RESEARCH ARTICLE

Effects of Stellate Ganglion Block on the Peri-operative Vasomotor Cytokine Content and Intrapulmonary Shunt in Patients with Esophagus Cancer

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Abstract

Objective: To investigate the effects of stellate ganglion block (SGB) on the peri-operative vasomotor cytokine content and intrapulmonary shunt in patients with esophagus cancer who underwent thoracotomy. Materials and Methods: Forty patients undergoing elective resection of esophageal cancer patients who had I~II American Society of Anesthesiologist (ASA) were randomly divided into total intravenous anesthesia group (group N, n=20) and total intravenous anesthesia combined with SGB group (group S, n=20, 0.12 mL/kg 1% lidocaine was used for SGB 10 min before induction). Heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary arterial pressure (MPAP) and continuous cardiac output (CCO) were continuously monitored. The blood from internal jugular vein was drawn respectively before induction (T_0), and 30 min (T_1), 60 min (T_2) and 120 min (T_3) after one-lung ventilation (OLV), and 30 min (T4) after two-lung ventilation. The contents of plasma endothelin (ET), nitric oxide (NO) and calcitonin gene-related peptide (CGRP) were detected with enzyme linked immunosorbent assay (ELISA). Meanwhile, arterial and mixed venous blood samples were collected for determination of blood gas and calculation of intrapulmonary shunt fraction (Qs/Qt). Results: During OLV, ET contents were increased significantly in two groups ($P<0.05$), and no significant difference was presented ($P>0.05$). NO content in group S was obviously higher than in group N at T3 ($P<0.05$), whereas CGRP content in group N was markedly lower than in group S at each time point ($P<0.05$). Qs/Qt was significantly increased in both groups after OLV, but there was no statistical significant regarding the Qs/Qt at each time point between two groups. Conclusions: Total intravenous anesthesia combined with SGB is conducive to regulation of perioperative vasomotor cytokines in thoracotomy, and has little effect on intrapulmonary shunt at the time of OLV.

Keywords: Stellate ganglion block - one-lung ventilation - endothelin - nitric oxide - calcitonin gene-related peptide - intrapulmonary shunt

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Introduction

One-lung ventilation (OLV) has been widely applied to cardiothoracic surgery. In spite of unilateral lung ventilation during OLV, bilateral lungs are perfused, which is bound to result in reduced oxygenation, even hypoxemia (Karzai et al., 2009). Hypoxic pulmonary vasoconstriction (HPV) is a phenomenon that the body regulates respiratory and circulatory functions to maintain the oxygen supply within the normal range under the conditions of decreased oxygen partial pressure. The formation mechanism is relatively complicated. Most studies believe that HPV is the direct effect of hypoxia on pulmonary arterial smooth muscle cells and endothelial cells (Evans et al., 2011; Swenson, 2013), but the effect of intrapulmonary vasomotor cytokines cannot be ignored. The composition of stellate ganglion has two possibilities: One is the fusion between the 7th and 8th cervical sympathetic ganglia and the 1st thoracic sympathetic ganglion. If the cervical sympathetic ganglia do not get fused with the 1st thoracic sympathetic ganglion, the 1st thoracic sympathetic ganglion is the stellate ganglion (Shi et al., 2010). Stellate ganglion block (SGB) can suppress the cardiovascular stress arising from the medical operation (García-Morán et al., 2013), so it is applied in surgeries. It suppresses the excitation of sympathetic-adrenal system and mitigates the sympathetic tone generated by stress. Besides, it also relieves stress reactions induced by pituitary gland-adrenaline-cortex by maintaining the stability of internal environment with the regulation of

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Table 1. Comparison of Preoperative General Conditions between two Groups (n=20, $\bar{x}\pm s$)

Groups	n	Height (cm)	Weight (kg)	Age (y)	Gender (Male/female)	Operation time (min)	OLV time (min)
Group S	1/21	167±8	60±13	56±6	10/10	165±25	121±18
Group N	1/21	165±8	62±11	55±5	10/10	176±27	127±21

hypothalamus (Taneyama et al., 2009; Amino et al., 2007). The study has revealed that substances like NO can be used to regulate the vascular activities after postganglionic fiber of stellate ganglion is blocked (Garneau et al., 2011). This study aimed to observe the effects of SGB on the perioperative vasomotor cytokine content and intrapulmonary shunt in patients with esophagus cancer.

Materials and Methods

General data

Forty patients undergoing elective resection of esophageal cancer who had I~II American Society of Anesthesiologist (ASA) were selected. They were at the age of 50~65, weighing from 55~70 kg. Those with serious preoperative cardiovascular, hepatic and renal diseases, moderate or more severe anemia and abnormalities in lung function test, and FEV1/FVC<65% were excluded. This study was approved by Hospital Ethic Committee, and all patients or their family members signed the informed consent forms.

Anesthesia induction and maintenance

The peripheral vein was opened after patients entered the operating room, with intravenous injection of 0.05 mg/kg midazolam. Under local anesthesia, radial artery puncture and catheterization were performed. Right internal jugular vein puncture was performed and Swan-Ganz catheter was inserted until the pulmonary artery was reached. According to different anesthesia methods, the random number table method was adopted to divide the patients into total intravenous anesthesia group (group N, n=20) and intravenous anesthesia combined with SGB (group S, n=20). Group S was given the left SGB 10 min before induction of generalized anesthesia with 1% lidocaine (0.12 mL/kg). The patient was selected if Horner's syndrome appeared at the blocking side (sweating, flush, narrowing of eye fissure, enophthalmos and myosis, and presence of above symptoms >3 was determined to be positive). Otherwise, the patient was culled out from this study. Patients in two groups were intravenously injected with propofol (1.5~2 mg/kg), sufentanil (0.4 μg/kg) and rocuronium bromide (0.6~0.8 mg/kg) for rapid induction of general anaesthesia. After direct vision orotracheal intubation, bronchial blocker tube was inserted, anesthesia workstations were connected to perform mechanical control respiration, bronchial blocker tube was positioned and fixed by bronchoscopy, the controlled respiration tidal volume was 8~10 mL/kg, concentration of oxygen inspired (FiO_2) was 100%, the ratio of inspiration to expiration was 1:2, respiratory rate was 10~12 bpm, and the end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) was maintained between 30~35 mmHg. During OLV, the above respiration parameters remained unchanged. During operation, the patient was continuously injected by pump with propofol (4~10 $mg\bullet kg^{-1}\bullet h^{-1}$), sufentanil (0.2 $\mu g\bullet kg^{-1}\bullet h^{-1}$) and vecuronium bromide (0.1 $mg\bullet kg^{-1}\bullet h^{-1}$) to maintain the anesthesia, and the bispectral index (BIS) was maintained between 45~60.

Monitoring indicators

Electrocardiogram (ECG), heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), continuous cardiac output (CCO) and pulse oxygen saturation (SpO_2) were continuously monitored during operation.

Blood sample collection and intrapulmonary shunt detection

3 mL venous blood was drawn from the internal jugular vein in two groups of patients respectively before induction (T_0), and 30 min (T_1), 60 min (T_2) and 120 min (T_3) after OLV, and 30 min (T_4) after two-lung ventilation. Enzyme linked immunosorbent assay (ELISA) was used to determine the contents of plasma endothelin (ET), nitric oxide (NO) and calcitonin gene-related peptide (CGRP). Meanwhile, radial arterial blood and mixed venous blood (1.5 mL) were drawn to test the blood gas, and intrapulmonary shunt rate was calculated according to the formula $Qs/Qt= (Cc'O_2\sim CaO_2)/ (Cc'O_2\sim CvO_2)\times 100\%$. ELISA reagent kit was from Canada YES BIOTECH LABORATORIES LTD.

Statistical data analysis

SPSS 13.0 statistical software was used for statistical analysis. All measurement data were expressed using the mean ± standard deviation ($\bar{x}\pm s$). Two-factor analysis of variance was adopted for intra-group comparison of parameters at all time-points, and one-factor analysis of variance and q test for the comparison of parameters among groups at all time-points. $P<0.05$ represented there was significant difference.

Results

Basic information

Clinical basic information was first compared between two groups. The results showed that there was no statistical significance regarding the preoperative general conditions between two groups ($P>0.05$) (Table 1).

Effect of SGB on intrapulmonary shunt rate

In order to explore whether SGB increased the intrapulmonary shunt, Qs/Qt was adopted to evaluate the changes of intrapulmonary shunt rate before and after induction. Before anesthesia induction, significant difference was not presented with regard to Qs/Qt between groups S and N, and the parameters were all within the normal range. After OLV, Qs/Qt was increased and reached the peak at T_1, but there was no statistical

Table 2. Comparison of Haemodynamics and Respiration in Two Groups (n=20, $\bar{x}\pm s$)

Groups	Time	MAP (mmHg)	MPAP (mmHg)	HR (time/min)	CVP (cmH_2O)	CI ($L.min^{-1}.m^2$)	PaO_2 (mmHg)	Qs/Qt (%)
S	T_0	90.0±8.0	17.2±2.5	65.0±14.0	6.9±1.7	2.8±0.6	83.0±12.0	1.4±0.7
	T_1	94.0±12.0	21.0±4.6#	73.0±18.0	9.8±2.7#	3.6±0.8#	198.0±92.0*#	43.7±7.4#
	T_2	85.0±17.0	21.3±2.8	70.0±17.0	9.4±3.1	3.8±0.2#	182.0±69.0*#	41.1±8.7#
	T_3	78.0±14.0	22.2±5.1	65.0±12.0	9.3±2.3	3.6±0.3	193.0±77.0*#	33.4±7.6#
	T_4	81.0±12.0	20.7±4.1	68.0±18.0	9.1±2.8	3.7±0.6	405.0±76.0#	24.4±5.7#
N	T_0	88.0±14.0	16.3±1.9	64.0±13.0	7.1±2.3	3.0±0.5	84.0±13.0	1.3±0.9
	T_1	101.0±16.0#	22.2±5.7#	80.0±14.0#	9.9±1.7#	3.9±0.6#	164.0±85.0#	42.1±6.2#
	T_2	94.0±11.0	21.9±4.9	77.0±13.0	9.5±3.8	4.2±0.3#	158.0±74.0#	41.4±9.6#
	T_3	76.0±20.0	23.1±4.2	73.0±19.0	8.9±3.2	4.4±0.6	161.0±56.0#	35.5±4.9#
	T_4	78.0±16.0	21.0±3.3	69.0±20.0	8.9±2.3	4.6±0.7	398.0±67.0#	26.3±3.0#

Compared with group N, *P<0.05; Compared with T_0, #P<0.05

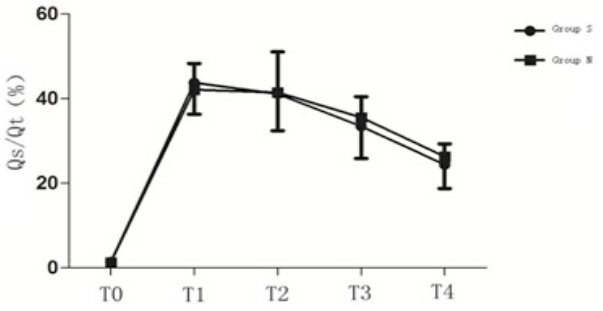

Figure 1. Changing Trend of Peri-operative Intrapulmonary Shunt Rate

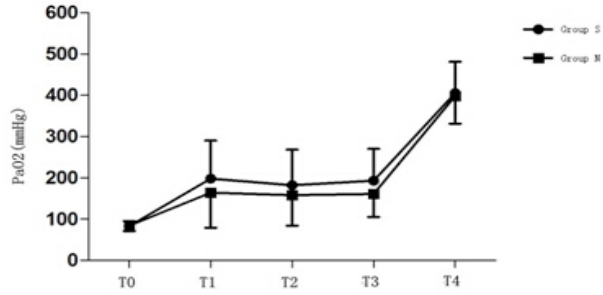

Figure 2. Trend of Peri-operative Arterial Partial Pressure of Oxygen

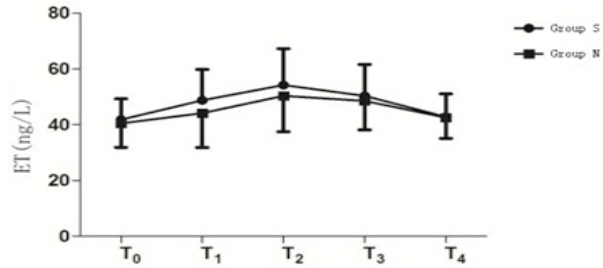

Figure 3. Changing Trend of Peri-operative ET Content

significance between two groups (P>0.05). Meanwhile, both arterial partial pressures of oxygen in two groups were significantly decreased after OLV, but the decreased degree in group N was more conspicuous, and the difference was significant when compared with group S (P<0.05). These results indicated that SGB did not affect the intrapulmonary shunt, but improved oxygenation to some extent (Table 2, Figure 1~2).

Effect of SGB on vasomotor cytokines under anesthesia condition

In order to further explain the reason of SGB on intrapulmonary shunt, the changes of the factors (ET, NO and CGRP) closely associated with vasomotion in plasma were detected in this study. The results revealed that ET content was significantly increased in two groups during OLV when compared with at T_0 (P<0.05), but the significant differences were not presented at each time point between two groups (P>0.05), indicating that SGB did not significantly affect the ET change after OLV and induced by operative stress reactions (Table 3, Figure 3).

Table 3. Comparison of Peri-operative Plasma ET, NO and CGRP Contents in Two Groups (n=20, $\bar{x}\pm s$)

Groups	Time	ET (ng/L)	NO (ng/L)	CGRP (ng/L)
S	T_0	41.85±7.46	38.51±9.49	133.14±16.35
	T_1	48.79±11.06#	37.96±11.30	130.85±11.63
	T_2	54.21±13.07#	38.44±10.65	134.82±20.21*
	T_3	50.36±11.27#	48.39±8.77*#	137.67±16.56*
	T_4	42.85±8.27	44.39±10.23*#	125.48±17.46
N	T_0	40.50±8.63	38.19±8.54	134.06±17.56
	T_1	44.18±12.37	37.83±9.36	122.67±14.09
	T_2	50.37±12.86#	38.67±9.33	108.59±17.66#
	T_3	48.56±10.37#	41.30±8.07	112.58±13.07#
	T_4	42.59±7.46	37.51±9.12	123.76±20.54#

Compared with group N, *P<0.05; Compared with T_0, #P<0.05

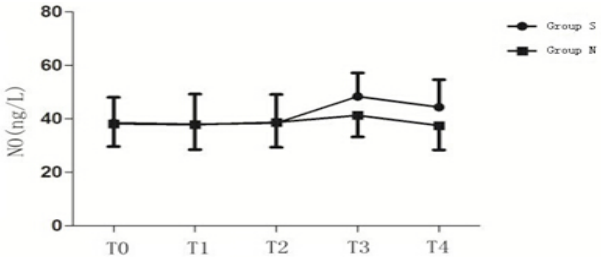

Figure 4. Changing Trend of Peri-operative NO Content

The increase of NO content in group S at T_3 was more significant than in group N (P<0.05), and plasma NO level in group S at T_3 and T_4 was higher than before induction (T_0), but that in group N had no significant change at each time point by comparison to that before induction (T_0), indicating that SGB could significantly increase endogenous NO plasma level, which may hereby cause vascular dilation (Table 3, Figure 4).

The plasma CGRP level in group S displayed no significant changes at each time point after anesthesia induction when compared with anesthesia induction (T_0), but that in group N had the significant down-regulation after anesthesia induction (P<0.05), and the CGRP content

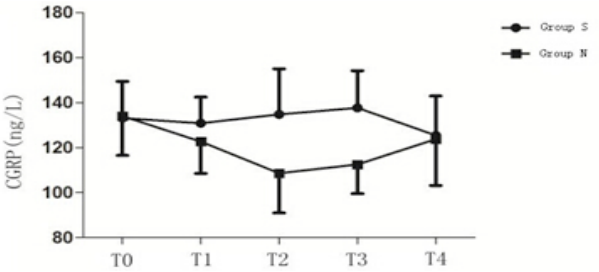

Figure 5. Changing Trend of Peri-operative CGPR Content

in group N at each time point was lower than in group S (P<0.05), showing that SGB could not only relieve CGRP decrease induced by general anesthesia, but also significantly stabilize plasma CGRP level (Table 3, Figure 5).

Discussion

OLV is conductive to performing the surgery, but induces the perioperative ventilation/flow ratio abnormality and relevant immune and inflammatory responses, which are the reasons for hypoxemia that occurs during operation (Ng et al., 2011). HPV is a compensatory mechanism specific to the lung. OLV can make the ventilated lung receive more blood perfusion and non-ventilated lung get reduced perfusion volume, so that PaO_2 can be maintained at a relatively high level (Roze et al., 2011). Lungs contain rich autonomic sensory nerves and numerous scattered neuroendocrine cells, and can secret a large quantity of neurotransmitters, modulators or regulatory peptides with hormonal action. The system formed by these vasoactive peptides plays an important regulatory role in pulmonary angiotasis.

Some studies demonstrated that acute anoxia could stimulate mRNA expression of vascular ET and its release (Weigand et al., 2006; Li et al., 2013). In the meantime, ET has the functions of promoting the proliferation of vascular smooth muscles and endothelial cells to further induce the changes in ultrastructures of vascular walls. The increase of ET plasma content indicates increased synthesis and release of ET in the lung, and its reactivity to the body enhances. CGRP is widely distributed in the pulmonary neuroendocrine cells. Known as the strongest non-adrenergic, non-cholinergic receptor type vasodilating active substance at present, CGRP can promote the functional recovery of injured vascular endothelial cells, effectively suppress ET synthesis and release under the pathological condition and antagonize its effects. After anoxia, the ability of secreting CGRP in the lung goes down (Brain et al., 2004; Sardi et al., 2014). Endogenous NO is one of the important factors that maintain the pulmonary at the low resistance circulation status. It was indicated in some studies that ET synthesis accelerated the vascular endothelial functional disorder and aging (Donato et al., 2009). ET could also promote the pulmonary vascular endothelial cells to synthesize NO so as to lower its vasoconstrictive action (Bourque et al., 2011). This study demonstrated that in the early stage of OLV, ET content was increased significantly, and plasma NO and CGRP contents were decreased by varying degrees.

Stellate ganglia are formed by the aggregation of posterior cervical sympathetic neurons and chest 1st sympathetic neuron (Böttger et al., 2011), and some sympathetic postganglionic fibers are distributed in pulmonary vascular smooth muscles and endodermis to regulate the pulmonary vasomotor activity (Feletou et al., 2001). In this study, NO and CGRP contents in group S were significantly higher than that in group N, and CGRP content in group N dropped significantly when compared with pre-OLV, indicating that there is a possible relevancy with the increase of CGRP and NO after the postganglionic fiber of stellate ganglia was blocked. During the experiment, the time of NO increase lagged behind ET, considering that the possible mechanism was the anoxia status in the early stage of OLV induced the vascular endothelial injury and decreased transient secretion of NO, and with the improvement of anoxia status, relief of stress reactions and NO release in endothelial cells after ET increase, NO level went up increasingly. Meanwhile, some study revealed that the decrease of NO generation in the case of acute anoxia was associated with HPV mediation (Nilsson et al., 2011). Since the pulmonary ability to secret CGRP decreased after anoxia, the plasma CGRP content in group N significantly dropped.

This study also performed conventional monitoring on perioperative hemodynamic parameters, such as MAP, HR and CI. Compared with group N, the hemodynamic parameters of group S decreased at some time points, and significant difference was presented. The overall trend indicated the perioperative hemodynamic parameters of group S tended to be more stable than that of group N. The mechanism may be associated with the following reactions: SGB can, to some extent, suppress the conduction of cardiopulmonary sympathetic nerves, surgically stimulate the nerve conduction and lower the sympathetic tension to decrease the sympathetic excitability (Merriam et al., 2010), while the general anesthesia suppresses the relative excitation of vagus nerves so that the haemodynamic parameters can remain stable.

The changes of vascular vasomotor cytokines after OLV in group S were more significant than in group N, but no significant effect was exerted on the intrapulmonary shunt. The possible reasons are as follows: (1) The body has numerous factors affecting vasomotor cytokines. It was found in the study that plasma ET content did not display consistent changes with NO and CGRP contents during OLV, indicating that there were still other vasomotor cytokines that participated in the pulmonary vascular regulatory activities before and after SGB. (2) The concomitant rise in plasma NO and CGRP contents and ET content in group S during peri-operative period can antagonize the excessive stress reactions of the body and stabilize the circulation, which reduces the injury on vascular endothelium caused by hemodynamic instability to some extent, especially the injury on pulmonary vessels, and facilitates the guarantee of oxygen supply in the body, improves oxygenation and reduces intrapulmonary shunt. (3) Due to the unilateral, SGB can only block the sympathetic tension arising at the blocking side, so the effect has a certain limitation. Some study pointed

that unilateral SGB can increase the oxygen content in ipsilateral tissues to make the oxygen content in contralateral tissues drop relatively (Kasahara et al., 2012). When OLV is performed, the ipsilateral SGB can also exert a beneficial effect on the intrapulmonary shunt. The differences in the distribution of the postganglionic fiber of the bilateral stellate ganglionic sympathetic ganglion create different influences on the heart function after block. Although bilateral SGB can generate changes in blood pressure and heart rate, the cardiac sympathetic innervation by the preganglionic fiber originating from right SGB is superior to that from left SGB (Li et al., 2001). The left SGB stimulation can induce the expansion of conduction block areas at the site of myocardial ischemia, further inducing the increased possibility of arrhythmia. Left SGB can induce the significant increase in left ventricular diastolic pressure and oxygen consumption of heart muscle, while the right SCG can reduce the myocardial oxygen consumption (Yildirim et al., 2007). The right SGB is more easily apt to induce hypotension, the effect of slowing heart rate is relatively strong, and the possibility of significantly elevated blood pressure induced by left SGB is higher than the right SGB (Yokota et al., 2013). However, some reports also demonstrated that in animal experiments and clinical applications, the left SGB did not exert significant effects on hemodynamics, but had a possibility of improving the heart function (Liu et al., 2010).

To sum up, the total intravenous anesthesia in combination with SGB is conductive to regulating perioperative vasomotor cytokines, relieving the decreased oxygenation index and having a little effect on intrapulmonary shunt during OLV, which can be safely applied to thoracic surgery.

Acknowledgements

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