic effect. The above-mentioned alterations influence the energy status, the electrophysiology, and the mechanical properties of cardiac cells. In recent studies, the role of activated neutrophils on cardiac arrhythmias development has been proved [11–13]. Leukocytes exert their action through the generation of oxygen free radicals. Moreover, free radicals seem to provoke rhythm disturbances to the heart through inhibition of sarcolemmal Na/K-ATPase activity [14]. It has been established that many antioxidants such as allopurinol, deferroxamine, or glutatheione have led to decrease of arrhythmias due to oxidative stress, incriminating the whole spectrum of oxygen free radicals for their generation [15–17].

Many studies have proved the central role of free radicals for the development of pulmonary hypertension [18–24]. During reperfusion the superoxide production via an NADPH oxidase pathway is increased at the vascular smooth muscle layer, which enhances the 5-hydroxytryptamine pulmonary vasoconstriction. Furthermore, the generated oxygen reactive species stimulate the production and the action of endothelin-1, which is a powerful vasoconstrictor.

Although oxidative stress is considered to play an important role in postresectional pulmonary edema [2,3], no case was recorded in our study. The exact pathophysiology of this complication is complex and includes many factors such as perioperative fluid overload, alveolar injury, and impaired lymphatic drainage. Postresectional pulmonary edema clinical presentation usually takes place on the 2nd to 3rd postoperative day. In our study the oxidative stress subsided after the first 12 postoperative hours. One might hypothesize that free radicals is the main cause of postresectional pulmonary edema in two ways: either through an initial insult whose pathologic results evolve subclinically for 36 h or due to a persisting oxidative stimulus that expands the oxidative stress up to 48–72 h postoperatively.

In conclusion, prolonged (>1 h) OLV should be considered a potential cause for cardiovascular complications through the generation of severe oxidative stress due to lung reexpansion.

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