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The impact of preoperative micronutrient supplementation in lung surgery. A prospective randomized trial of oral supplementation of combined α-ketoglutaric acid and 5-hydroxymethylfurfural☆

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Abstract

Objective: Preoperative micronutrient supplementation in fast-track surgery programs have shown to reduce complications, shorten recovery, and thereby lower costs. In a prospective randomized study, the metabolic effects of a combination of α-ketoglutaric acid (α-KG) and 5-hydroxymethylfurfural (5-HMF) were evaluated concerning their impact on improvement of exercise capacity and reduction of oxidative stress in lung surgery. **Methods:** Thirty-two consecutive patients admitted for lung resection due to NSCLC were randomized to the study protocol. All patients received preoperative nutritional guidelines according to general recommendations. In 16 (study group), a supplementation of 7.2 g α-KG and 720 mg 5-HMF/day (SANOPAL®) was administered from days 1 to 10. Spiroergometric evaluation was carried out at baseline and day 10 after micronutrient supplementation. Blood samples for the determination of oxidative stress, i.e. carbonyl proteins (CPs) and isoprostanes (IPs) were taken on at baseline, in the operating room just before resection treatment, and 25 min after single lung ventilation (SLV). **Results:** Spiroergometric re-evaluation showed a significant increase of $\dot{V}_{O_2\,max}$ ($p = 0.0108$) and Watt's ($p = 0.011$) in favor of the study group. Determination of oxidative stress showed a significant reduction of CPs before ($p = 0.048$) and after SLV ($p = 0.0001$) for the study group compared to the control group. The same is true for IPs before ($p = 0.003$) and after SLV ($p = 0.02$). Hospitalization and intensive care unit (ICU) of the study group showed a significant reduction compared to the control group ($p = 0.03$ and $p = 0.02$, respectively). **Conclusions:** Simple oral supplementation using a combination of α-KG and 5-HMF of preoperative micronutrition may therefore be one further step in a multimodality approach of fast-track surgery programs also in lung surgery.

Keywords: Preoperative micronutrient supplementation; Lung cancer; Preoperative care; Surgery; Preconditioning

1. Introduction

Surgical resection remains the treatment of choice for non-small cell lung cancer (NSCLC) and some other benign diseases of the lung.

However, the presence of associated diseases increases the risk of death and surgical complications of patients undergoing lung resection. There is a wide range of postoperative complication rates, which in part depends on different definitions. Mortality rates following lung resection are between 3 and 5% [1]. Attention is now being directed towards standardization of surgical care, and evaluation of new treatment concepts in the pre- and perioperative period. The aims of these efforts are a shortening of the recovery period and a decrease of necessary hospital resources [2,3].

It has been shown that the surgical trauma itself as well as intra-operative maneuvers, such as single lung ventilation (SLV), cause oxidative stress injury with endocrine—metabolic inflammatory changes, systemic inflammatory response

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syndrome, and organ dysfunction [4,5]. In recent literature this phenomenon is best described by an increase of isoprostanes (IPs) [6]. This has shown to be the gold standard as it is the most sensitive biomarker of the radical-catalyzed lipid peroxidation and carbonyl proteins (CPs) [7], as an index of oxidative damage during lung ischemia and reperfusion.

On the other hand, lung resection implicates a reduction of both the ventilatory and the circulatory surface, compromising both oxygenation and cardiac function.

The prospective assessment of the severity of concomitant organ dysfunction and evaluation of micronutrient deficiencies with adequate preoperative treatment and/or supplementation has been tried to reduce both morbidity and mortality associated with resection of lung cancer.

However, none of these nutrition regimens has been focused on optimization of parameters, such as preoperative exercise capacity and a reduction of oxidative stress parameters, i.e. IPs and CPs.

Interestingly, the combination of oral intake of α-ketoglutaric acid (α-KG) and 5-hydroxymethylfurfural (5-HMF) as micronutrient supplementation of professional sportsmen (triathlon, skiing, and biking) has been shown to increase the training efficacy as documented with an increase of exercise capacity. Furthermore, a reduction of oxidative stress, i.e. CPs, has been found during competitions [8].

However, it has been well documented by a statement of the Austrian National Anti-doping Agency that oral supplementation of α-KG and 5-HMF is not doping (Seibersdorf Research; ULC 72/2005).

α-KG is an intermediate of the citric acid cycle and the natural ubiquitous collector of amino groups in body tissues. It has a potent 'sparing' effect on endogenous glutamine pools and a synergistic effect on the syntheses of glutamine. In addition, α-KG dramatically increases the synthesis of arginine, proline, and polyamines, which also play key roles in metabolic adaptation after surgery.

Furthermore, the recent literature suggests that α-KG improves gut morphology and functions, counteracts trauma-induced dysimmunity, and exerts anabolic/anti-catabolic actions on protein metabolism [9—11].

5-HMF is a common product of the Maillard reaction, which occurs in many foods and drinks (dried fruits, honey, caramel products) in high concentrations exceeding 1 g/kg [12]. It is also well known that heated sterilization of parenteral solutions induces hexose decomposition to 5-HMF at low pH [13].

5-HMF has also shown to be the causative component in honey that affects the pre-systemic metabolism and pharmacokinetics of glycyrrhizin in vivo [14].

The very complex biochemical effects of 5-HMF are simply best described in consuming singlet oxygen and in its interaction with hydroxyl radicals and super oxide forming further RONS, like H_2O_2- and peroxynitrite ($ONOO^-$).

In recent literature, there is no evidence that 5-HMF poses a serious health risk, even though the highest concentrations in specific foods approach the biologically effective concentration range in cell systems [12]. Dosages of parenterally administered 5-HMF exceeding 75 mg/kg body weight have led to some toxic effects including increased activity of hepatic enzymes, altered serum—protein fractions, and hepatic fatty degeneration. Approximately 50% of parenterally administered 5-HMF is oxidized and eliminated by the kidneys [13].

The aim of this prospective randomized study was to evaluate (1) the metabolic effects of increasing the exercise capacity of α-KG and 5-HMF as a simple oral micronutrient supplementation and (2) the reduction of oxidative stress parameters in patients with relevant comorbidity undergoing lung surgery due to NSCLC cancer.

2. Materials and methods

In an observer-blinded, prospective randomized trial, 32 consecutive patients with relevant comorbidity admitted for lung resection due to non-small cell lung cancer to the Department of Surgery, Division of Thoracic Surgery, University Medical Hospital of Graz were included to the study protocol. Randomization to the study and control group was done after final staging, spiroergometry, acceptance for resection treatment, and the signing of informed consent.

The study protocol was reviewed and accepted by the Ethics Committee of the Medical University School, Graz, Austria.

All patients included in the study protocol had impaired cardiopulmonary reserves and a higher operative risk as well as risk of complications. The demographic data of both study group and control group, including age, sex, nutritional status (body mass index), risk factors (comorbidity, induction chemotherapy), type of resection, and time of single lung ventilation, are depicted in Table 1.

In all patients a spiroergometric evaluation ($V_{O_2\,max}$, O_2-pulse, and maximum Watts per kg) [15] as well as measurement of the oxidative stress parameters (carbonyl proteins and isoprostanes) out of plasma were done at baseline. EDTA-blood samples were collected from individuals, allowed to clot, and centrifuged immediately; plasma was stored at $-70\,^{\circ}C$ until measurement.

For the determination of CPs oxidized bovine serum albumin (BSA) was prepared for standardization as described elsewhere [16]. Serum samples and standards were diluted to give a final protein concentration of 4 mg/ml. Measurement of CP was performed after derivatization with dinitrophenylhydrazine (DNPH) by a chemiluminescence technique on a chemiluminescence reader (Lumistar, BMG, Germany) with adding 200 μl/well Super Signal Maximum Sensitivity substrate (Pierce, Rockford, USA). Serum protein was measured with the bicinchoninic assay (BCA; Pierce, Rockford, USA).

A commercial competitive enzyme immunoassay kit (Assay Designs, Inc., Ann Arbor, MI, U.S.A.) was used for the quantitative determination of total 8-iso-$PGF_{2\alpha}$ in heparinized plasma samples.

Prior to analysis, plasma samples stored at $-70\,^{\circ}C$ were hydrolyzed in an excess of 10N NaOH at 45 °C for 2 h. The cooled samples were neutralized by adding 10N HCl and centrifuged 20 min at 4000 rpm. The clear supernatants were used for running the assay according to manufacturing instructions. The optical density in absorbance units (AU) was read at 405 nm on a micro plate reader (Spectra Count™, Packard Instrument Company, Meriden, U.S.A.). Data were analyzed by the plate reader's immunoassay software

Table 1
Patient characteristics

	Study group	Control group	Significance
Sex	12 males/4 females	10 males/6 females	n.s.
Age	64.1years ± 8.6	62.4 years ± 10.2	n.s.
Body mass index	25.4 ± 4.1	24.9 ± 4.0	n.s.
Induction chemotherapy	*n* = 4	*n* = 5	n.s.
Comorbidity	COPD (*n* = 16) Diabetes mellitus (*n* = 3) Coronary heart disease (*n* = 5) Myocardial ischemia (*n* = 2) Hypertension (*n* = 8) Tuberculosis (*n* = 3)	COPD (*n* = 16) Diabetes mellitus (*n* = 5) Coronary heart disease (*n* = 7) Myocardial ischemia (*n* = 2) Hypertension (*n* = 7) Tuberculosis (*n* = 4) Renal insufficiency (*n* = 1)	
Type of operation	Lobectomy (*n* = 7) Bilobectomy (*n* = 2) Sleeve lobectomy (*n* = 4) Limited resection (*n* = 3)	Lobectomy (*n* = 6) Bilobectomy (*n* = 4) Sleeve lobectomy (*n* = 6)	
Single lung ventilation/min	55.9 min ± 17.2	53.8 min ± 15.3	n.s.
Complications	Postoperative bleeding (*n* = 1) Minor air leak (*n* = 4) Prolonged air leak (*n* = 1)	Postoperative bleeding (*n* = 1) Minor air leak (*n* = 5) Prolonged air leak (*n* = 3) Myocardial ischemia (*n* = 1) Pneumonia (*n* = 1) Wound healing problem (*n* = 1)	
Intensive care unit	0.6 ± 0.5	2.6 ± 2.0	$p = 0.02$
Hospitalization	9.9 days ± 3.6	16.2 days ± 5.5	$p = 0.04$

package (I-Smart; Packard Instrument Company, Meriden, U.S.A.) utilizing the four-parameter logistic curve-fitting program. The concentrations of 8-iso-$PGF_{2\alpha}$ in the original plasma samples are given in ng/ml and were obtained after correction of the measured 8-iso-$PGF_{2\alpha}$ concentrations for the dilution of the original samples during the hydrolysis and neutralization step.

All patients had nutritional support according to the recommendations for the local dietary guidelines for preoperative nutrition of at least 10 days. The dietary protocol for both groups consisted of the daily intake of 30 kcal/kg body weight (proteins 1.8 g/kg BW, fat 1.2 g/kg BW, and carbohydrates 4 g/kg BW) distributed on different local easily available food recommendations, as well as suggestions for breakfast, lunch, and dinner dishes, based on typically Austrian menus.

In the study group (*n* = 16), 7.2 g α-KG and 0.720 mg 5-HMF/day subdivided into three doses were given as oral micronutrient supplementation. The single preparation of both substances was a drinking ampoule of 30 ml (SANOPAL®, CYL Pharmazeutika GmbH, A-8301 Lassnitzhöhe, Styria, Austria) diluted either with cold pure water or orange juice.

On day 10 of the study protocol all patients were questioned about their subjective impression concerning changes in their physical performance and spiroergometry was repeated. Lung resection was scheduled for days 11–12 after initiation of the oral supplementation treatment. Redetermination of the oxidative stress parameters was done in the operating theatre just before and 25 min after single lung ventilation.

All lung resections were performed by one senior surgeon (A.M.). In all patients a posterolateral thoracotomy and lobectomy, bilobectomy or sleeve lobectomy with complete lymph node dissection was done. The time of single lung ventilation was 55 min ± 17.2 for the study group and 53.8 min ± 15.3 for the control group.

3. Statistics

All spiroergometric data are shown as mean ± standard deviation (SD). Significance of correlation is based on linear regression and was set at $p < 0.05$. Mean values of study and control group and patients at time of inclusion were compared using paired *t*-test. Oxidative stress parameters are shown as mean ± standard deviation. Significance of correlation is based on linear regression using Mann–Whitney test.

4. Results

No side effects of the daily oral intake of 7.2 g α-KG and 720 mg 5-HMF could be observed in the study group. The fruity and fresh tasting drink was well accepted by the patients.

$V_{O_2\,max}$ and Watts of each patient was set to 100% at baseline. Spiroergometric re-evaluation on day 10 of supplementation with 7.2 g α-KG and 720 mg 5-HMF showed a significant difference in favor of the study group at the level of maximum exercise capacity concerning $V_{O_2\,max}$ (114.6 ± 9.5%; $p = 0.0010$) and Watts per kg (108.4 ± 4.8%; $p = 0.011$) (Figs. 1a and 2a) compared to the control group ($V_{O_2\,max}$: 102.1 ± 5.0%; Watts: 94.7 ± 3.7%). The same is true for the aerobic/anaerobic level for $V_{O_2\,max}$ (study group: 117.6 ± 7, control group: 104.3 ± 10; $p = 0.005$ and Watts

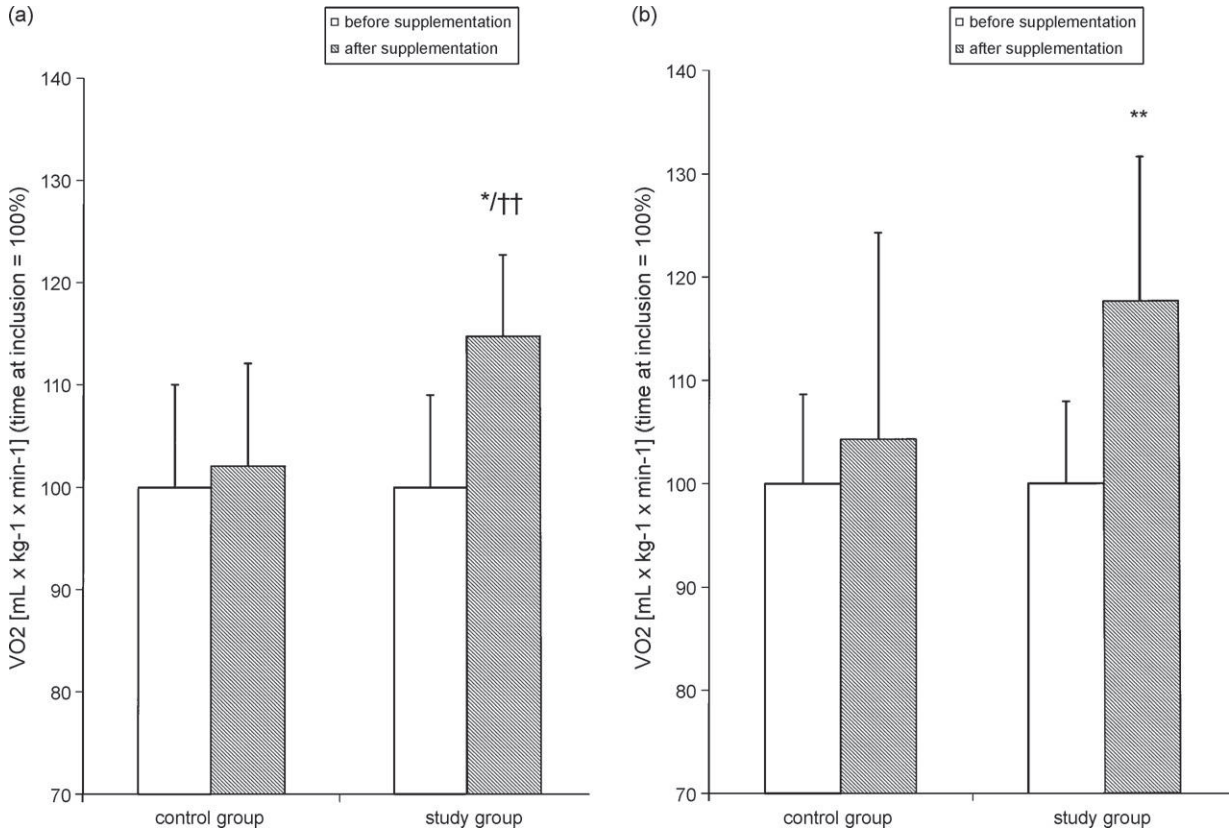

Fig. 1. Spiroergometric evaluation of $V_{O_2\,max}$ at the level of maximum exercise capacity (a) and the aerobic/anaerobic level (b). $V_{O_2\,max}$ levels before supplementation of the control and study group was set to 100%. (*) Significance of $V_{O_2\,max}$ levels of the study group before and after supplementation ($p = 0.011$). (**) High significance of $V_{O_2\,max}$ levels of the study group before and after supplementation ($p = 0.005$). (††) High significance of $V_{O_2\,max}$ levels between control and study group after supplementation ($p = 0.0010$).

study group: 122.1 ± 6.6, control group: 93.3 ± 6.2; $p = 0.002$) as seen in Figs. 1b and 2b.

Furthermore, the study group showed a significant increase of 22.2% for the aerobic/anaerobic level concerning Watts per kg ($p = 0.0003$) (Fig. 2b), and also at the level of maximum exercise capacity (Figs. 1a and 2a) for $V_{O_2\,max}$ of 14.7% ($p = 0.011$) and Watts of 8.4% ($p = 0.012$).

Determination of CPs (Fig. 3) comparing the levels at baseline (374 ± 66 pmol/mg) to the levels before SLV (581 ± 286 pmol/mg) showed no significant difference in the control group. However, after SLV a significant increase of CPs was estimated (991 ± 268 pmol/mg; $p = 0.0001$).

CPs in the study group before (368 ± 157 pmol/mg) and after SLV (425 ± 120 pmol/mg) maintained at the same level as estimated before supplementation (327 ± 152 pmol/mg).

Comparing CP levels of the study group with the control group a significant decrease was estimated before SLV (374 ± 66 pmol/mg vs 581 ± 286 pmol/mg; $p = 0.048$) and a high significant decrease after SLV (425 ± 120 pmol/mg vs 991 ± 268 pmol/mg; $p = 0.0001$), whereas at baseline no change in the amount of CP between study and control group was estimated.

Determination of IPs (Fig. 4) showed similar levels in both groups at baseline (control group: 1.75 ± 0.47 pmol/ml; study group: 1.47 ± 0.82 pmol/ml). After supplementation a high significant reduction of IPs was measured in the study group (1.15 ± 0.21 pmol/ml) compared to the control group (2.1 ± 0.47 pmol/ml; $p = 0.003$) before SLV and a significant reduction after SLV (control: 2.05 ± 0.71 pmol/ml, study group: 1.28 ± 0.50 pmol/ml; $p = 0.049$).

Hospitalization of patients in the study group was 9.9 days $\pm$ 3.6 and in the control group 16.2 days $\pm$ 5.5, which results in a significance ($p = 0.04$) as shown in Table 1. The same was true for intensive care unit (ICU): study group 0.6 days $\pm$ 0.5 and for the control group 2.6 days $\pm$ 2.0 ($p = 0.02$).

Risk factors, type of resection treatment, time of single lung ventilation, and complications of both groups are depicted in Table 1.

There was no mortality in either group.

5. Discussion

Recent findings in perioperative pathophysiology have shown a need for multimodality concepts in order to reduce postoperative morbidity and mortality [17]. Such efforts represent an extension of conventional 'clinical pathways', focusing on preoperative optimization of organ dysfunction [18], reversal of malnutrition, pain physiology and treatment, anesthesia, surgical technique, and early mobilization and rehabilitation including enforced postoperative feeding. The terminology for such programs has included such expressions as 'fast track' or 'accelerated recovery programs'

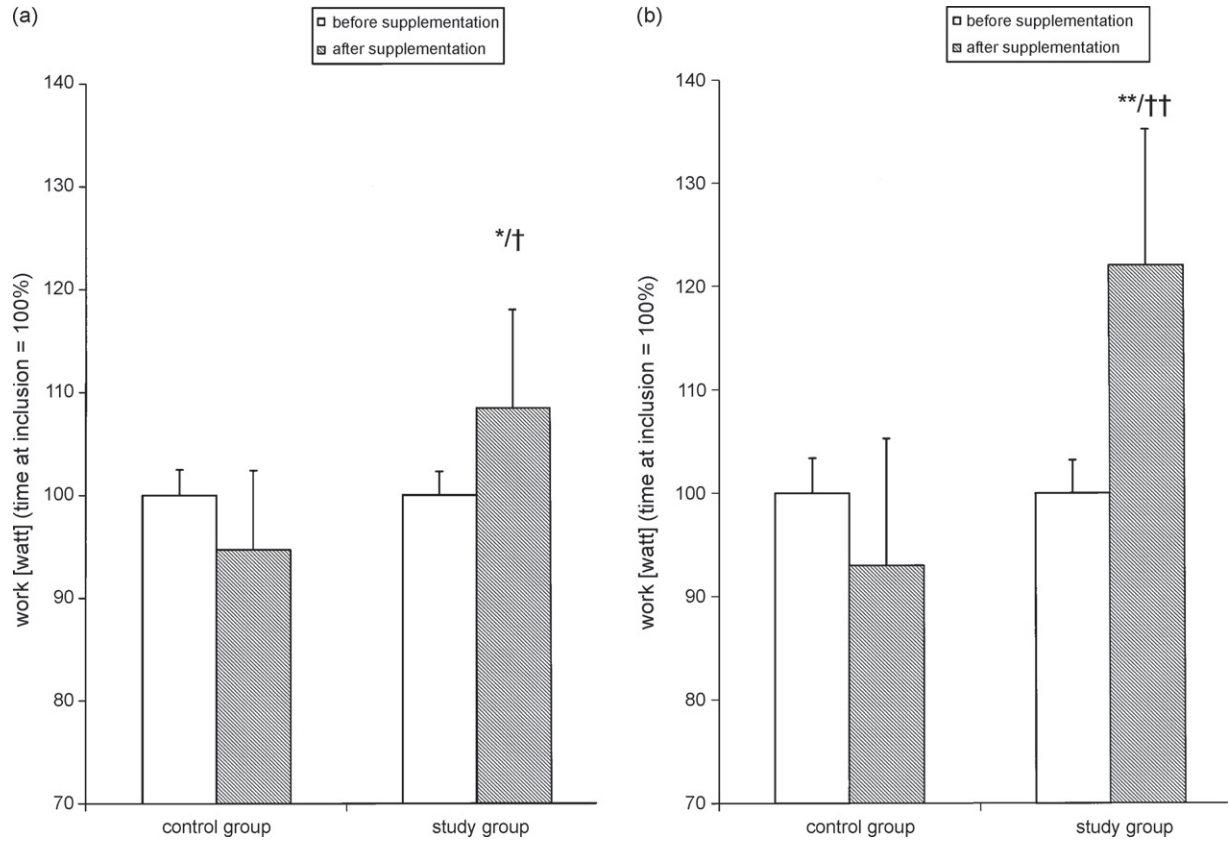

Fig. 2. Spiroergometric evaluation of Watts at the level of maximum exercise capacity (a) and the aerobic/anaerobic level (b). Watt levels before supplementation of the control and study group was set to 100%. (*) Significance of Watts of the study group before and after supplementation ($p = 0.011$). (**) High significance of Watts of the study group before and after supplementation ($p = 0.002$). (†) Significance of Watts between the control and study group after supplementation ($p = 0.012$). (††) High significance of Watts between the control and study group after supplementation ($p = 0.0003$).

with the common feature of a shortening of hospital stay with lower morbidity and lower overall costs.

These programs are based on a variety of measures to increase preoperative exercise capacity, reduce stress-induced organ dysfunction, and accompanying morbidity that otherwise results in the subsequent need for hospitalization and complication management.

Obviously, lung resection will lead to a decrease in lung function. However, the very patients requiring lung cancer surgery are more and more likely to suffer from concomitant pulmonary and circulatory disorders, usually caused by cigarette smoke. Since their tolerance of resection is limited, preoperative evaluation of these patients includes spiroergometry and estimation of postoperative pulmonary function based upon radioisotope ventilation—perfusion studies. Because the resection itself and the functional adaptation during postoperative period are extensively demanding on both the circulatory and respiratory reserve, the determination of preoperative exercise capacity ($V_{O_2\,max}$) has been shown to be the most sensitive predictor of postresection morbidity and mortality [1,19].

The increased exercise capacity in patients supplemented with a combination of α-KG and 5-HMF as found in the present study ($17 \pm 3\%$ vs $2 \pm 5\%$) is best explained by the biochemical mechanisms of the substances as reported in literature [10—12,14,20].

There is increasing evidence that during intense exercise or surgical trauma, 2—5% of total electron flux through the cytochrome chain results in super oxide radical formation [21,22]. This may substantially increase the formation of reactive oxygen and nitrogen species (RONS) in different tissues like muscle fibers, endothelium, lung, heart, or liver cells [23,4].

In recent years the measurement of CPs and IPs has been focused on the metabolism of RONS, damaged proteins, lipid peroxidation, and DNA [24,25] during and after exercise. In this context, elevated level of CPs and IPs is generally a sign not only of exercise or surgical trauma-induced oxidative stress but also of disease-derived dysfunctions. Therefore, reaction of reactive oxygen and nitrogen species and free radicals with proteins forming CPs and lipid peroxidation forming IPs was on one hand an indicator for oxidative stress determination but on the other hand an effective tool proving antioxidative capacity of different micronutrient supplements like α-KG and 5-HMF.

This is in good agreement with the results of this study showing significant decreased levels of oxidative stress parameters (IPs and CPs) for the study group.

Pulmonary parenchyma is one of the largest reservoirs for neutrophils, monocytes, and macrophages. Oxidative stress injury resulting from intra-operative manipulation, ischemia, or non-ventilation eventually causes cellular hypoxic injury

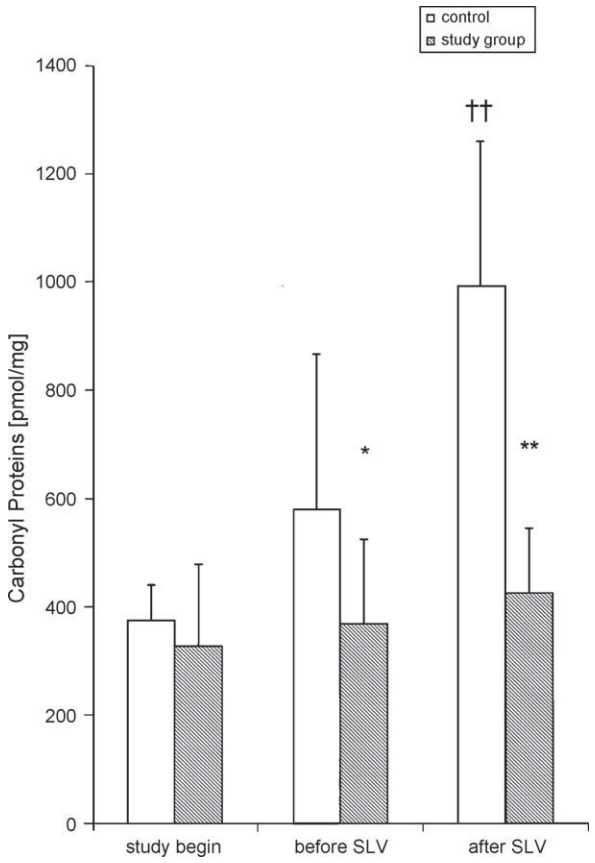

Fig. 3. Determination of carbonyl proteins (CPs) of the control and study group before supplementation, before and after single lung ventilation (SLV). (*) Significance between the study group and control group ($p = 0.048$). (**) High significance between the study group and control group ($p = 0.0001$). (††) High significance of the control group before supplementation and after SLV ($p = 0.0001$).

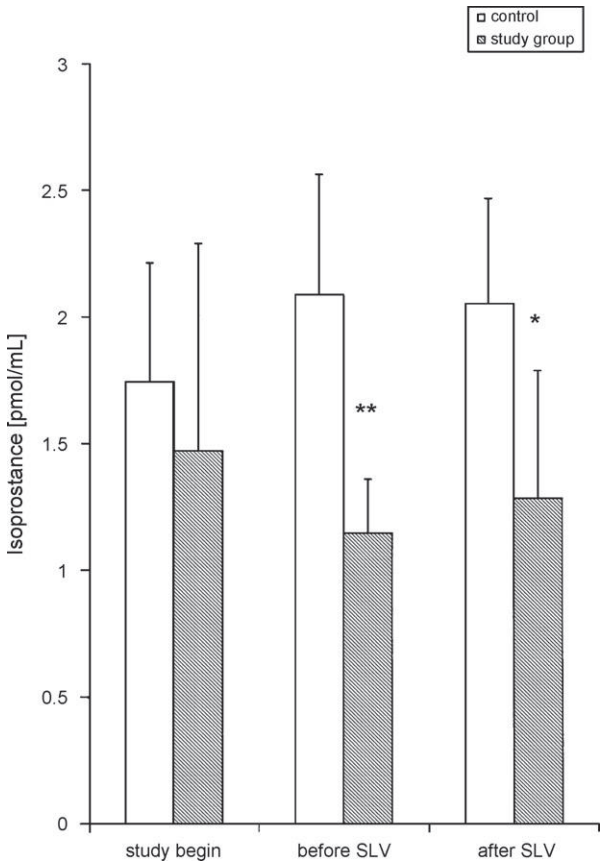

Fig. 4. Determination of isoprostanes (IPs) of the control and study group before supplementation, before and after single lung ventilation (SLV). (*) Significance between the study group and control group ($p = 0.049$). (**) High significance between the study group and control group ($p = 0.003$).

[4]. Moreover, atelectasis leads to hypoxic vasoconstriction whereas subsequent re-expansion along with oxygen re-entrance through the airways induces reactive pulmonary vascular dilatation during reperfusion of the lung. Any ischemia—reperfusion sequence is associated with the formation of oxygen free radicals. They interact with cellular structural molecules provoking dysfunction mostly of endothelial cells. Considering these pathophysiological pathways, complications after major surgery, especially lung surgery, may be related to factors in the surgical stress response with endocrine—metabolic and inflammatory changes [4,5]. The reduction of the most sensitive parameters, IPs and CPs, for detection of oxidative stress in lung surgery documented the additive effect of simple oral micronutrient supplementation of α-KG and 5-HMF.

However, the generated data of this study support the hypothesis that a significant reduction of oxidative stress and improvement of preoperative exercise capacity with its complex pathophysiological pathways correlate with the clinical outcome, i.e. reduction of ICU, hospitalization, and, last but not the least, overall costs.

Furthermore, the results of preoperative micronutrient optimization using α-KG and 5-HMF lead to the hypothesis that the perioperative use in parenteral and oral preparations may increase these effects.

In conclusion, simple oral micronutrient supplementation using a combination of α-KG and 5-HMF, with the metabolic effects of increasing the exercise capacity and reduction of the oxidative stress injury, may therefore be one further step towards introducing a multimodality approach in major surgery, with the goals of lower hospitalization, morbidity, and overall costs.

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