小潮气量机械通气期间肺开放策略对肺损伤标志物的影响

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摘 要：【目的】探索外科手术中小潮气量机械通气期间应用间断肺复张手法(RM)联合中等水平呼气末正压(PEEP)构成的肺开放策略(OLS)对血浆中肺损伤标志物晚期糖基化终产物可溶性受体(sRAGE)及Clara细胞蛋白(CC16)浓度的影响。【方法】本研究纳入行择期腹腔镜结直肠癌切除术的患者100例，随机(1∶1)分为开放策略组(OLS)和非开放策略(NOLS)组。两组均使用小潮气量机械通气；OLS组机械通气期间间断给予RM并设置PEEP为6~8 cmH_2O，NOLS组不予RM及PEEP。麻醉诱导前(T_1)、术毕后即刻(T_2)及术后第3天(T_3)分别取血检测血浆sRAGE、CC16浓度。【结果】在T_1、T_2、T_3 3个时间点，血浆sRAGE、CC16浓度组间均无统计学差异($P > 0.05$)。所有患者中，T_2、T_3 sRAGE浓度高于T_1，T_3sRAGE浓度高于T_2，T_3 CC16浓度高于T_1、T_2，均有统计学差异($P < 0.05$)。【结论】术中小潮气量机械通气期间，应用间断RM联合中等水平PEEP的肺开放策略不能改变术后三天内血浆肺损伤标志物sRAGE和CC16的水平。

关键词：肺开放策略；小潮气量机械通气；肺损伤标志物；晚期糖基化终产物可溶性受体；Clara细胞蛋白
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The Effects of Open-Lung Strategy on Lung Injury Markers in Patients under General Anesthesia with Low-tidal-volume Ventilation

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Abstract: 【Objective】To determine the effects of an open-lung strategy (OLS) comprising moderate positive end-expiratory pressure (PEEP) and intermittent recruitment manoeuvres (RMs) on plasma levels of lung epithelial injury markers [i.e. soluble receptor for advanced glycation end products (sRAGE) and Clara cell protein (CC16)] during low-tidal-volume ventilation for surgery. 【Methods】One hundred patients who were undergoing laparoscopic colorectal cancer resection under low-tidal-volume ventilation were enrolled in this study. They were randomly assigned (1∶1) to the OLS group (using PEEP of 6~8 cmH_2O and intermittent RM), or the NOLS group (without using PEEP and RM). Blood samples were taken before anesthesia induction (T_1), immediately after surgery (T_2) and the postoperative day 3 (T_3) to measure the plasma concentrations of sRAGE and CC16. 【Results】Significant differences were not observed in the concentrations of sRAGE and CC16 at T_1, T_2 and T_3 between the two groups (all $P > 0.05$). For all the enrolled patients, the concentrations of sRAGE at T_2 and T_3 were higher than that at T_1, the concentration of sRAGE at T_3 was higher than that at T_2, and the concentration of CC16 at T_3 was higher than that at T_1 and T_2 (all $P < 0.05$). 【Conclusions】In patients under general anesthesia with low-tidal-volume ventilation, the using of an OLS comprising medium PEEP and intermittent RMs can not alter plasma levels of lung epithelial injury markers (sRAGE and CC16) in three days after surgery.

Key words: open-lung strategy; low-tidal-volume ventilation; lung epithelial injury markers; soluble receptor for advanced glycation end products; Clara cell protein

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小潮气量容量控制机械通气是外科手术中常用的通气模式[1-3]。然而,它也有导致肺不张、肺内炎症等肺损伤的风险[4-6]。肺开放策略(open-lung strategy, OLS)由肺复张手法(recruitment manoeuvre, RM)和呼气末正压(positive end-expiratory pressure, PEEP)两种策略构成,其对急性肺损伤/急性呼吸窘迫综合征(acute lung injury/acute respiratory distress syndrome, ALI/ARDS)患者的肺不张性损伤具有保护作用[6-7]。晚期糖基化终产物可溶性受体(soluble receptor for advanced glycation end products, sRAGE)和Clara细胞蛋白(Clara cell protein, CC16)已被证明在ALI/ARDS患者血浆中高表达[8-11],因此许多研究将它们作为肺损伤的标志性因子。外科手术中机械通气期间不同的呼吸策略是否会导致肺损伤程度的差异,从而影响围术期循环中肺损伤标记物sRAGE、CC16的浓度,目前仍不明确。我们推测,在手术过程中小潮气量机械通气期间,应用间断肺复张手法联合中等水平PEEP的肺开放策略可减少肺不张性损伤,从而降低循环中sRAGE、CC16的浓度。

1 材料与方法

1.1 研究概况

这是一项大样本临床随机对照试验的子研究。研究方案通过了中山大学附属第六医院伦理委员会的审核、批准(2017ZSLYEC-002),并在ClinicalTrials.gov网站上进行了研究注册(NCT03160144)。

研究纳入了2017年1月至7月间在中山大学附属第六医院行择期腹腔镜结直肠癌切除术的患者100例。纳入标准:年龄>40岁,预计气腹时间≥1.5 h,脉搏氧饱和度(pulse oxygen saturation, SpO_2)≥92%,术后肺部并发症风险分级[12]≥2级。排除标准:美国麻醉医师协会体质分级≥Ⅳ级,近一月内有肺炎、急性呼吸衰竭或脓毒血症史,体质量指数≥30 kg/m^2,有严重慢性阻塞性肺气肿、肺大泡和进行性神经肌肉疾病,参与了其他干预性研究。随机入组前已获所有患者的知情同意。随机将患者分入OLS组或NOLS组,每组50例。随机数字由SPSS17.0软件包(SPSS Inc., Chicago, IL, USA)产生,并由专人保管和分发。进行血浆标志物检测的人员和患者对分组情况不知情。

1.2 干预措施及其麻醉管理

入组的患者均接受按期望体质量[13]计算的小潮气量(6~8 mL/kg)机械通气。麻醉诱导时,两组均以纯氧预给氧5 min。气管插管后调节吸入氧浓度在40%~50%之间,吸气暂停时间占吸气时间30%,并调整呼吸频率使呼气末CO_2分压维持在30~50 mmHg。OLS组设置PEEP为8 cmH_2O,气管插管后立即给患者一次肺复张手法后开始机械通气,随后每30 min给予一次肺复张手法直至拔出气管导管。肺复张手法是依潮气量递增法[14]进行的。NOLS组气管插管后直接予机械通气,不予肺复张手法及PEEP。麻醉方案及其它呼吸管理措施均无差异。机械通气时,如SpO_2 < 92%,两组均以氧浓度10%递增予以补救处理。

麻醉诱导前,予常规监测及500~700 mL的预扩容治疗,并在脊椎T_{12}~L_1或L_1~L_2间隙进行硬膜外穿刺置管。所有患者均置入中心静脉导管并以10~12 mL/kg/h的速率给予术中补液,确保血流动力学稳定。以咪达唑仑、异丙酚、芬太尼、顺阿曲库铵滴定给药进行麻醉诱导,并以七氟醚吸入及瑞芬太尼和异丙酚静脉泵注维持麻醉平稳,按时静脉注射顺阿曲库铵保持肌肉松弛,术中不予硬膜外麻醉用药,术后予连续硬膜外镇痛。术中如出现严重外科并发症或手术开始后快速中转开腹(气腹时间< 1 h),则将该患者剔除研究。

1.3 研究主要指标及其检测方法

本研究的主要指标是围术期血浆中肺损伤标志物(sRAGE、CC16)浓度的变化。麻醉诱导前(T_1)、术毕后即刻(T_2)、术后第3天(T_3)分别留取血标本3 mL置入含EDTA的抗凝试管中,4 ℃冰箱保存。血标本在8 h内以1 500 ×g离心10 min,分离血浆标本放入-80 ℃冰箱保存待测。所有标本收集完毕后,使用酶联免疫吸附法(ELISA)测定血浆sRAGE及CC16浓度【试剂盒(BioVendor-Laboratorni medicina a. s. Czech Republic),sRAGE试剂盒批号:E16-073P02;CC16试剂盒批号:E17-013】。

1.4 统计分析

使用SPSS 17.0软件包对收集的数据进行统计分析。正态分布的计量资料如年龄、气道平台压、sRAGE和CC16浓度等以均数±标准差($\bar{x} \pm s$)表示,两组比较采用独立样本t检验;sRAGE及CC16不同时间点的差值比较采用配对t检验;不

符合正态分布的计量资料如SpO_2、呼吸频率、吸入氧浓度等以中位数（四分位间距）[$M(P_{25}\sim P_{75})$]表示，两组比较采用 Mann-Whitney U 检验。两组性别、吸烟史等率的比较使用卡方检验（COPD 病史等项目理论频数小于 5，改用 Fisher 确切概率法）。$P<0.05$，为差异有统计学意义。血浆肺损伤标志物浓度以各时间点获取的有效数据进行统计。所有入组患者资料均纳入肺开放策略的安全性评价指标（术中潜在有害低血压、需要血管活性药物等）分析。

2　结　果

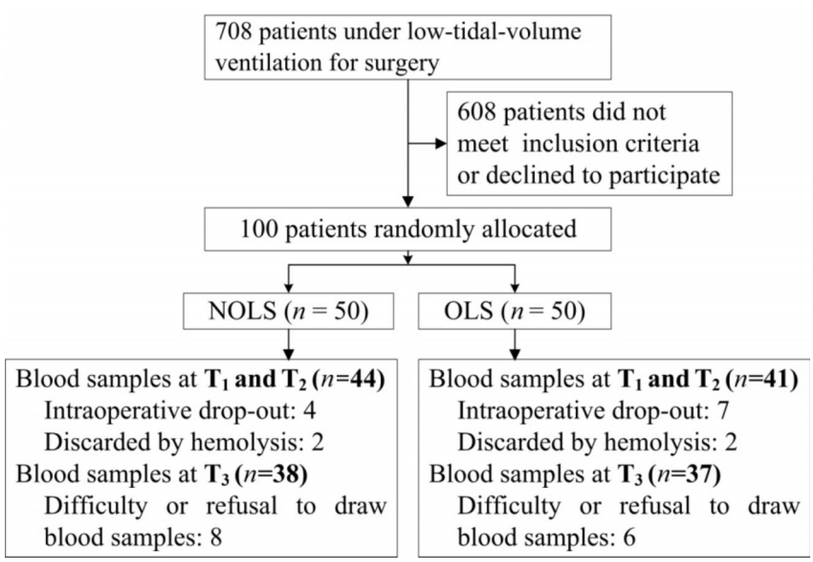
患者术前一般情况、术中情况见表 1、2。NOLS 组 4 例，OLS 组 7 例患者被剔除研究。研究流程及术中术后获取血标本的情况见图 1。OLS 组肺复张手法中位数次数为 7 次。未发现患者出现气胸及 $SpO_2<92\%$ 需补救治疗。

表 1　患者术前资料

Table 1　Preoperative characteristics of the patients　[$(\bar{x}\pm s)$ or $M(P_{25}\sim P_{75})$ or n]

Parameter	NOLS (n = 46)	OLS (n = 43)	$t/Z/\chi^2$	P
Age/years	70.9 ± 5.7	69.8 ± 6.1	0.859	0.393
Body mass index/(kg/m^2)	22.06 ± 2.59	23.06 ± 2.85	−1.742	0.085
Predicted body weight/kg	57.3 ± 8.0	58.3 ± 9.8	0.540	0.590
Male	31	30	0.058	0.824
ASA physical status (II/III)	34/12	29/14	0.450	0.641
PPC risk factor class (2/3)	44/2	42/1		1.000
Pulse oxygen saturation/%	97(96~97)	96(96~97)	−1.219	0.223
Current smokers	9	7	0.163	0.786
COPD	1	1		1.000
Cardiocerebral diseases	5	5	0.013	1.000
White blood cells count/(10^9/L)	5.88 ± 2.14	6.42 ± 2.04	−1.218	0.227

OLS: open-lung strategy; NOLS: non-OLS; ASA: American Society of Anesthesiologists; PPC: postoperative pulmonary complication; COPD: chronic obstructive pulmonary disease



T_1: before anesthesia induction; T_2: immediately after surgery; T_3: postoperative day 3; OLS: open-lung strategy; NOLS: non-OLS

图 1　研究流程图

Fig.1　Trial profile

表2 患者术中情况

Table 2 Intraoperative characteristics [$(\bar{x} \pm s)$ or $M(P_{25}\sim P_{75})$ or n]

Items	NOLS(n = 46)	OLS(n = 43)	$t/Z/\chi^2$	P
Plateau pressure-T_4/cmH_2O	11 ± 2	14 ± 2	−7.199	<0.001
Plateau pressure-T_5/cmH_2O	18 ± 3	21 ± 3	−4.197	<0.001
Tidal volume-T_4/(mL/kg PBW)	7.59 ± 0.52	7.43 ± 0.64	1.257	0.209
Tidal volume-T_5/(mL/kg PBW)	7.17 ± 0.78	6.95 ± 0.70	1.342	0.183
PEEP-T_4/cmH_2O	0(0~0)	8(8~8)	−8.617	<0.001
PEEP-T_5/cmH_2O	0(0~0)	8(6~8)	−8.558	<0.001
Fraction of inspired oxygen-T_4/%	45(45~45)	45(45~46)	−0.728	0.466
Fraction of inspired oxygen-T_5/%	45(44~45)	45(45~45)	−1.594	0.111
Respiratory rate-T_4/(breaths/min)	12(12~12)	12(12~12)	−1.455	0.146
Respiratory rate-T_5/(breaths/min)	18(16~18)	18(16~18)	−0.229	0.819
Duration of surgery/min	213 ± 83	211 ± 71	0.094	0.926
Duration of mechanical ventilation/min	235 ± 86	230 ± 71	0.301	0.764
Trendelenburg position	39	31	2.131	0.197
Pneumoperitoneum pressure/mmHg	11(11~12)	11(11~12)	−0.821	0.412
Urine output/mL	500(275~750)	500(287~663)	−0.337	0.736
Blood loss/mL	50(50~100)	50(50~100)	−0.345	0.730
Volume of infusion/mL	3 083 ± 749	3 121 ± 630	−0.256	0.799
Crystalloid/mL	2 027 ± 523	1 930 ± 539	0.852	0.397
Need for vasopressors[1)]	4	10		0.148
Potentially harmful hypotension[2)]	2	6		0.269

1) Mean arterial pressure (MAP) ≤ 55 mmHg or vasopressor to be needed assessed by anesthesiologist and used when MAP < 65 mmHg; 2) MAP = 50~55 mmHg and lasting longer than 1 minute. OLS: open-lung strategy; NOLS: non-OLS; PBW: predicted body weight; PEEP: positive end-expiratory pressure; T_4: immediately before pneumoperitoneum induction; T_5: 1.5 h after pneumoperitoneum induction

本研究主要指标结果见表3。在T_1、T_2、T_3,血浆sRAGE、CC16浓度组间差异均无统计学意义($P > 0.05$)。对于所有患者,T_2及T_3 sRAGE浓度高于T_1[T_2-T_1平均差值153.5 pg/mL,95%置信区间为(102.3, 204.7) pg/mL;T_3-T_1: 946.1(884.6, 1007.6) pg/mL];T_3 sRAGE浓度高于T_2[T_3-T_2: 786.1(714.5, 857.7) pg/mL];T_3 CC16浓度高于T_1及T_2[T_3-T_1: 8.73(6.99, 10.48) ng/mL;T_3-T_2: 9.15(7.36, 10.94) ng/mL]。

3 讨 论

3.1 主要发现

本研究显示,在小潮气量机械通气下行外科手术的患者中,术毕后即刻血浆sRAGE浓度相对术前升高,术后第3天血浆sRAGE和CC16浓度相对术前和术后即刻均升高。然而,机械通气期间应用肺开放策略(间断RM联合中等水平PEEP)

表3　血浆sRAGE和CC16浓度的围术期变化

Table 3　Plasma concentrations of sRAGE and CC16 in the perioperative period

Items	NOLS		OLS		t	P
	n	$\bar{x} \pm s$	n	$\bar{x} \pm s$		
sRAGE-T_1/(pg/mL)	44	827.7 ± 291.7	41	787.1 ± 205.9	0.752	0.461
sRAGE-T_2/(pg/mL)	44	978.9 ± 409.6[1)]	41	943.1 ± 332.1[1)]	0.443	0.659
sRAGE-T_3/(pg/mL)	38	1715.8 ± 292.7[1)2)]	37	1775.0 ± 247.8[1)2)]	−0.945	0.348
CC16-T_1/(ng/mL)	44	6.51 ± 2.14	41	6.27 ± 1.81	0.567	0.572
CC16-T_2/(ng/mL)	44	6.07 ± 1.92	41	5.89 ± 1.48	0.475	0.638
CC16-T_3/(ng/mL)	38	13.95 ± 7.37[1)2)]	37	15.18 ± 8.71[1)2)]	−0.640	0.524

1) $P < 0.05$ compared with preoperative. 2) $P < 0.05$ compared with postoperative. OLS: open-lung strategy; NOLS: non-OLS; sRAGE: soluble receptor for advanced glycation end products; CC16: Clara cell protein; T_1: before anesthesia induction; T_2: immediately after surgery; T_3: postoperative day 3

并不能改变术毕后即刻和术后第3天血浆sRAGE和CC16浓度。

3.2　sRAGE浓度与呼吸机相关肺损伤

sRAGE是一种Ⅰ型肺泡上皮细胞相关性蛋白[9]。正常情况下，sRAGE在肺部高表达，在其他部位低表达。ALI/ARDS患者长期机械通气期间Ⅰ型肺泡上皮细胞发生凋亡或坏死，循环中sRAGE浓度升高[8]。血浆sRAGE水平与ALI/ARDS患者机械通气期间的肺损伤程度呈正相关[11]。目前，众多研究表明术中机械通气策略的不同可引起围术期肺损伤的程度不同[2]。因而，术中机械通气策略的不同也可能引起血浆sRAGE浓度的改变。

本研究结果显示，小潮气量通气过程期间，无论是否应用肺开放策略，术毕后即刻血浆sRAGE浓度相对于术前均升高，术后第3天sRAGE浓度相对术前和手术后即刻均升高，然而所有时间点组间比较均无统计学差异。Determann等[15]的研究显示，在经历了5 h的术中机械通气后，血浆sRAGE水平在小潮气量通气(6 mL/kg)加PEEP(10 cmH_2O)组及单纯大潮气量通气(12 mL/kg)组均较术前升高，但组间sRAGE浓度无统计学差异。Jabaudon等[16]的研究则显示，相对于非肺保护性通气组(大潮气量通气不加PEEP)，肺保护性通气组(小潮气量通气+PEEP+RM)术后早期血浆sRAGE水平相对于术前明显降低，术后第3天sRAGE水平相对于术前也有所降低，而非肺保护通气组无此效应。Serpa等[17]的大样本研究显示，在同为小潮气量通气的情况下，术后即刻和术后第5天血浆sRAGE水平在高PEEP(12 cmH_2O PEEP+RM)组和低PEEP(≤ 2 cmH_2O)组间均无统计学差异；相对于术前水平，两组在术后即刻和术后第5天血浆sRAGE水平均未呈现明显变化趋势。

基于机械通气相关肺损伤的理论和不同机械通气策略会导致了肺损伤差异化的假设，患者在经历了数小时术中机械通气的术毕后即刻循环中sRAGE浓度相对术前应有所上升且两研究组间sRAGE浓度应有所差异。然而，从本研究和类似研究[16-17]的结果来看，并不能得出这样肯定的结论。可能的解释为短时程机械通气所致肺损伤程度较轻，尚不至于引起循环中sRAGE浓度的明显改变。另外，现有研究结果中普遍存在sRAGE浓度的离散度大，不同研究结果的可比性差等特点。因而，拟通过术毕后即刻循环中sRAGE浓度的差异来判断不同机械通气模式所致肺损伤程度的差异这种设想，可能达不到预期的结果。不同机械通气策略对术后(第3天或第5天)循环中sRAGE浓度影响的研究相对有限，我们的结果也提示术中通气策略对其影响不大。

3.3 CC16浓度与呼吸机相关肺损伤

CC16是由衬覆于远端细支气管的非纤毛、非黏液分泌细胞(即Clara细胞)分泌的一种分子量为15.8 ku的小分子蛋白[9]。不仅在呼吸机相关肺炎患者中可见血浆CC16水平的升高[10],在一些亚临床肺损伤模型(如暴露于吸烟环境中,或吸入臭氧等)中也可见CC16水平的升高[9]。因而,循环中CC16水平可能成为一种反映短时程机械通气肺损伤水平的生物学标志物。

本研究结果显示,在术中小潮气量通气过程中,无论是否应用肺开放策略,术毕后即刻血浆CC16水平相对术前无变化,术后第3天CC16水平相对术前和术毕后即刻均有升高;然而,在术毕后即刻和术后第3天,其浓度组间均无统计学差异。Determann等[15]的研究显示,单纯大潮气量通气(12 mL/kg)策略组与小潮气量通气(6 mL/kg)加PEEP(10 cmH_2O)策略组患者经历了5 h术中机械通气后,CC16浓度在组间亦无统计学差异,但血浆CC16水平均较术前明显升高。另一研究[18]也显示,机械通气1 h后,大潮气量通气(10 mL/kg)组和小潮气量通气(6 mL/kg)组血浆CC16水平组间无统计学差异。Serpa等[17]的大样本研究则显示,小潮气量通气期间高PEEP(12 cmH_2O PEEP+RM)和低PEEP(≤2 cmH_2O)组间术后即刻和术后第五天的血浆CC16水平均无统计学差异。

总之,目前相对有限的研究得出较为一致的结论:术毕后即刻不同通气策略组间循环中CC16浓度差异无统计学意义;术后第3天或第5天的资料更为有限,据我们的结果,其结论应与术后即刻的结论基本一致。

3.4 总 结

综上所述,术中机械通气期间应用间断肺复张手法联合中等水平PEEP的肺开放策略不能改变术后即刻及术后第3天血浆sRAGE和CC16浓度。结合相关文献,我们认为,术后早期和术后3~5 d血浆sRAGE和CC16浓度在评价术中不同通气策略所致肺损伤差异方面具有局限性,其应用价值有限。我们后续将进一步探索肺开放策略对术中氧合损伤及术后并发症的影响以明确其是否具有肺保护作用。本研究不足之处在于未将术毕后即刻及术后第3天肺损伤标志物浓度与患者的临床预后进行相关性研究。

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