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Transcutaneous Stimulation of Auricular Branch of the Vagus Nerve Attenuates the Acute Inflammatory Response After Lung Lobectomy

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Abstract

Objectives Systemic inflammation is a potentially debilitating complication of thoracic surgeries with significant physical and economic morbidity. There is compelling evidence for the role of the central nervous system in regulating inflammatory processes through humoral mechanisms. Activation of the afferent vagus nerve by cytokines triggers anti-inflammatory responses. Peripheral electrical stimulation of the vagus nerve in vivo during lethal endotoxemia in rats inhibited tumor necrosis factor synthesis and prevented shock development. However, the vagal regulatory role of systemic inflammation after lung lobectomy is unknown.

Methods One hundred patients who underwent lobectomy via thoracotomy were recruited and equally randomized to treated group or controls. Intermittent stimulation of the auricular branch of vagus nerve in the triangular fossa was applied in the treated group using neurostimulator V (Ducest®, Germany), starting 24 h preoperatively and continued till the 4th postoperative day (POD). Inflammatory interleukins (IL) were analyzed using ELISA preoperatively, on the 1st and 4th POD.

Results On the 1st POD, patients who underwent neurostimulation had reduced serum concentrations of CRP ($p = 0.01$), IL6 ($p = 0.02$) but elevated IL10 ($p = 0.03$) versus controls. On the 4th POD, serum concentrations of CRP, IL6 and IL10 were similar in both groups. Moreover, the treated group was associated with lower incidence of pneumonia ($p = 0.04$) and shorter hospitalization time ($p = 0.04$) versus controls.

Conclusions Modulations in the brain stem caused by noninvasive transcutaneous stimulation of the vagus nerve after lung lobectomy attenuate the acute postsurgical inflammatory response by the regulation of IL6 and IL10, resulting in reduced incidence of postoperative pneumonia and short hospitalization time.

Clinical Trial Registry Number NCT03204968.

Introduction

Video-assisted thoracoscopic surgery (VATS) is the accepted surgical modality for early-stage lung cancer and has been gradually applied to more advanced disease [1]. However, thoracotomy remains the preferred approach in more than 50% of lobectomies. The conversion rates from thoracoscopic to open thoracotomy range from 2 to 23% and are due to advanced oncological conditions, intraoperative complications and technical or anatomical problems [2]. Thoracotomies are associated with higher grades of

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surgical trauma, local and systemic inflammatory responses. The systemic inflammatory response and its related hemodynamic response are caused by hormonal, metabolic and immunological mediators. Following trauma, the coagulation system is early and readily activated; thus, thrombin activates C5a in the complement system to mediate the immune response [3]. Afterward, monocytes and endothelium in the injured area release proinflammatory cytokines including interleukin (IL)-1-β, IL-6, IL-8, tumor necrosis factor (TNF)-α and interferon (IFN)-γ [4]. The complex network of cytokines balances the pro- and anti-inflammatory effects. Therefore, a postsurgical imbalance or uncontrolled production of cytokines can result in excessive inflammatory response. The central nervous system plays also an essential regulatory role in the inflammatory response [5]. Afferent nerve impulses to the brain triggered by pain and cytokines in the wound induce systemic cytokines production and produce the acute phase response including fever, leukocytosis, hypothalamic–pituitary–adrenal axis stimulation of the catabolic hormones, acute phase protein synthesis in the liver and immune activation [6]. Evidence revealed that afferent vagus nerve fibers sense peripheral inflammatory molecules and play a role in the central regulation. Moreover, afferent vagus signaling plays a role in the integration of visceral sensory information and coordination of autonomic function and behavioral response through its neural contacts between brainstem nuclei, the hypothalamus and forebrain regions [7]. It has been shown that vagus nerve stimulation suppresses local and serum proinflammatory cytokine including TNF, IL-1β and IL-18, suggesting an anti-inflammatory role for the efferent vagus nerve [8, Fig. 1]. Accordingly, several trials attempt to utilize the anti-inflammatory properties of vagus nerve [9]. Chemical vagal stimulation and direct electrical stimulation have proved to be effective in vagus nerve stimulation, however, with more side effects and relatively high financial costs. Noninvasive methods as transcutaneous stimulation of the auricular branch of the vagus nerve are a considerable step forward. Anatomically, the auricular branch of the vagus nerve supplies sensory innervation to the skin of the ear canal, tragus and auricle. Thus, a transcutaneous electrical stimulation of the ear auricle resulted in stimulation of this nerve. Evidences suggest therapeutic benefits of this method in many conditions including atrial fibrillation, diabetes, endotoxemia and myocardial infarction [10, 11]. However, the postsurgical anti-inflammatory role of vagus nerve stimulation is unknown and the current work focused on this issue.

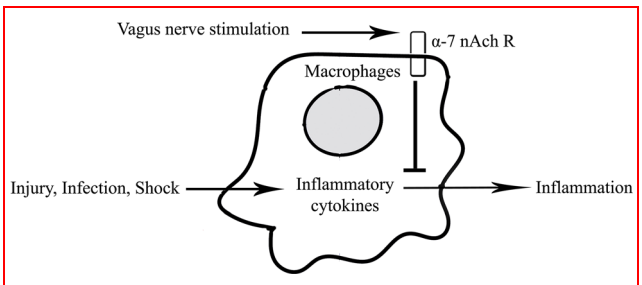

Fig. 1 Illustration of the effect vagus nerve stimulation on the production of inflammatory Interleukins in the immune cells. α7 nACh R: Alpha7 nicotinic acetylcholine receptor

Patients and methods

Patients

The Clinical Trial was registered under the number: NCT03204968 and approved by the Ethics Committee of the City of Vienna. After power analysis ($\alpha = 0.05$, mean1 = 110, mean2 = 161, sigma = 85, power = 80%), 100 adult patients suffering from resectable non-small cell lung cancer and scheduled for open anatomical resection (lobectomy or pneumonectomy), who gave informed consent to participate, were enrolled and randomized via block randomization equally either in treated group or in controls. Thoracotomy was indicated for locally advanced or centrally located tumors. Patients presenting with any signs of inflammation, bacterial infection or being under immunosuppression or preoperative anti-inflammatory medications such as nonsteroidal anti-inflammatory drugs or steroids were excluded. Further exclusion criteria were intra- or postoperative blood transfusion, postoperative re-intubation or reopening (Fig. 2).

Postoperatively, patients were transferred to intermediate care unit (IMCU) under continuous cardiorespiratory monitoring and appropriate noninvasive oxygen support. IMCU stay depended on the referring individual postoperative condition. All included patients received intraoperative thoracic epidural analgesia and postoperative medication with metamizole sodium and acetaminophen intravenously for pain control. Respiratory failure was diagnosed if $pO2 < 60$ mm Hg while breathing room air. Pneumonia was diagnosed radiologically in patients with clinical symptoms of pneumonia as well as elevated CRP and leukocytosis in the laboratory test.

Routine blood examinations were performed on hospital admission and on the 1st postoperative day (POD) or when clinically indicated. Additional whole blood samples were obtained at 24 h prior to operation, on the 1st and 4th POD. All samples were centrifuged at 3000 rpm for 10 min to separate serum, then coded and snap-frozen.

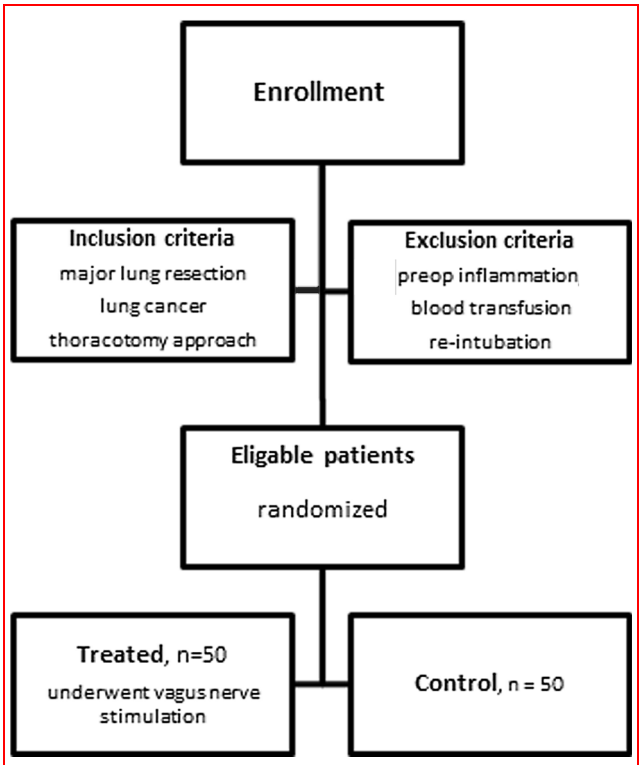

Fig. 2 Consort diagram of study enrollment

Vagus stimulation

Neurostimulator V (Ducest, Mattersburg, Germany) was used according to the manufacturer's protocol for the transcutaneous stimulation of vagus nerve. The stimulation needle was placed in the triangular fossa of the external acoustic meatus, to stimulate the auricular branch of the vagus nerve. The device was placed on the lateral side of the neck. The stimulation phase continued for 40 min followed by 20-min pause. The stimulatory pulse duration was 200 μs ± 20% with an effective voltage /current of 2.3 mV/230 nA at 10 kΩ. The stimulation started 24 h prior to the operation and continued till the 4th POD.

Enzyme-linked immunosorbent assay

Enzyme-linked immunoassay (ELISA) kits for IL6, IL18, IL10, IL1β and TNFα (RayBiotech, Norcross, GA) were used according to the manufacturer's protocol. Briefly, standard or serum samples were added to each monoclonal antibody pre-coated well and incubated for 2.5 h. Biotinylated antibody was then added and incubated before streptavidin was finally added. Substrate reaction was quantified spectrophotometrically by using iMark microplate photometer (Bio-Rad, CA) at 450 nm [12]. The reference ranges for CRP, IL6, IL18, IL10, IL1β and TNFα were <5 pg/l, <7 pg/ml, <70 pg/ml, <9 pg/ml, <3 pg/ml and <200 pg/ml, respectively.

Statistical analysis

All parameters were compared between patient groups by chi-square test, *T* test and analysis of variance (one-way ANOVA; Tukey's post hoc test) according to the scale of the variable (categorical or continuous). In the case of skewed data, a nonparametric test (Mann–Whitney test) was applied. Repeated measures ANOVA examined the changes of serum cytokines overtime. SPSS system for Windows, version 21 (SPSS, IBM, Armonk, NY), was used. The statistical significance was set at $p < 0.05$.

Results

Patient clinical characteristics

There was no significant difference between both study groups regarding the basic clinical data or preoperative comorbidities. However, patients underwent vagus stimulation had a statistically significant lower incidence of postoperative pneumonia ($p = 0.04$) and respiratory failure comparing to controls. Although the duration of chest tubes was comparable in both groups, the treated group has a significantly shorter hospitalization time comparing to controls ($p = 0.04$, Table 1).

Vagus stimulation attenuates postoperative CRP

The treated group had significantly lower serum CRP levels on 1st POD (90 ± 42 mg/l) comparing to controls (157 ± 83 mg/l, $p = 0.01$). On the 4th POD, the control group still had higher CRP (138 ± 101 mg/l); however, this was not significantly different to treated group (77 ± 94 mg/l, $p = 0.12$; Fig. 3).

Repeated measures ANOVA determined significant alterations of CRP overtime in controls ($F = 7.7$, $p < 0.02$). Namely, post hoc test revealed a significant elevation of CRP on the 1st POD ($p < 0.001$) comparing to preoperative CRP concentrations. On the 4th POD, there was a slight reduction in CRP, which was still significantly different compared to preoperative levels ($p < 0.04$) but not to those on the 1st POD ($p = 0.4$). The treated group showed also elevated CRP concentrations during the postoperative course; however, this increase never reached the significance level when compared to preoperative levels ($F = 1.5$, $p < 0.2$; Fig. 3).

Table 1 Demographic and clinical characteristics of study patients

	All patients $n = 100$	Controls $n = 50$	Treated $n = 50$	p value
Mean age, years	63 ± 9	64 ± 9	62 ± 8	0.64
Sex (male, %)	50, 50%	24, 48%	26, 52%	0.42
Operating time (mean hours ± SD)	3 ± 0.6	3 ± 0.8	3 ± 0.4	0.96
Resected lobe (*n*, %)				0.88
RUL	28, 28%	15, 30%	13, 26%	
ML	5, 5%	2, 4%	3, 6%	
RLL	26, 26%	12, 24%	14, 28%	
LUL	15, 15%	7, 14%	8, 16%	
LLL	20, 20%	11, 22%	9, 18%	
Pneumonectomy	6, 6%	3, 6%	3, 6%	
Comorbidities				
Coronary artery disease (*n*, %)	11, 11%	6, 12%	5, 10%	0.41
Atrial fibrillation (*n*, %)	11, 11%	6, 12	5, 10%	0.73
Arterial hypertension (*n*, %)	50, 50%	29, 58%	21, 42%	0.61
COPD (*n*, %)	16, 16%	7, 14%	9, 18%	0.55
FEV1% (mean ± SD)	74.6 ± 16	76.8 ± 15	74.1 ± 17	0.56
DLCO% (mean ± SD)	70.2 ± 15	66.8 ± 18	71.2 ± 15	0.34
Smoking, pack-year (mean ± SD)	32 ± 14	31 ± 15	35 ± 10	0.51
Current smoker (*n*, %)	51, 51%	24, 48%	27, 54%	0.21
Former smoker (*n*, %)	30, 30%	17, 34%	13, 26%	0.32
Dyspnea (*n*, %)	5, 5%	3, 6%	2, 4%	0.92
CHF (*n*, %)	3, 3%	1, 2%	2, 4%	0.34
Peripheral vascular disease (*n*, %)	1, 1%	1, 2%	0	0.44
Diabetes mellitus (*n*, %)	10, 10%	6, 12%	4, 8%	0.49
Neoadjuvant chemotherapy	31, 31%	14, 28%	17, 34%	0.97
Histological Staging (*n*, %)				0.31
IIA	28, 28%	16, 32%	12, 24%	
IIB	34, 34%	12, 24%	22, 44%	
IIIA	28, 28%	15, 30%	13, 26%	
IIIB	7, 7%	5, 10%	2, 4%	
IVAss	3, 3%	2, 4%	1, 2%	
Complications (*n*, %)				
Pneumonia	10, 10%	7, 14%	3, 6%	**0.04**
Respiratory insufficiency	11, 11%	7, 14%	4, 8%	0.06
Postop. atrial fibrillation	4, 4%	2, 4%	2, 4%	0.17
Glucose, mg/dl	115 ± 25	130 ± 28	108 ± 10	0.06
Chest tube duration (mean day ± SD)	5 ± 4	5 ± 3	6 ± 4	0.36
Hospitalization time (mean day ± SD)	11 ± 9	15 ± 14	9 ± 7	**0.04**

CHF congestive heart failure, *COPD* chronic obstructive pulmonary disease, *DLCO* diffusing capacity of the lungs for carbon monoxide, *FEV*1 forced expiratory volume in 1 s, *LLL* left lower lobe, *LUL* left upper lobe, *ML* middle lobe, *RLL* right lower lobe, *RUL* right upper lobe, *SD* standard deviation

Bold values indicate statistical significance $p < 0.05$

Vagus stimulation modulates postoperative acute phase cytokines

The preoperative serum concentrations of IL-6 were considered as baseline and were comparable between the groups. Vagus nerve stimulation was associated with significantly lower serum IL-6 concentrations on 1st POD (154.8 ± 93 pg/ml) comparing to controls (258.6 ± 110 pg/ml, $p = 0.02$; Fig. 4a).

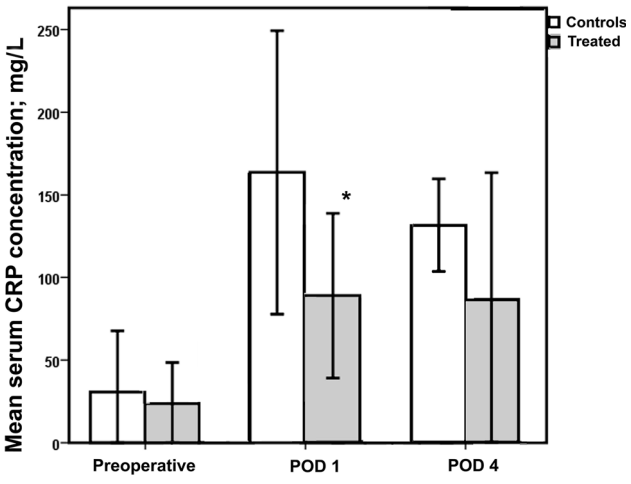

Fig. 3 Vagus nerve stimulation attenuates postoperative CRP concentration. CRP concentrations on the 1st operative day were significantly lower in treated group as compared to controls. *, $p = 0.01$. POD: postoperative day

Repeated measures ANOVA with post hoc test revealed elevated postoperative serum IL-6 concentrations in controls (258.6 ± 110 pg/ml) and treated group (154.8 ± 93 pg/ml) as compared to their preoperative levels (63.4 ± 29 pg/ml, $p = 0.01$ and 53.2 ± 20 pg/ml, $p = 0.03$, respectively; Fig. 4a). Thereafter, serum IL-6 concentrations decreased overtime and reached near-baseline levels on 4th POD (in controls 98.3 ± 39.7 pg/ml; $p = 0.06$ and treated group 93.7 ± 32.9; $p = 0.05$; Fig. 4a).

On the anti-inflammatory side, the preoperative baseline of IL-10 concentration was comparable in both groups. In the treated group, repeated measures ANOVA revealed significant changes of IL-10 concentrations overtime ($F = 7.7$, $p < 0.008$). Post hoc tests revealed a significant elevation of serum IL-10 concentrations on the 1st POD as compared to preoperative levels ($p = 0.03$; Fig. 4b). Moreover, IL-10 concentrations decreased significantly on 4th POD as compared to the 1st POD ($p < 0.002$) and became comparable to the preoperative baseline ($p = 0.45$; Fig. 4b). Serum IL-10 concentrations increased also postoperatively in controls with partial remission on the 4th POD, however without statistical significance ($F = 0.87$, $p = 0.4$; Fig. 4b).

IL-10 correlated significantly with IL-6 in the treated group (r_s: 0.75, $p < 0.008$) but not in controls (r_s: 0.35, $p < 0.3$). Such significant correlation suggests that vagus nerve stimulation might contribute to simultaneous modulation of both IL-6 and IL-10, which in turn triggers an anti-inflammatory response.

In contrast, repeated measures ANOVA did not reveal any significant changes in serum concentrations of IL-1β ($F = 0.02$, $p = 0.95$ in controls and $F = 0.64$, $p = 0.52$ in treated group; Fig. 5a) and IL-18 ($F = 1.7$, $p = 0.22$ in controls and $F = 2.8$, $p = 0.12$ in treated group; Fig. 5b). Likewise, both groups showed no significant changes in serum TNF-α concentrations overtime ($F = 0.67$, $p = 0.48$ and $F = 0.26$, $p = 0.74$, respectively; Fig. 5c).

Furthermore, glucose concentrations on the 1st POD were lower in treated group (108 ± 10 mg/dl) as compared to controls (130 ± 28 mg/dl).

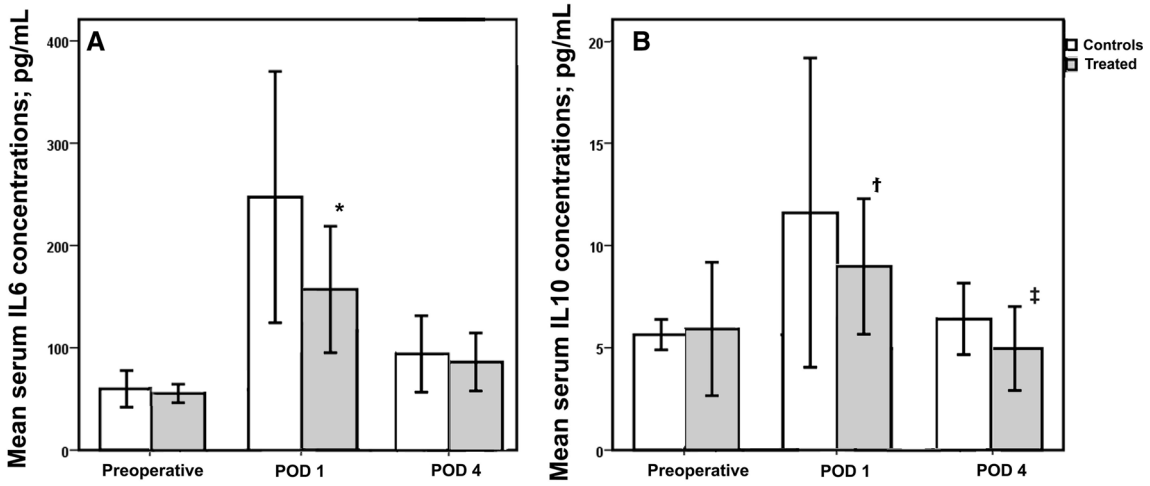

Fig. 4 Vagus stimulation modulates postoperative acute phase cytokines. **a** Vagus nerve stimulation attenuates IL-6 concentration on the 1st postoperative day as compared to controls, *, $p = 0.02$. **b** Vagus nerve stimulation induces IL-10 production in the treated group on the 1st postoperative day as compared to preoperative levels (†, $p = 0.03$) with significant remission on the 4th postoperative day (‡, $p < 0.002$) as compared to the 1st postoperative day. POD: postoperative day

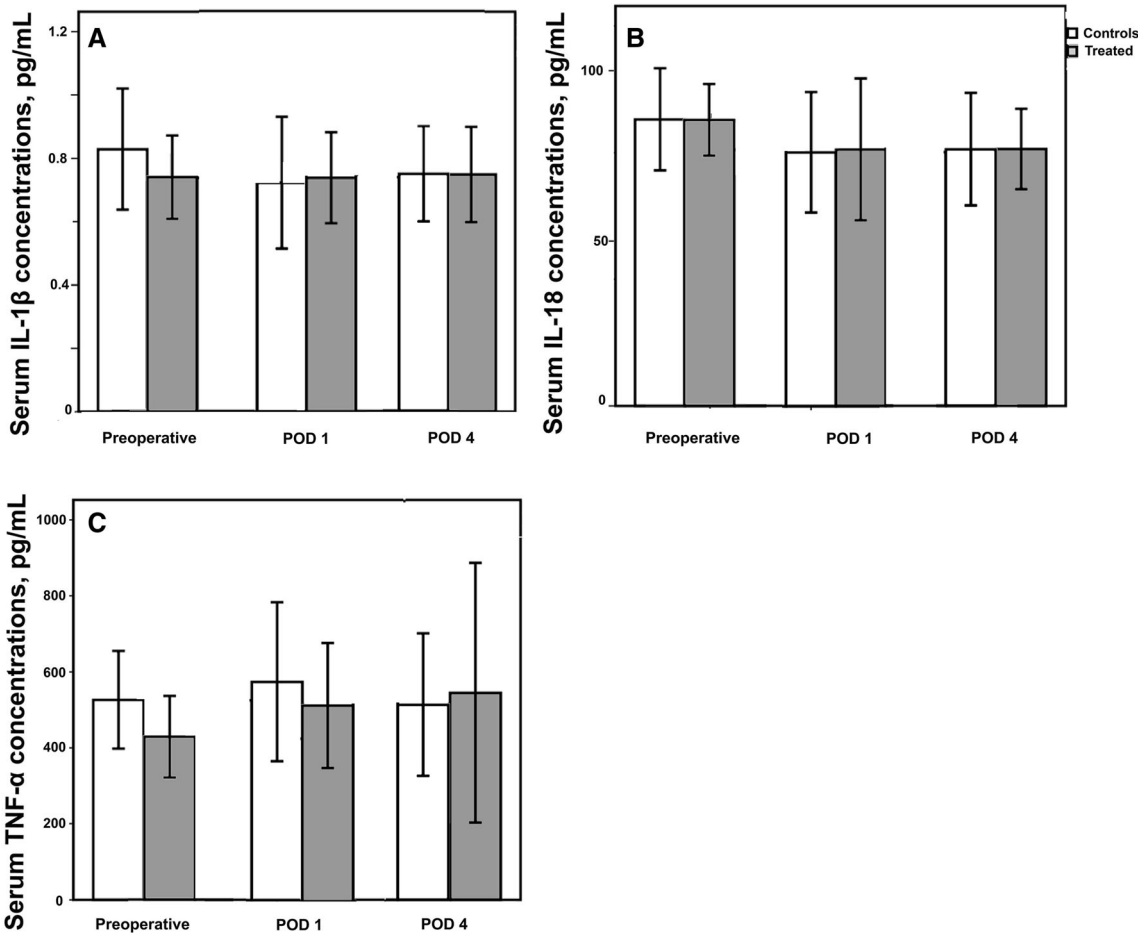

Fig. 5 Serum concentrations of **a** IL-1β, **b** IL-18 and **c** TNF-α were not affected by vagus nerve stimulation. POD: postoperative day

Discussion

Surgical stress starts early in the preoperative phase and continues after postoperatively. It is the end result of a variety of stimuli evoked by psychological stress, tissue injury, alterations in circulation, anesthetic agents and postoperative complications [10]. Cytokines contribute to surgical stress by stimulating the hypothalamic–pituitary–adrenal axis to produce stress hormones. Thoracic operations with manipulation and resection of the lung provoke local inflammatory responses which correlate with the trauma magnitude. Local mediators including kinins, arachidonic acid metabolites and histamine in the traumatized tissue increase capillary permeability and tissue edema and stimulate the recruitment of immune cells. Monocytes and endothelium in the injured area release proinflammatory cytokines as IL-1-β, TNF-α, IL-6, IL-8 and IFN-γ [4]. TNF-α and IL-1 stimulate in turn immune cells to secrete cytokines such as IL-6 and IL-8 and IL-10 [13]. IL-6 is one of the important trauma-associated cytokines that is detectable in plasma shortly after trauma. IL-6 stimulates the hepatic acute phase protein synthesis inducing CRP and procalcitonin. The secretion of IL-6 correlates with the trauma magnitude, the duration of surgery and the risk of postoperative complications [14]. In the setting of thoracic surgery, IL-6 is believed to be a reliable predictor of postoperative systemic inflammatory response syndrome (SIRS) [15]. Evidence suggests that IL-6 is able to detect postoperative SIRS even before the onset of the clinical symptoms [15]. The main key finding of the current study is that vagus nerve stimulation significantly attenuates the incidence of postoperative pneumonia and respiratory insufficiency. We believe that this finding is a direct consequence of reduced IL-6 levels after vagus nerve stimulation. Toward this end, previous studies focused on the important role of efferent vagus nerve cholinergic signaling in immune regulation and suppression of proinflammatory cytokine [16]. The cholinergic anti-inflammatory pathway was described as an efferent vagus nerve-based arm of the inflammatory reflex, which can be centrally regulated through the muscarinic acetylcholine receptors [8]. On the

other hand, the α7-nicotinic acetylcholine receptor (α7nAChR) expressed in macrophages, monocytes, dendritic cells, T cells, endothelial and other non-neuronal cells mediate the anti-inflammatory signaling of the vagus efferent arm of the inflammatory reflex in peripheral tissues [9]. Upon vagus nerve stimulation, α7nAChR induces downregulation of Toll-like receptors-4 and cluster of differentiation 14 expression in immune cells, resulting in inhibition of proinflammatory cytokines including IL-6 [17]. In concert with this, our finding revealed an inhibition of CRP after vagus nerve stimulation, which is obviously a result of the suppression of the IL-6.

Previous studies revealed also a strong association between the level of plasma cytokines including IL-6 and the extent of the tissue injury and sustained surgical stress [18, 19]. This fact in accordance with our current findings ensures the important role of IL-6 in the postoperative inflammatory response and closes the gap between incipient inflammatory reaction and the onset of clinical signs [15].

Another key finding of this study is the potential role of IL-10 in the postoperative phase. IL-10 is an important regulatory cytokine with both immunosuppressive and immunostimulatory properties. The elevated postoperative IL-10 in treated and control groups emphasizes the controversial role of IL-10. The elevated IL-10 in controls is considered as a natural inhibitor of the excessive postsurgical inflammatory response. The concomitant elevation of IL-10 and other proinflammatory interleukins in controls together with the increased incidence of pulmonary inflammation and prolonged hospitalization indicates the immunosuppressive role of IL-10, which impairs the immune system to counter-regulate the inflammatory process [20, 21]. Previous evidence revealed that excessive production of IL-10 immediately after the surgery contributes to sepsis-induced immunosuppression and is associated with prolonged ICU stay and higher mortality [22]. On the other hand, vagus nerve stimulation resulted in downregulation of IL-6 with simultaneous elevation of IL-10. This fact suggests that vagus nerve stimulation might contribute to adequate posttraumatic immune modulation. Consequently, patients who underwent vagus nerve stimulation were associated with lower incidence of postsurgical inflammation and shorter hospitalization.

In addition, patients who underwent vagal stimulation tend to have lower serum glucose levels. Accordingly, it has been shown that the afferent stimuli from injured tissue induce neurohumoral responses in the form of cytokines and the stress hormones, resulting in rapid metabolic response. The initial catabolic phase (3–8 days) with increased glycogenolysis, gluconeogenesis from proteins and insulin resistance results in hyperglycemia [23]. Our finding verifies that vagal stimulation could modulate the postsurgical catabolic response.

On the contrary, IL-1β, IL-18 and TNF-α levels were similar in both study groups. This might be because these cytokines are mainly locally released from injured tissue rather than centrally regulated and have a short half-life (IL-1 is 20 min and TNF-α 6 min) which impedes with their measurements [24, 25].

Finally, vagus stimulation was started 1 day prior to the planned surgical intervention and continued till the 4th postoperative day. The duration of vagal stimulation was planned according to the already published evidence that IL-6 rises promptly postoperatively and returns to baseline within 2–3 days [26, 27]. Similar pharmacodynamics of IL-6 could be seen in the current study.

Clinical impact: transcutaneous stimulation of the vagus nerve might contribute to adequate immune regulation after lung resection and attenuate the acute postsurgical inflammatory response, which in turn reduces postoperative complications and shortens hospitalization time.

Study limitations

Patients and providers were not blinded to the experimental group, and selection bias cannot be excluded completely. Secondly, although the pre- and perioperative morbidities were comparable in both groups, the effect of the different morbidities on the postoperative inflammation could not be separately analyzed in the current study. Finally, a separate group of patients with a matched control undergoing minimally invasive lobectomies was not included, although this cohort actually establishes the vast majority of our services. We decided to restrict to procedures with a higher grade of invasiveness with the expectation of a more marked influence of vagus stimulation.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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