·临床研究·

肺保护性通气策略对开胸单肺通气时炎性因子的影响

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Effects of the Lung Protective Ventilatory Strategy on Proinflammatory Cytokine Release During One-lung Ventilation

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[ABSTRACT] BACKGROND&OBJECTIVE: A prolonged period of one-lung ventilation (OLV) is required during thoracic surgery and this may activate cytokine release and cause lung inflammatory response. The lung protective ventilatory strategy has reduced lung and systemic cytokine release and achieved remarkable curative effect in patients with acute respiratory distress syndrome (ARDS). This study was to investigate the effect of the lung protective ventilatory strategy on proinflammatory cytokine release during OLV in patients underwent thoracic surgery. METHODS: Forty patients underwent esophagectomy were randomly divided into conventional ventilation (CV) group (n=20) and protective ventilation (PV) group (n=20). In CV group, all patients received two-lung ventilation (TLV) and OLV with a tidal volume (V_T) of 10 mL/kg and an inspiration/expiration ratio (I/E) of 1:1.5. In PV group, all patients received TLV with a V_T of 10 mL/kg and an I/E ratio of 1:1.5, and received OLV with a V_T of 5-6 mL/kg and an I/E ratio of 1:1, along with positive end-expiratory pressure (PEEP) preset at 3-5 cm H_2O. Blood samples of 3 mL were extracted at three time courses, which were after tracheal intubation (T1), 120 min after OLV (T2) and 24 h after operation (T3), to analyze concentrations of interleukin (IL)-6 and IL-8 in the two groups. Values of airway peak pressure (Ppeak), airway plateau pressure (Pplat), and airway resistance (Raw)were also recorded using side stream spirometry. RESULTS: In CV group, concentrations of IL-6 and IL-8 at T2 [(269.4±57.2) ng/L, (180.8±35.0) ng/L] and T3[(335.8±98.7) ng/L, (178.5±18.3) ng/L] were significantly increased as compared with those at T1 [(17.0±5.4) ng/L, (18.2±2.8) ng/L](P<0.05). In PV group, concentrations of IL-6 and IL-8 at T2 [(209.3±55.7) ng/L], (115.3±71.5) ng/L] and T3 [(278.2±100.8) ng/L, (124.2±40.1) ng/L] were significantly increased as compared with those at T1[(20.0±7.1) ng/L, (15.3±3.6) ng/L] (P<0.05). Concentrations of IL-6 and IL-8 at T2 and T3 were significantly higher in CV group than in PV group (P<0.05). Ppeak, Pplat and Raw at T2 were significantly higher in CV group [(33.6 ±4.6 cmH_2O, (21.5 ±3.1) cmH_2O, (26.3±2.1) $cmH_2O.L^{-1}.s^{-1}$] than in PV group [(26.7±3.5) cmH_2O, (12.4±2.1) cmH_2O, (18.3±2.3) $cmH_2O.L^{-1}.s^{-1}$](P<0.05). CONCLUSIONS: Concentrations of IL-6 and IL-8 are increased during and after OLV in thoracic surgery. The lung protective ventilatory strategy can reduce the airway pressure and airway resistance during OLV, decrease the release of IL-6 and IL-8, and inhibit lung inflammatory responses during OLV and postoperatively.

KEYWORDS: Lung protective ventilation; Esophageal neoplasms/surgery; One-lung ventilation; Proinflammatory cytokine

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【摘 要】 背景与目的:开胸手术需长时间维持单肺通气,这一过程可引起炎性细胞激活并释放大量炎性因子,引起肺部炎性反应及并发症。肺保护性通气策略在呼吸窘迫综合症(acute respiratory distress syndrome,ARDS)的治疗中取得显著疗效,关键在于减少炎性因子释放,减轻肺炎性反应。但它应用于正常肺组织单肺通气时,能否减少炎性因子释放尚不清楚。本研究探讨肺保护性通气策略对开胸单肺通气时炎性因子的影响。**方法**:40 例择期行食管癌根治手术病人,随机分为常规通气组(conventional ventilation, CV 组)和保护性通气组(protective ventilation,PV 组),每组 20 例。CV 组病人双肺及单肺通气参数设定:潮气量(tidal volume,V_T)10 mL/kg,吸/呼比(inspiration: expiration, I:E)为 1:1.5。PV 组病人双肺通气时参数设定同 CV 组,但单肺通气时 V_T 为 5~6 mL/kg,I:E=1:1,并给予呼气末正压(positive end-expiratory pressure, PEEP)3~5 cmH_2O。两组患者均在气管插管后(T1)、单肺通气 120 min (T2)和术后 24 h(T3)各时点抽取静脉血 3 mL 检测白细胞介素 6 (interleukin-6,IL-6) 及白细胞介素 8 (interleukin-8,IL-8)的浓度;用旁气流通气监测法监测两组呼吸力学参数。**结果**:CV 组 IL-6、IL-8 浓度在 T2 时点[(269.4±57.2)ng/L],[(180.8±35.0)ng/L]、T3 时点 [(335.8±98.7)ng/L],[(178.5±18.3)ng/L]较 T1 时[(17.0±5.4)ng/L],[(18.2±2.8)ng/L]增高,差异有统计学意义(P<0.05)。PV 组 IL-6、IL-8 浓度在 T2 时 [(209.3±55.7)ng/L],[(115.3±71.5)ng/L]、T3 时 [(278.2 ±100.8)ng/L],[(124.2 ±40.1)ng/L] 较 T1 时[(20.0±7.1)ng/L],[(15.3±3.6)ng/L]增高,差异有统计学意义 (P<0.05)。但 CV 组 IL-6、IL-8 浓度在 T2、T3 时点高于 PV 组,差异有统计学意义(P<0.05)。CV 组气道峰压、平台压、气道阻力 (33.6±4.6 cmH_2O,21.5±3.1 cmH_2O,26.3±2.1 $cmH_2O \cdot L^{-1} \cdot s^{-1}$)在 T2 时点高于 PV 组(26.7±3.5 cmH_2O、12.4±2.1 cmH_2O、18.3±2.3 $cmH_2O \cdot L^{-1} \cdot s^{-1}$),有统计学意义($P$<0.05)。**结论**:开胸手术单肺通气期间及术后 IL-6、IL-8 显著增加。采用肺保护性通气策略可显著降低单肺通气时气道压力及阻力,显著减少单肺通气期间及术后 IL-6、IL-8 的释放,减轻肺炎性反应。

关键词:肺保护性通气; 食管肿瘤/外科手术; 单肺通气; 炎性因子

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机械通气时大潮气量或气道压力过高可刺激炎性因子的大量释放,诱发或加重肺损伤,并易导致术后肺部并发症[1,2]。开胸手术需长时间单肺通气以维持开胸侧肺萎缩,为手术提供条件。有报道,在单肺通气时亦伴随着血浆中炎性因子的大量增加,出现全身及肺部炎性反应。这可能与相对较大的潮气量及高气道压力,导致肺泡过渡膨胀及萎陷有关[2-5]。

以小潮气量,低气道压、低 PEEP 为策略的肺保护性通气在 ARDS 的治疗中取得了显著的疗效,它减轻机械通气对肺泡的损伤,减少炎性因子释放并改善肺泡氧合[6]。肺保护性通气应用于正常肺组织,特别是单肺通气期间个体化肺保护性通气策略的应用能否减少炎性因子释放,减轻炎性反应尚不清楚。本研究拟探讨其对开胸食管癌手术病人单肺通气时炎性因子的影响。

1 资料与方法

1.1 临床资料

选择 2005 年 5 月至 2006 年 2 月期间,中山大学肿瘤防治中心胸外科收治的食管癌患者 40 例,拟全麻下行食管癌根治术。其中男性 31 例,女性 9 例。年龄 41~65 岁,中位年龄 55 岁。所有患者无高血压及心脏病病史,肺功能检查无异常,术前无呼吸道及肺部感染。随机分为常规通气组(CV 组)和保护性通气组(PV 组),每组 20 例。

1.2 麻醉方法

两组麻醉诱导相同:静脉注射咪唑安定 0.1 mg/kg, 芬太尼 4 μg/kg, 异丙酚 1 mg/kg, 维库溴铵 0.15 mg/kg,3min 后插入双腔导管, 听诊法及纤支镜(Pentax FI-10P2,Pentax 公司,日本)检查来确定导管的正确位置,Ohmeda Aestiva 7100 麻醉机控制呼吸。麻醉维持:两组均用瑞芬太尼 0.08~0.15 $\mu g \cdot min^{-1} \cdot kg^{-1}$,异丙酚 3~4 $mg \cdot kg^{-1} \cdot h^{-1}$,维库溴铵 0.06~0.08 $mg \cdot kg^{-1} \cdot h^{-1}$ 持续泵注, 维持脑电双频指数(BIS 值)在 50 左右。两组均不用吸入麻醉药。CV 组患者双肺及单肺机械通气参数设定:V_T 10 mL/kg,I:E=1:1.5。调节呼吸频率使 $P_{ET}CO_2$ 在 4~4.7 kPa (1 kPa=7.5 mmHg)。PV 组患者双肺通气时参数设定同 CV 组,但单肺通气时 V_T 为 5~6 mL/kg, I:E=1:1,并给予 PEEP 3~5 cmH_2O, 调节呼吸频率维持 $P_{ET}CO_2$ 正常范围。两组患者均颈内静脉及桡动脉穿刺置管测压及采血样。GE Solar 8000 多功能监护仪(美国)监测生命体征;呼吸力学模块旁气流法监测:潮气量(tidal volume,V_T)、呼吸频率(respiration rate, RR)、呼气末正压 (PEEP)、气道峰压 (airway peak pressure,Ppeak)、平台压 (airway plateau pressure, Pplat)、气道阻力(airway resistance,Raw)、动态胸肺顺应性(dynamic compliance,Cdyn)。

1.3 项目观察

在气管插管后(T1)、单肺通气 120 min (T2)、术后 24 h(T3)时点,采集静脉血 3 mL 加入 EDTA 抗凝管,以 3 000 r/min 离心 10 min 后取上清液放置于-70℃保存待测。同时抽取动脉血,用 I-STAT 床边血气分析仪(美国)行血气分析,并计算氧合

指数(index of oxygenation, OI):OI=PaO_2/FiO_2。用ELISA法测定血中IL-6、IL-8的浓度。采用深圳晶美公司提供的试剂盒,按照说明书进行操作。最低测定浓度为10 ng/L。

1.4 统计学处理

采用SPSS11.5统计软件进行统计学分析,计量资料以均数±标准差($\bar{x}\pm s$)表示,组内比较采用单因素方差分析,组间比较采用成组t检验,计数资料比较采用卡方检验(单侧检验),$P<0.05$为差异有统计学意义。

2 结 果

2.1 两组患者一般情况及术中情况比较

单肺通气时两组潮气量差异有统计学意义($P=0.023$)。其余指标差异无统计学意义($P>0.05$)。见表1。

表1 两组患者一般情况及术中情况

Table 1 Clinical and intraoperative date of patients in conventional ventilation group(CV) and protective ventilation group (PV)

Item	PV Group	CV Group	*P* value
Gender			
(Male / Female)	15/5	16/4	0.472
Median age (yrs)	55	54	0.421
Body weight (kg)	55.3±11.8	58.4±15.7	0.460
Open chest surgery			
Left / Right	16/4	15/5	0.432
Surgery duration (min)	230±31	241±32	0.431
Mechanical ventilation duration (min)	260±54	256±43	0.423
One lung ventilation duration (min)	142±21	154±32	0.321
Tidal volume (mL/kg, OLV)	5.4±0.2	9.4±1.1	0.023
Respiratory rate (times/min)	13±3.2	11±2.1	0.323

2.2 两组患者炎性因子变化

与T1比较,两组T2、T3时点血浆中IL-6、IL-8的浓度显著增加($P<0.05$)。但T2、T3时点IL-6、IL-8的浓度CV组显著大于PV组($P<0.05$)。见表2。

2.3 两组患者呼吸力学参数的比较

CV组中Ppeak、Pplat、Raw、Cdyn在T2时显著大于PV组($P<0.05$)。PV组的OI在T2、T3时点显著高于CV组($P<0.05$)表3。术后1 d床边胸片检查,CV组2(2/20)例可疑肺不张,位于左下肺,均为非通气侧肺。PV组3(3/20)例,位于左下肺,均为非通气侧肺,二者比较差异无统计学意义($P=0.8$)。通过吸痰、改善胸腔负压引流后,第三天复查胸片无异常。

表2 两组各时间点IL-6、IL-8的比较

Table 2 Comparisons of concentrations of IL-6 and IL-8 between CV group and PV group at different time course

Item	Group	T1	T2	T3
IL-6(ng/L)	PV	20.0±7.1	209.3±55.7[a]	278.2±100.8[a]
	CV	17.0±5.4	269.4±57.2[a,b]	335.8±98.7[a,b]
IL-8(ng/L)	PV	15.3±3.6	115.3±71.5[a]	124.2±40.1[a]
	CV	18.2±2.8	180.8±35[a,b]	178.5±18.3[a,b]

T1: after tracheal intubation; T2: 120 min after one-lung ventilation; T3: 24 h after operation. [a]$P<0.05$, vs. T1; [b]$P<0.05$, vs. PV group.

表3 两组呼吸参数及氧合指数比较

Table 3 Comparisons of respiratory variables and oxygenation indexes between CV group and PV group

Item	Group	T1	T2	T3
Ppeak(cmH_2O)	CV	17.3±1.8	33.6±4.6	–
	PV	16.9±2.1	26.7±3.5[a]	–
Pplat(cmH_2O)	CV	15.2±2.9	21.5±3.1	–
	PV	15.4±2.7	12.4±2.1[a]	–
Raw($cmH_2O\cdot L^{-1}\cdot s^{-1}$)	CV	18.1±1.8	26.3±2.1	–
	PV	17.9±1.7	18.3±2.3[a]	–
Cdyn(mL/cmH_2O)	CV	43.6±7.9	48.8±8.9	–
	PV	45.6±8.9	40.5±6.3[a]	–
OI(mmHg)	CV	450±60	360±54	310±34
	PV	460±55	401±56[a]	360±32[a]

Ppeak, airway peak pressure; Pplat, airway plateau pressure; Raw, airway resistance; Cdyn, dynamic compliance; OI: oxygenation index. T1: after tracheal intubation; T2: 120 min after one-lung ventilation; T3: 24 h after operation. [a]$P<0.05$, vs. CV group.

3 讨 论

机械通气是临床麻醉和重症治疗中常用的治疗手段。但机械通气致肺损伤已日益引起重视。动物实验证实,肺泡上皮细胞、血管内皮细胞受到机械牵拉后,激活基因转录表达,IL-6、IL-8等炎性因子转录水平增加。这些因子在诱发肺损伤中起重要作用[2,7],这对弄清及防治机械通气相关性肺损伤有重要意义。单肺通气时临床较多关注预防低氧血症,通常采用与双肺通气时一样的潮气量。有研究认为这对于单肺通气而言则属于相对大潮气量,加之侧卧位的影响,导致气道压明显增高[4,8]。本研究发现,两组患者在单肺通气时呼吸力学指标及炎性因子有显著差异,Ppeak、Pplat、Raw及单肺通气120 min时IL-6、IL-8等在PV组显著低于CV组,与上述结果相似,提示保护性通气可能通过降低通气压力及气道阻力,增加呼吸系统顺应性等来减轻机械通气对肺泡的刺激,减少炎性因

子释放。

IL-6 由肺组织内不同细胞，如肺泡巨噬细胞、内皮细胞等在受到牵拉等刺激时激活产生。其水平的急剧上升可看作急性期反应的表现,即炎性因子的大量激活。它与肺损伤、肺部并发症密切相关[9]。IL-8 也由肺泡巨噬细胞产生,作为中性粒细胞趋化因子,可引起中性粒细胞聚集和脱颗粒,发生呼吸爆发,并产生弹性蛋白酶,导致肺组织损伤。IL-8 水平亦与肺损伤密切相关[10]。由此可知二者是具有观察意义的炎性因子,减少它们的产生可有效防止肺部并发症。Abe 等[11]发现食管癌围术期 IL-6 显著增高,提示机体及肺组织产生炎性反应,认为与机械通气及手术刺激有关。多项研究表明[13,13]，V_T 和 Ppeak 是引起肺炎性反应的主要危险因素。本研究中，两组在单肺通气 120 min 时 IL-6、IL-8 显著增高并持续到术后 1 d，同时伴随着 OI 的进行性降低,提示存在肺炎性反应及肺损伤的可能,与上述结果相似。但程度上 PV 组显著低于 CV 组,进一步说明大 V_T 和高 Ppeak 的危害性，它可能诱发肺泡“首次打击”甚至导致“二次或三次打击”[8]。保护性通气的实质就是减少潮气量及降低气道压力,避免肺泡过渡膨胀及萎陷，减少剪切力等对肺的损伤[6,13]。目前对于肺功能正常的病人单肺通气时潮气量的确定尚无定论。也有人认为,“小潮气量”其实是“正常潮气量”[8]。本研究设定为 5~6 mL/kg,参考了有关文献并进行了预实验[13]。与对照组比较,只要双腔导管对位良好,气道压力及阻力显著下降,肺顺应性改善,就对炎性因子释放及减轻炎性反应而言,PV 组显著优于 CV 组,这一结果可能使肺功能低下的手术患者受益。

食管癌手术要求单肺通气的时间长,本研究中两组单肺通气时间均超过 2 h。但术中无持续低氧血症及高二氧化碳血症出现,说明 V_T 5~6 mL/kg 单肺通气,不会引起氧供不足及二氧化碳蓄积,是安全的,这与应用低 PEEP 有关[14]。考虑到吸入麻醉药对炎性因子的影响,本研究中两组均未用吸入麻醉药,这是与其它报道不同之处[3,13]。

小潮气量通气可能出现肺不张、肺泡过早闭合等通气不足情况,特别是开胸、侧卧位时。Cai 等[15]报道在双肺通气时通过 CT 扫描检查，发现小潮气量通气并不增加肺不张的发生率。也有研究认为[14],PEEP 能有效防止肺泡萎陷及不张,保持呼吸末肺泡相对开放,同时也能使已经塌陷的肺泡重新开放。本研究中,PV 组采用低水平 PEEP,并适当延长了吸气时间(I:E=1:1),术后 1 d 胸片检查无通气侧肺不张发生。提示小 V_T 通气时结合低 PEEP 可有效防止肺不张的发生,与上述研究结果一致。至于肺保护性通气策略能否直接起到减少肺部并发症,改善术后肺功能等作用,有待于进一步观察。

综上所述,开胸手术单肺通气期间及术后 IL-6、IL-8 显著增加。采用肺保护性通气策略可显著降低单肺通气时气道压力及阻力,显著减少单肺通气期间及术后 IL-6、IL-8 的释放,减轻肺炎性反应。

[参 考 文 献]

[1] Fernandez-Perez E, Keegan M, Brown D R, et al. Intraoperative tidal volume as a risk factor for respiratory failure after penumonectomy [J]. Anesthesiology, 2006,105(1):14-18.

[2] Gama de Abreu M, Heintz M, Heller A, et al. One-lung ventilation with high tidal volumes and zero positive end-expiratory pressure is injurious in the isolated rabbit lung model [J]. Anesth Analg, 2003,96(1):220-228.

[3] Schilling T, Kozian A, Huth C, et al. The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery [J]. Anesth Analg, 2005,101(4):957-965.

[4] 马武华,高婉菱,关键强,等. 单肺通气时预防低氧血症及肺内分流的临床研究 [J]. 中山大学学报:医学科学版, 2003,24(1): 81-84.

[5] Tandon S, Batchelor A, Bullock R, et al. Peri-operative risk factors for acute lung injury after elective oesophagectomy [J]. Br J Anaesth, 2001,86(5):633-638.

[6] Petrucci N, Iacovelli W. Ventilation with smaller tidal volumes: A quantitative systematic review of randomized controlled trials[J]. Anesth Analg, 2004,99(1):193-200.

[7] Vlahakis N E, Schroeder M A, Limper A H, et al . Stretch induces cytokine release by alveolar epithelial cells in vitro [J]. Am J Physiol, 1999,277(1):167-173.

[8] Schultz M J, Haitsma J J, Slutsky A S, et al. What tidal volumes should be used in patients without acute lung injury? [J]. Anesthesiology, 2007,106(6):1226-1231.

[9] Aosasa S, Mochizuki H, Tsujimoto H, et al. Activation of monocytes and endothelial cells depends on the severity of surgical stress [J].World J Surg, 2000,24(1):10-16.

[10] Tsukada K, Hasegawa T, Miyazaki T, et al. Predictive value of interleukin-8 and granulocyte elastase in pulmonary complication after esophagectomy [J]. Am J Surg, 2001,181(2):167-171.

[11] Abe K, Oka M, Tangoku A, et al. Interleukin-6 production in lung tissue after transthoracic oesophagectomy [J]. J Am Coll Surg, 2001,192(3):322-329.

[12] Slinger P. Low tidal volume is indicated during one-lung ventilation [J]. Anesth Analg, 2006,103(2):268-270.

[13] Michelet P, D'Journo X B, Roch A, et al. Protective ventilation influences systemic inflammation after esophagectomy: a randomized controlled study [J]. Anesthesiology, 2006,105(5): 911-919.

[14] Michelet P, Roch A, Brousse D, et al. Effects of PEEP on oxygenation and respiratory mechanics during one-lung ventilation[J]. Br J Anaesth, 2005,95(2):163-173.

[15] Cai H, Gong H, Zhang L, et al. Effect of low tidal volume ventilation on atelectasis in patients during general anesthesia: a computed tomographic scan [J]. J Clin Anesth, 2007,19(2):125-129.

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