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Left T7 paravertebral nerve blockade activate the α7nAChR-Dependent CAP in patients undergoing thoracoscopic lobectomy: a prospective controlled study

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Abstract

Objective This study aimed to observe the impact of Tthoracic paravertebral nerve blockade(TPVB) at left T7 level on the α7nAChR-dependent cholinergic anti-inflammatory pathway in patients undergoing thoracoscopic lobectomy.

Methods Scheduled thoracoscopic lung surgery patients at the First Affiliated Hospital of Nanchang University from August to September 2023 were divided into two groups according to the surgical site. The experimental group underwent left T7 paravertebral nerve blockade (LTPVB group), while the control group underwent right T7 paravertebral nerve blockade (RTPVB group). Relevant clinical data were collected, and Doppler ultrasound was used to measure the resistive index (RI) of the splenic artery before and after blockade. Additionally, perioperative α7nAChR levels and the expression levels of the inflammatory factors IL-1β, IL-6, and TNF-α were determined.

Results There were no significant differences in general conditions, perioperative blood pressure, heart rate, or pain VAS scores between the two groups ($p > 0.05$). Splenic Doppler ultrasound showed that compared to before blockade, the RI of the splenic artery in the LTPVB group significantly decreased ($p < 0.05$). The α7nAChR levels at 12 h and 24 h postoperatively were significantly increased ($p < 0.05$) in both groups, and the levels of IL-1β, IL-6, and TNF-α gradually increased over time in both groups. However, the levels were significantly lower in the LTPVB group compared to the RTPVB group at 12 h and 24 h postoperatively ($p < 0.05$).

Conclusion TPVB at left T7 can activate the α7nAChR-dependent cholinergic anti-inflammatory pathway, thereby alleviating the postoperative inflammatory response in patients undergoing thoracoscopic lobectomy.

Keywords Sympathetic nerve block, Thoracoscopic surgeries, Lobectomy, Cholinergic Anti-inflammatory Pathway, Alpha7 Nicotinic Acetylcholine Receptor, Inflammatory response

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Introduction

Acute lung injury (ALI) during the perioperative period can occur at various stages such as anesthesia induction, maintenance, intraoperatively, and postoperatively, and can be caused by multiple factors including ischemia, hypoxia, oxygen toxicity, endogenous and exogenous stimuli, mechanical injury, and reperfusion [1, 2]. Although the etiology of perioperative acute lung injury varies, exacerbation of inflammatory responses leading to damage of pulmonary endothelial and epithelial cells is a crucial pathophysiological mechanism [3]. During ALI, a large amount of pro-inflammatory cytokines are released, which can activate inflammatory signaling pathways, leading to enhanced expression of inflammatory mediators such as TNF-α, IL-1β, IL-6, thereby exacerbating the "cascade-like" chain reaction of inflammation in ALI [4, 5]. Some patients may progress to acute respiratory distress syndrome (ARDS), resulting in irreversible respiratory failure [6–8]. Therefore, the inhibition of the occurrence and development of inflammatory responses plays a crucial role in alleviating ALI."

The cholinergic anti-inflammatory pathway (CAP) is a neuroimmune regulatory pathway that depends on the autonomic nervous system. It activates CAP by stimulating the vagus nerve to release acetylcholine, which then binds to the α7 nicotinic acetylcholine receptor (α7nAChR) [9, 10], thereby inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and other signaling pathways to suppress the synthesis and release of inflammatory mediators such as TNF-α, IL-1β, and IL-6, thus alleviating the inflammatory response [11, 12]. In an ischemia-reperfusion model, electrical stimulation increases the expression of α7nAChR, leading to decreased release of inflammatory mediators and mitigating lung injury following ischemia-reperfusion [13]. In a mouse model of rheumatoid arthritis, activation of α7nAChR can inhibit TNF-α expression and alleviate arthritis [14]. Numerous domestic and international studies have shown that α7nAChR plays a key role in regulating the inflammatory response in the cholinergic anti-inflammatory pathway, and α7nAChR is expressed in various tissues, including immune cells and in the blood [15, 16]. The spleen, as a peripheral lymphoid organ, plays an important role in CAP. The nerves in the spleen mainly consist of sympathetic and sensory nerve fibers, with the sympathetic nerve fibers mainly originating from the celiac ganglion of the thoracic and upper lumbar segments [17]. During the inflammatory response, inflammatory products signal through sensory nerves to the solitary tract nucleus, which then activates the release of acetylcholine from efferent nerve terminals, leading to the activation of the janus kinase 2 / signal transducer and activator of transcription 3 (JAK2/STAT3) signaling pathway within immune cells, inhibiting NF-κB signaling and suppressing the release of inflammatory mediators, thus reducing the inflammatory response [18–21].

This study selected patients undergoing single-port thoracoscopic lung surgery and compared the clinical data, a7nAChR expression levels, and perioperative inflammatory response levels between patients receiving left-sided and right-sided paravertebral nerve block (TPVB) at the T7 level. TPVB primarily acts on spinal nerves and may influence sympathetic nerves through rami communicantes, effectively inhibiting the transmission of nociceptive signals [22]. The aim was to observe the impact of these interventions on the α7nAChR-dependent cholinergic anti-inflammatory pathway, with the goal of identifying new methods and targets for reducing perioperative inflammatory response in patients undergoing lung lobectomy.

Methods

Study design and subject selection

This experiment was conducted in accordance with the ethical review requirements of the Ethics Committee of the First Affiliated Hospital of Nanchang University, with the ethics number: (2022) CDYFYYLK(07−003), and has been registered with the Chinese Clinical Trial Registry, registration number: ChiCTR2300073438, Date of first registratio:11/07/2023. A total of 84 patients who underwent single-port thoracoscopic lung surgery at our hospital from August to September 2023 were selected.

Inclusion criteria were as follows: (1) Patients undergoing unilateral lobectomy or segmentectomy via thoracoscopic surgery, regardless of gender, (2) ASA grade II-III, (3) Age 20–70 years.

Exclusion criteria were: (1) Hypersensitivity, including allergic reactions that occurred within one week or allergies to local anesthetics, (2) Infection, including recurrent infections or infections at the site of puncture, (3) Severe preoperative lung function impairment or inflammatory and rheumatic diseases, (4) Intraoperative or postoperative blood transfusion, (5) Emergency surgery, patients in shock, or comatose patients.

Study protocol

According to the surgical site, the experimental group undergoing left T7 paravertebral nerve block (LTPVB group) was performed, while the control group underwent right T7 paravertebral nerve block (RTPVB group). Clinical data, including age, gender, ASA classification, height, weight, postoperative nausea and vomiting incidence, and postoperative VAS score, were collected. Blood samples of 2 ml were collected from the patients at the preoperative (T1), 30 min after the start of the surgery (T2), at the end of the surgery (T3), 12 h postoperatively (T4), and 24 h postoperatively (T5). Blood pressure

and heart rate at the corresponding time points were also recorded.

Upon patient admission, peripheral venous access was established, and the patient received oxygen via a face mask while vital signs including ECG, SpO2, BP, and HR were monitored. The patient underwent general anesthesia with double lumen tube intubation. Prior to induction, radial artery cannulation for direct arterial pressure measurement was performed under local anesthesia. The patient received a bolus of fentanyl 0.2-0.5ug/kg, cisatracurium 0.1 mg/kg, and propofol 1-2 mg/kg. Anesthesia maintenance was achieved using target-controlled infusion of propofol at an effect-site concentration of 2–3 ng/ml and remifentanil at 0.02 mg/kg/h, along with a continuous infusion of cisatracurium at 0.5 mg/kg/h. Anesthesia depth was monitored throughout the procedure using the Bispectral Index (BIS) from the A-2000 BISTM (Medical System Company, USA), maintaining BIS values between 40 and 60. Intraoperative heart rate and blood pressure were controlled within 30% of baseline values. Intravenous fluids were warmed to maintain intraoperative body temperature at 36–37 °C. Postoperatively, patient-controlled intravenous analgesia was used to maintain a VAS score below 4. For patients with a VAS≥4, we initially use intravenous morphine 5 mg as the first rescue analgesic. After the administration of the first rescue analgesic, a gap of 30 min is allowed before administering the second rescue analgesic, ibuprofen 400 mg as the second rescue analgesic. Blood pressure, heart rate, postoperative nausea and vomiting incidence, and 2 ml blood samples were collected at various time points. Serum samples were obtained by centrifugation and stored at -80 °C for subsequent measurement of IL-1β, IL-6, TNF-a, and α7nAChR levels using ELISA.

TPVB method

All the TPVB procedures were performed by one anesthesiologist. Prior to anesthesia induction, under ultrasound guidance, the TPVB was performed on the surgical side with the patient in the lateral decubitus position under sterile conditions. The skin entry point was located 2.5–3 cm lateral to the T7 spinous process, and 2 ml of 2% lidocaine was administered for local anesthesia. Under ultrasound guidance, the transverse process of the upper rib and the pleura were visualized in the plane, and after confirming no blood return upon needle entry into the paravertebral space, 20 ml of 0.375% ropivacaine was administered into the T7 paravertebral space. Ten minutes after the block, the resistive index of the splenic artery was measured using ultrasound, with the probe placed in the left upper abdominal oblique section, and color Doppler showing the splenic artery at the splenic hilum. Using pulsed-wave Doppler, the peak systolic velocity (Vs) and end-diastolic velocity (Vd) were measured, and the resistive index (RI) was calculated using the formula RI=(Vs-Vd)/Vs (Fig. 1).

Outcomes

The primary outcome measures include the effects of TPVB on the splenic artery at the splenic hilum and the changes in the perioperative inflammatory response in patients. Secondary observation indicators encompass the general condition of the patients, perioperative blood pressure and heart rate, postoperative pain scores, and the incidence of nausea and vomiting. All outcomes related to clinical data were recorded and collected by one person. All of laboratory testing were operated and collected by the others, with each individual working independently.

Sample size estimation

According to preliminary experimental results, we assessed the required sample size to detect significant differences between different treatment groups. The specific observed indicator is the inflammatory factor IL-1β, with a baseline value of 15.29±4.18 pg/ml, and in the control group, the postoperative value is 51.34±13.71 pg/ml. We aim to reduce IL-1β levels by 10% through the intervention, so that the postoperative mean of the intervention group is significantly lower than that of the control group. Choosing $\alpha=0.05$ and $1-\beta=0.8$, along with the variance and mean differences obtained from the preliminary study, it was calculated that the required sample size is 56. Therefore, the ratio of the experimental group to the control group is 1:1, with 28 cases in each group. Considering a 30% attrition rate, a total required sample size of 80 cases is needed.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 software. Continuous data are presented as mean±standard deviation, and categorical data are presented as frequency (percentage). The chi-square test was used for analysis. Normality of the data was assessed, and the continuous data were found to be normally distributed. Independent sample t-tests were used for between-group comparisons, and one-way analysis of variance (ANOVA) was used for within-group comparisons. A significance level of $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

From August to September 2023, a total of 84 patients were recruited for eligibility assessment in this study. Nineteen cases were excluded, with 15 patients failing to meet the inclusion criteria and 4 cases withdrawing consent. This resulted in a total of 65 patients being enrolled. Upon random allocation, one patient in the

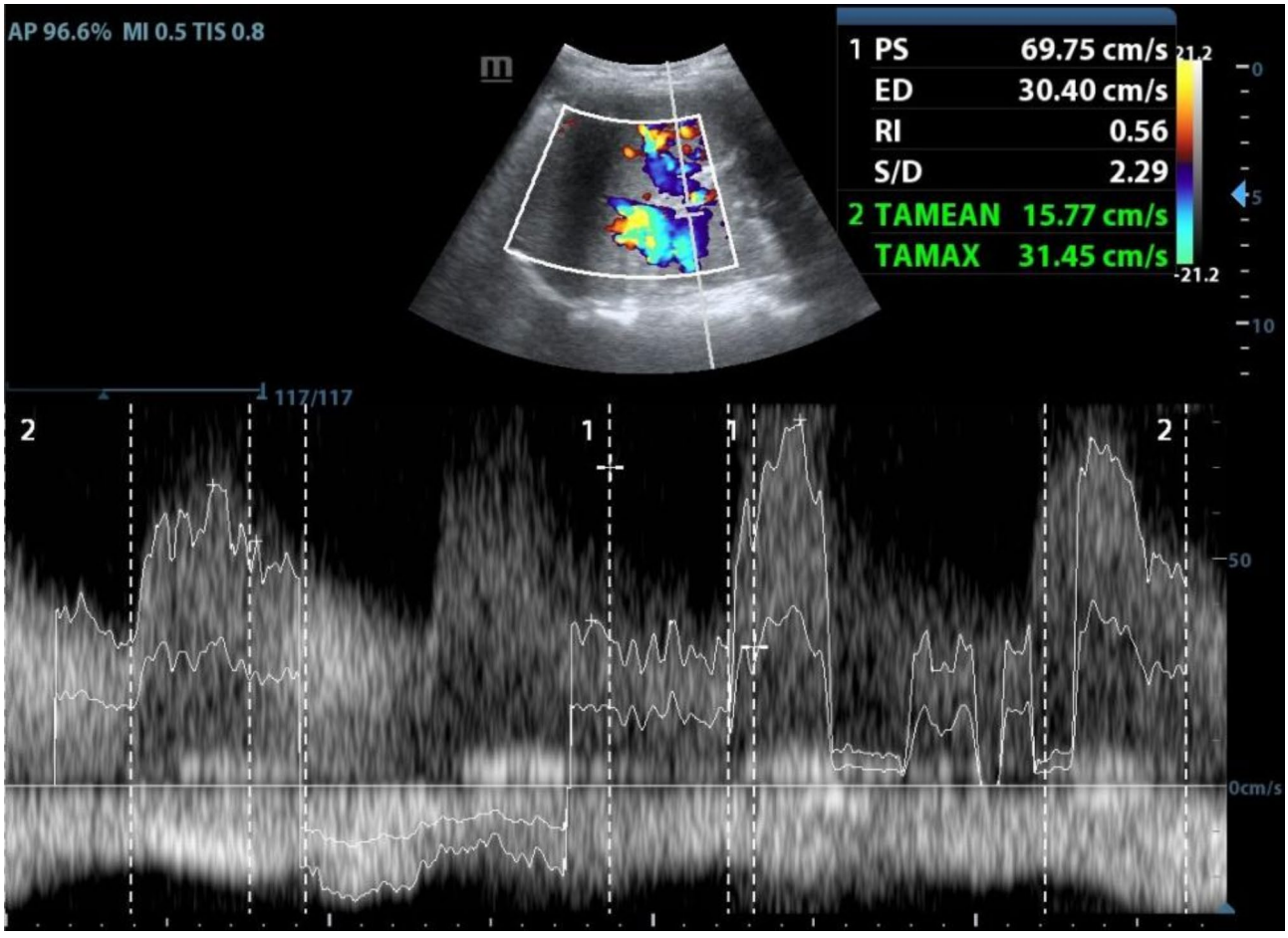

Fig. 1 Doppler ultrasound spectrum of splenic artery blood flow. PS: Peak systolic blood flow velocity. ED: End diastolic blood flow velocity. RI: Resistance index. S/D: Peak systolic blood flow velocity/end diastolic blood flow velocity. TAMEAN: time-averaged mean velocity. TAMAX: time-averaged max velocity

LTPVB group was converted to open chest surgery during the operation, and one patient was lost to follow-up postoperatively. In the RTPVB group, one patient was converted to open chest surgery during the operation, and three patients were lost to follow-up postoperatively. Ultimately, there were 30 patients in the LTPVB group and 29 patients in the RTPVB group. The patient enrollment process is illustrated (Fig. 2).

Comparison of General Clinical Data and Hemodynamics between the Two Groups The statistical analysis of clinical data (Table 1) revealed no significant differences in age, gender, ASA classification, height, and weight between the two groups ($p>0.05$). Additionally, there were no significant differences in the incidence of postoperative nausea and vomiting or postoperative VAS scores ($p>0.05$). Hemodynamic comparisons (Fig. 3)between the two groups showed no statistically significant differences in blood pressure and heart rate at various time points for the LTPVB and RTPVB groups ($p>0.05$).

LTPVB reduces splenic artery resistive index

To further observe the changes in splenic artery blood flow following TPVB, splenic artery Doppler ultrasound examination was performed. As shown in Fig. 3, changes in splenic artery blood flow were detected at the splenic hilum, with spectral Doppler calculating the peak systolic velocity (PS), end-diastolic velocity (ED), and resistive index (RI). The RI reflects vascular resistance, with higher values indicating greater resistance and lower values indicating lesser resistance, to some extent reflecting the diastolic condition of the splenic artery.(Fig. 1) The results demonstrated that compared to pre-blockade values, the RI of the splenic artery significantly decreased after LTPVB at T7 level ($p<0.05$), while there was no significant change in the splenic artery RI after RTPVB at T7 level ($p>0.05$) (Table 2). This indicates that after LTPVB at T7 level, there is a significant increase in splenic artery diastole, while RTPVB at T7 level has no significant effect on the splenic artery.

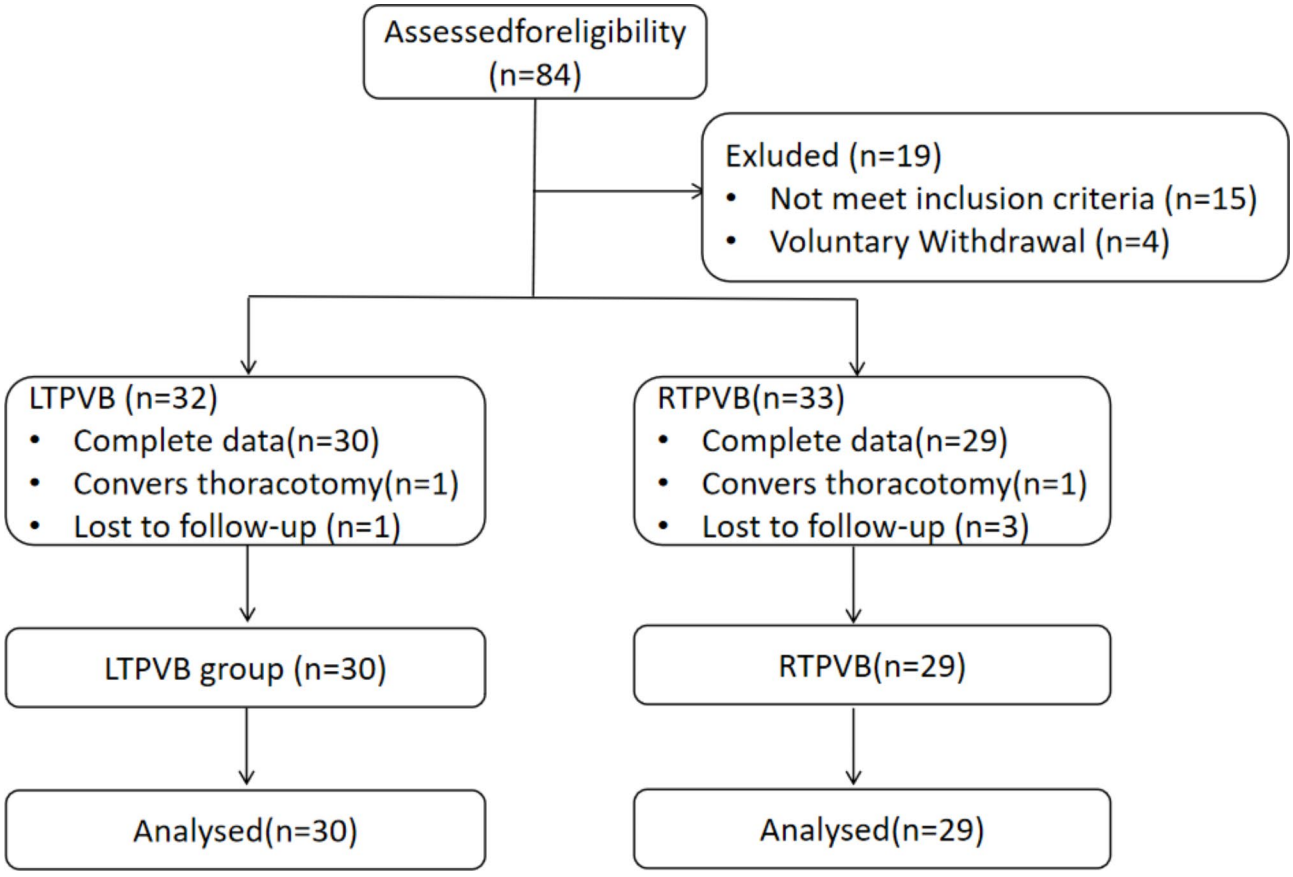

Fig. 2 Flowchart of patient experimental grouping

Table 1 General information on two groups of patients

Characteristics	LTPVB(*n* = 30)	RTPVB9(*n* = 29)	*P* value
Age	55.33 ± 9.19	58.30 ± 7.58	0.178
Gender, n			
Male	13	12	0.793
Female	17	18	
Height	160.43 ± 7.52	159.83 ± 7.82	0.763
Weight	57.90 ± 8.80	60.47 ± 12.29	0.356
ASA classification, n			
II	14	19	0.192
III	16	10	
Diabetes, n	11	13	0.793
Thrombosis, n	3	1	0.612
Surgical Duration, min	90.6 ± 31.7	91.5 ± 34.2	0.917
One lung ventilation time, min	55.7 ± 18.4	52.3 ± 20.7	0.507
Type of surgery, n			
Lobectomy	26	27	0.671
Segment resection	4	2	
Histology, n			
Malignant	25	26	0.707
Benign	5	3	
VAS	2.43 ± 1.83	1.63 ± 1.30	0.056
Nausea and Vomiting, n			
Yes	3	5	0.233
No	27	24	

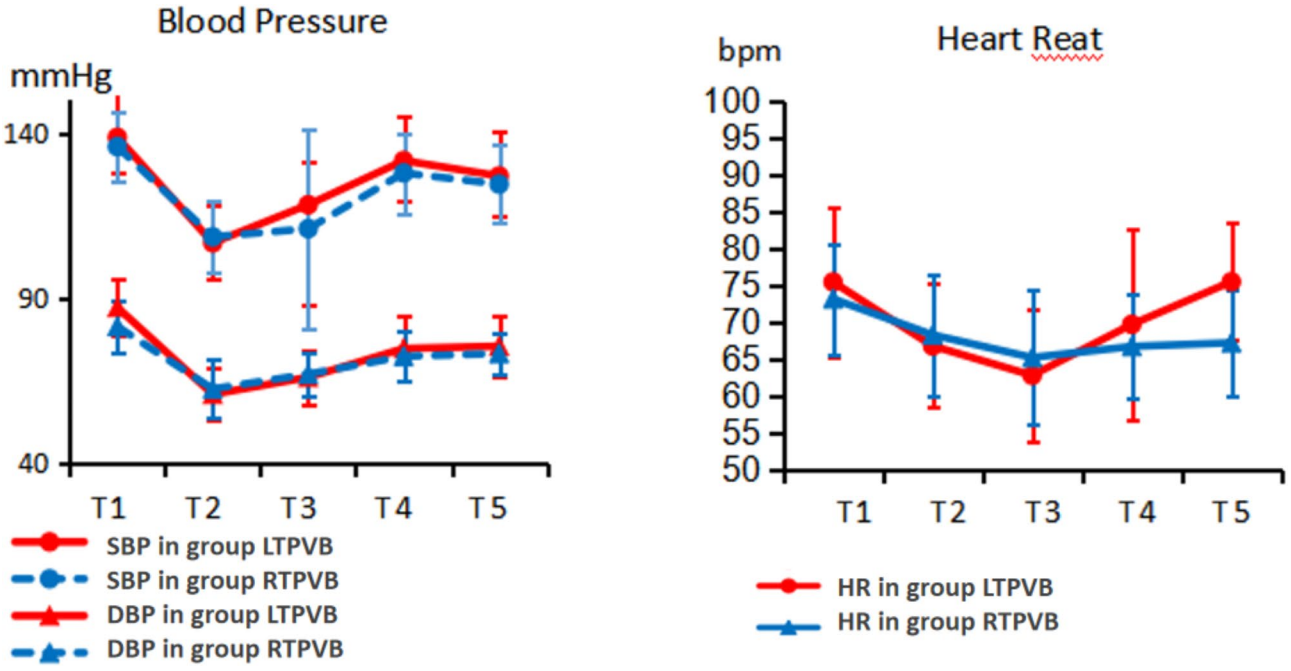

Fig. 3 Changes in hemodynamics between two groups

Table 2 Resistive index of splenic artery before and after nerve blockade in two groups

RI	LTPVB	RTPVB	t	*P*
Before	0.55 ± 0.05	0.55 ± 0.08	0.306	0.761
After	0.52 ± 0.06	0.54 ± 0.03	1.558	0.125
t	2.522	0.701	-	-
P	0.014	0.487	-	-

LTPVB at left T7 level activates the CAP and suppresses early inflammatory response after pulmonary lobectomy

Compared to preoperative baseline values, the α7nAChR levels in the LTPVB group were significantly increased at 24 h postoperatively ($p<0.05$), while there was no significant change in α7nAChR levels in the RTPVB group. Additionally, the α7nAChR levels at 12 and 24 h postoperatively were significantly higher in the LTPVB group compared to the RTPVB group ($p<0.05$). Furthermore, the expression levels of inflammatory factors in both groups showed a significant increase in IL-1β, IL-6, and TNF-α at 12 and 24 h postoperatively compared to preoperative baseline values ($p<0.05$). However, when compared to the RTPVB group, the LTPVB group exhibited significantly lower levels of IL-1β, IL-6, and TNF-α at 12 and 24 h postoperatively ($p<0.05$) (see Table 3; Fig. 4).

Table 3 , The expression of α7nAChR levels and inflammatory factors in two groups

Characteristics		T1	T2	T3	T4	T5
a7nAChR (pg/ml)	LTPVB($n=30$)	29.09 ± 9.57	32.19 ± 11.56	38.40 ± 11.00	66.96 ± 12.78	90.5 ± 17.69
	RTPVB($n=29$)	30.60 ± 9.80	33.15 ± 12.37	41.56 ± 11.74	43.60 ± 10.98	41.7 ± 12.27
t		0.604	0.311	1.076	7.594	12.41
p		0.548	0.757	0.286	< 0.001	< 0.001
IL-1β(pg/ml)	LTPVB($n=30$)	15.12 ± 1.15	15.28 ± 2.52	25.31 ± 3.78	32.66 ± 3.17	46.21 ± 5.15
	RTPVB($n=29$)	14.89 ± 0.31	14.79 ± 1.51	24.74 ± 3.18	41.83 ± 3.26	57.18 ± 5.80
t		1.058	0.969	0.632	11.05	7.75
p		0.294	0.337	0.53	< 0.001	< 0.001
TNF-a (pg/ml)	LTPVB($n=30$)	30.03 ± 3.20	31.27 ± 3.79	30.25 ± 4.45	35.48 ± 3.80	37.03 ± 5.25
	RTPVB($n=29$)	30.12 ± 4.26	30.24 ± 4.55	30.78 ± 2.08	41.69 ± 4.57	46.37 ± 5.48
t		0.093	1.081	0.897	1.085	1.386
p		0.927	0.345	0.557	< 0.001	< 0.001
IL-6 (pg/ml)	LTPVB($n=30$)	3.38 ± 1.61	5.13 ± 4.96	21.13 ± 5.01	35.97 ± 6.65	37.69 ± 6.73
	RTPVB($n=29$)	3.80 ± 1.80	3.86 ± 2.05	22.61 ± 5.51	40.16 ± 5.14	49.32 ± 6.21
t		0.953	1.305	1.089	2.731	6.956
p		0.345	0.197	0.281	0.008	< 0.001

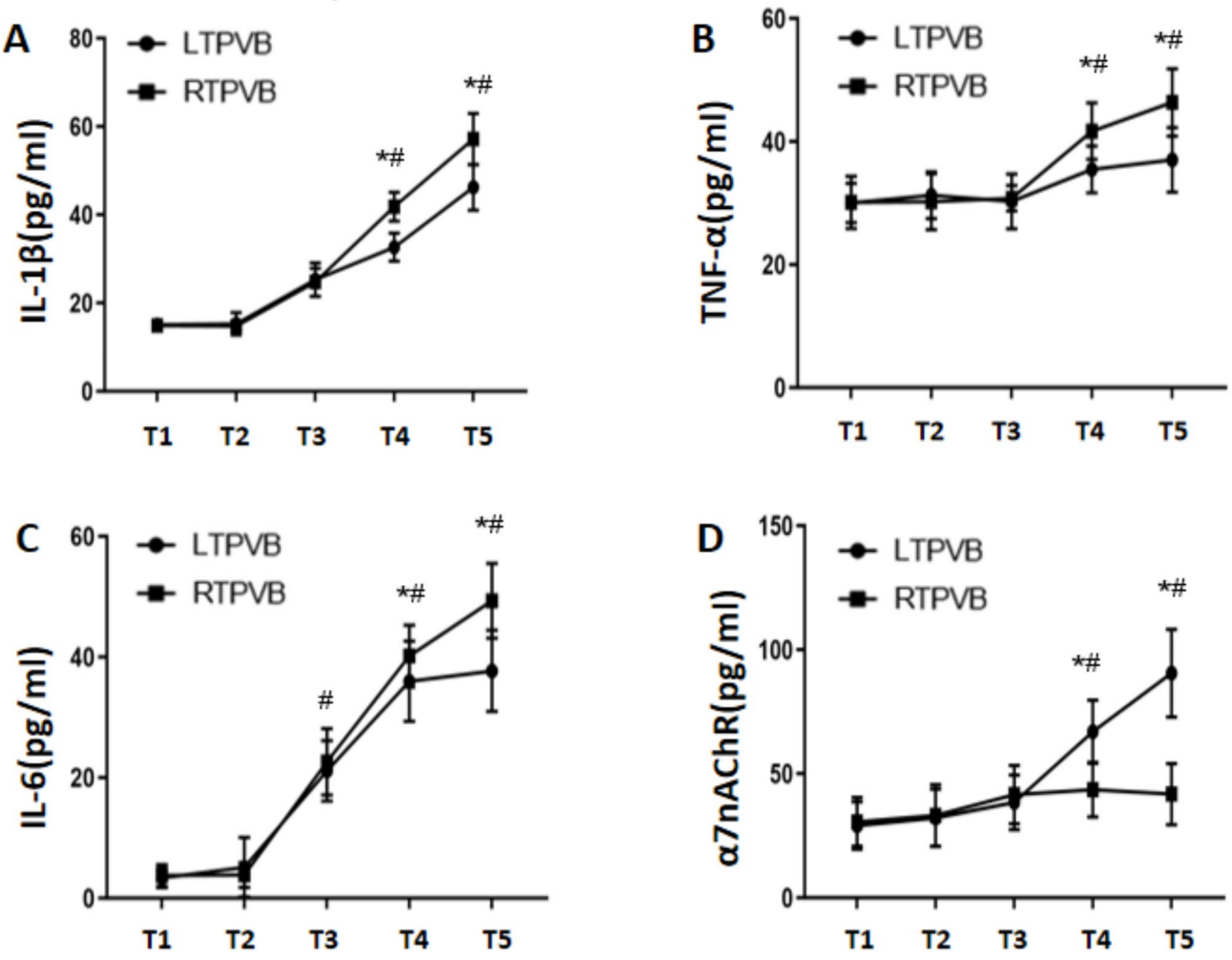

Fig. 4 Splenic sympathetic nerve blockade activates CAP to inhibit early inflammatory response after lung lobectomy. vs. RTPVB $^{*}P < 0.05$;vs. T1 $^{\#}P < 0.05$

Discussion

Video-assisted thoracoscopic surgery (VATS) pulmonary lobectomy has become the primary method for clinical treatment of pulmonary tumors in recent years [23]. Compared to traditional open chest surgery, VATS offers advantages such as minimal trauma, rapid recovery, reduced blood loss, and mild postoperative pain. However, acute lung injury caused by pain, surgical stimulation, oxidative stress, ischemia-reperfusion, and mechanical ventilation remains a significant concern. Multiple studies have demonstrated that thoracic paravertebral blockade (TPVB) can effectively alleviate pain by blocking the spinal dorsal root ganglia and intercostal nerves [24, 25]. TPVB can also affect the sympathetic nerves at the corresponding level, effectively inhibiting the transmission of noxious stimuli and relatively enhancing the excitability of the vagus nerve, thereby activating the "cholinergic anti-inflammatory pathway" [22].

Results showed that a volume of 20 ml of medication in TPVB can spread to an average of three vertebral levels [26, 27]. In single-port VATS, a 4 cm incision is made at the posterior axillary line between the 3rd and 4th or 4th and 5th ribs. Therefore, a single-point TPVB at the T7 level can achieve the required spinal dorsal root ganglia and intercostal nerves blockade and can also affect the sympathetic nerves. Studies have found that the analgesic effect of ropivacaine increases with the dose [28, 29]. Hence, we chose 0.375% ropivacaine for single-point blockade, which can provide adequate analgesia while reducing respiratory and circulatory suppression. In this study, the right TPVB was used as the control group, and the blockade effect was similar. Visual analogue scale (VAS) scores were used to evaluate postoperative pain levels. There were 2 cases of rescue analgesic use in each group, and there was no significant difference in the use of rescue analgesics between the groups, and there was no significant difference between the two groups. This

approach avoided the influence of perioperative pain stimulation on the results.

The general characteristics of the two groups, including height, weight, age, and ASA classification, were not significantly different. Blood pressure and heart rate were not significantly different at each time point, and the incidence of postoperative nausea and vomiting was low and did not differ significantly between the two groups. This indicates that TPVB primarily acts on segmental spinal nerves and indicate that, while it may have some influence on sympathetic nerves, it does not exclusively block them. Compared to thoracic epidural anesthesia, TPVB has a relatively smaller impact on systemic circulation [30].

Doppler ultrasound of the splenic artery showed that in the LTPVB group, the resistance index (RI) of the splenic artery significantly decreased after blockade, while in the RTPVB group, the RI of the splenic artery did not change significantly after blockade. This suggests that LTPVB at T7 level significantly dilated the splenic artery, while RTPVB at T7 level had no significant effect on the splenic artery. The decrease in splenic artery RI in the LTPVB group is likely due to the localized effect of TPVB on the ipsilateral spinal nerves and the sympathetic nerves, which may induce vasodilation in the corresponding segment.

The spleen plays a crucial role in the cholinergic anti-inflammatory pathway (CAP), and activation of the splenic cholinergic anti-inflammatory pathway through ultrasound can alleviate renal injury after ischemia-reperfusion [31]. Analysis has shown that TPVB can block the ipsilateral sympathetic nerves [18, 20, 21], and left-sided TPVB can block the sympathetic nerves of the spleen, thereby enhancing vagus nerve stimulation of the spleen, releasing acetylcholine to bind with α7nAChR, and activating CAP to reduce the release of inflammatory mediators such as TNF-α, IL-1β, and IL-6, thus mitigating the inflammatory response [12, 32, 33]. In this study, the impact of TPVB on the activation-dependent α7nAChR cholinergic anti-inflammatory pathway was assessed by observing the levels of α7nAChR and inflammatory factors at various perioperative time points. The results showed that the levels of IL-1β, IL-6, and TNF-α gradually increased over time during the perioperative period, but compared to the control group, the levels of α7nAChR significantly increased after LTPVB at T7 level, and the levels of inflammatory factors significantly decreased at 12 h and 24 h postoperatively. Therefore, LTPVB at T7 level can activate the α7nAChR-dependent CAP pathway, thereby alleviating the perioperative inflammatory response in thoracoscopic pulmonary lobectomy.

Despite advancements in the treatment of perioperative acute lung injury, its incidence remains significant and significantly affects patient outcomes [34, 35]. CAP, as a regulatory pathway between the cholinergic nervous system and the immune system, responds rapidly and sensitively, offering advantages over treatments targeting individual inflammatory mediators [36]. This study, through the LTPVB at T7 level, activation of the α7nAChR-dependent CAP pathway, and reduction of postoperative inflammatory response, provides a feasible clinical treatment measure for alleviating lung injury in thoracoscopic pulmonary lobectomy. However, LTPVB at T7 level did not involve a direct blockade of the splenic sympathetic nerves, and our study lacks a stratified analysis of the impact of age on outcomes, and confirmation through large-sample, multicenter clinical trials is still required.

In summary, during video-assisted thoracoscopic lobectomy, 20 ml of 0.375% ropivacaine administered at the left T7 level TPVB can activate α7nAChR-dependent CAP, reduce perioperative inflammatory response, and has no significant impact on the patient's perioperative hemodynamics.

Author contributions

Q.L., and P.Q. designed the study, F.X. and Z.R. wrote the main manuscript text , F.X., Z.R., Y.P. and W.S. prepared the tables and figures. All authors reviewed the manuscript.

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Data availability

All data generated or analysed during this study are included in this article.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. The patients/participants provided their written informed consent to participate in this study. All procedures adhere to CONSORT guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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