

doi: 10.13241/j.cnki.pmb.2018.04.027

单孔电视胸腔镜肺叶切除术治疗早期肺癌的效果及对血清 EGFR、VEGF 水平及免疫功能的影响 *

程 宇 尹晓清 程良昊 宁兴旺 杨 进[△]

(湖南中医药大学第一附属医院 胸心血管外科 湖南 长沙 410007)

摘要 目的:探讨单操作孔电视胸腔镜肺叶切除术治疗早期肺癌的临床效果及对血清表皮生长因子受体(EGFR)、血管内皮生长因子(VEGF)水平和免疫功能的影响。**方法:**选择 2014 年 2 月至 2017 年 2 月我院接诊的 60 例早期肺癌患者,采取随机数表法分作观察组(n=30)与对照组(n=30)。观察组采用单操作孔电视胸腔镜肺叶切除术,对照组采用传统胸腔镜三孔法。比较两组手术用时、切口长度、术中出血量、术后下床活动时间、术后住院时间、拔出引流管时间、术后总引流量,治疗前后血清 EGFR、VEGF 水平、CD4⁺、CD8⁺ T 细胞比例、CD4⁺/CD8⁺ 比值、NK 比例的变化及不良反应的发生情况。**结果:**治疗后,观察组的手术用时、术后住院时间、术后下床活动时间及拔出引流管时间均显著短于对照组(P<0.05);术中出血量、切口长度及术后总引流量均显著低于对照组(P<0.05)。观察组治疗后血清 EGFR、VEGF 表达均明显低于对照组(P<0.05),CD4⁺T、CD8⁺T、CD4⁺T/CD8⁺T、NK 水平均显著高于对照组(P<0.05),不良反应总发生率显著低于对照组(P<0.05)。**结论:**单操作孔电视胸腔镜肺叶切除术用于治疗早期肺癌的创伤小,患者恢复快,可有效降低血清中 EGFR、VEGF 的表达,改善其免疫功能,减少不良反应的发生。

关键词:早期肺癌;胸腔镜;肺叶切除术;疗效;免疫功能

中图分类号:R734.2 文献标识码:A 文章编号:1673-6273(2018)04-725-04

Curative Efficacy of Single Utility Port Complete Video-assisted Thoracic Surgery Lobectomy in the Treatment of Patients with Early Lung Cancer and Its Effects on the Serum EGFR, VEGF levels and Immune Function*

CHENG Yu, YIN Xiao-qing, CHENG Liang-hao, NING Xing-wang, YANG Jin[△]

(Department of thoracic and cardiovascular surgery, the First Affiliated Hospital of Hunan, Changsha, Hunan, 410007, China)

ABSTRACT Objective: To investigate the clinical effect of single-operation fluoroscopic thoracoscopic lobectomy in the treatment of early lung cancer and serum epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF) levels as well as the immune function. **Methods:** 60 patients of early lung cancer who were treated from February 2014 to February 2017 in our hospital were selected as the research objects. According to the random number table method, those patients were divided into the observation group (n = 30) and the control group (n = 30). The observation group was treated with single utility port complete video-assisted thoracic surgery lobectomy, while the control group was treated with traditional thoracoscopic three-hole method. Then the surgical use, cut length, intraoperative blood loss, postoperative time to get out of bed, postoperative hospital stay, pull out the drainage tube time, postoperative total drainage, serum EGFR, VEGF, CD4⁺ and CD8⁺ T cells, CD4⁺/CD8⁺ ratio, NK ratio changes and the incidence of adverse reactions were compared between two groups. **Results:** After treatment, the hospitalization time, time of bed removal and time of drainage were significantly shorter than those of the control group (P<0.05). The intraoperative blood loss, incision length and total postoperative drainage were significantly lower than those of the control group (P<0.05). The serum EGFR and VEGF levels of observation group were significantly lower than those of the control group (P<0.05). The CD4⁺T, CD8⁺T, CD4⁺T/CD8⁺T and NK of observation group were significantly higher than those of the control group (P<0.05). The incidence of adverse reactions in the observation group was significantly lower than that of the control group (P<0.05). **Conclusion:** Single-operation video-assisted thoracoscopic lobectomy could effectively reduce the serum EGFR, VEGF levels, improve the immune function and reduce in the treatment of patients with early lung cancer with small trauma.

Key words: Early lung cancer; Thoracoscopy; Lobectomy; Effect; Immune Function

Chinese Library Classification(CLC): R734.2 **Document code:** A

Article ID: 1673-6273(2018)04-725-04

* 基金项目:湖南省教育厅科研项目(16C1204)

作者简介:程宇(1982-),男,硕士研究生,主治医师,研究方向:胸心血管外科,E-mail: chengyu2005166@163.com

△ 通讯作者:杨进(1979-),男,硕士研究生,主治医师,研究方向:胸心血管外科,E-mail: 253867418@qq.com

(收稿日期:2017-04-21 接受日期:2017-05-15)

肺癌是一种常见的呼吸系统恶性肿瘤,其在全球的发病率及致死率均不断升高。其病因大致包括工作环境的影响、大气的污染、辐射电离和吸烟等,临床主要表现为胸闷、胸痛、咳嗽等,严重影响患者的生理心理健康和正常生活^[1]。随着现代医学的进步、诊断技术的升级和定期体检的推广,被发现的早期肺癌患者也越来越多,胸腔镜手术成为了治疗早期肺癌的有效方法。研究表明传统胸腔镜三孔法会对患者身体机能造成较大创伤,并影响免疫功能,对患者术后的恢复产生不利影响^[2-4]。而单操作孔电视胸腔镜肺叶切除术在临床上因其创伤较小、疼痛较轻、出血量较少、术后恢复快等多方面优点日益受到众多医务人员和患者的青睐^[5]。为进一步探究单孔胸腔镜手术对早期肺癌治疗中的应用价值,本研究选取 60 例早期肺癌患者,分别采用单操作孔电视胸腔镜肺叶切除术和传统胸腔镜三孔法进行治疗,均取得了较好的临床效果,现报道如下。

1 资料与方法

1.1 一般资料

将 2014 年 2 月到 2017 年 2 月我院接诊的 60 例早期肺癌患者选作研究对象。纳入标准^[6,7]:① 无放疗、化疗史;② 肿瘤直径 ≤ 5 cm;③ 无胸腔手术禁忌;④ 无胸膜粘连情况;⑤ TNM 分期属于 I~II 期肺癌;⑥ 无精神疾病。排除标准^[8,9]:① 存在免疫性疾病;② 肿瘤远端转移;③ 心肺功能不全,无法经受单肺通气和全身麻醉;④ 近期接受过胸腔手术。将所有患者随机分为观察组和对照组,每组各 30 例。观察组男 17 例,女 13 例,年龄 51~75 岁(60.26 ± 9.68),TNM 分期 I 期 22 例,II 期 8 例;其中腺癌 18 例、鳞癌 10 例,小细胞肺癌 2 例。对照组男 14 例,女 16 例,年龄 50~74 岁(64.39 ± 2.77),TNM 分期为 I 期 19 例,II 期 11 例;其中腺癌 16 例、鳞癌 13 例,小细胞肺癌 1 例。整个研究均在患者知情同意并签署知情同意书的情况下进行,两组患者一般资料比较差异均无明显统计学意义($P>0.05$),具有可比性。

1.2 方法

两组患者均采用静脉全麻,健侧卧位,术中单肺通气;观察组:腔镜观察孔选择于腋中线第 7、8 肋间,作 1.5 cm 的切口,主操作孔选择于腋前线第 5、4 肋间,作 2~3 cm 的切口。将切口保护套放置于孔内,胸腔镜下完成所有手术操作。肺叶切除术

具体处理方式:游离肺血管、肺门、支气管,切断肺部静脉,处理肺叶支气管,分离肺动脉,再处理肺组织,进行病变肺叶的切除,手术进行中均将含淋巴结等手术标本用作病理检查,术后根据病理检查可证明其均为肺癌,各淋巴结样本无转移现象,肺叶切除后对淋巴结系统进行清扫,右侧淋巴结常规包括 2、3、4、7、8、9 组,左侧常规为 5、6、7、8、9 组。术后在患者切口处放置闭式胸腔引流管以引流。对照组:腔镜观察孔选择在腋中线第 8、7 肋间,作 2 cm 的切口,主操作孔选择在腋前线第 5、4 肋间,作 2~3 cm 的切口,再在腋后线第 7 或 6 肋间选取 2~3 cm 的切口作为副操作孔,放置卵圆钳、分离钳与主操作孔器械进行相互配合。手术步骤和观察组同,术后在对照组患者的观察孔和操作孔均放置一根胸管用以引流。两组患者术后均使用舒芬太尼自控静脉镇痛泵进行镇痛。

1.3 观察指标

1.3.1 临床指标 检测患者各项临床指标:手术用时、切口长度、术中出血量、术后下床活动时间、术后住院时间、拔出引流管时间、术后总引流量。

1.3.2 血清 EGFR、VEGF 水平 分别取患者治疗前后静脉抽血,血清 EGFR、VEGF 水平使用双抗体夹心酶联免疫吸附法(ELISA)检测(试剂盒由安徽科亦生物科技有限公司提供)。

1.3.3 免疫功能 检测患者治疗前后免疫功能:CD4⁺T、CD8⁺T、CD4⁺T/CD8⁺T 及 NK 细胞比例。

1.3.4 不良反应 检测患者治疗前后不良反应:肺不张、肺感染、切口感染、心律失常、肩关节活动受限的发生情况及总发生率。

1.4 统计学分析

数据用 SPSS18.0 软件包进行处理,计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,采用 t 检验,计数资料的比较采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床指标的比较

观察组的手术用时、术后住院时间、术后下床活动时间及拔出引流管时间均显著短于对照组($P<0.05$);术中出血量、切口长度及术后总引流量均显著低于对照组($P<0.05$),见表 1。

表 1 两组临床指标的比较($\bar{x} \pm s$)

Table 1 Comparison of the clinical indicators between the two groups($\bar{x} \pm s$)

Groups	Operation time (min)	Cut length(cm)	Intraoperative blood loss(mL)	Postoperative time to get out of bed(d)	Postoperative hospital stay(d)	Pull out the drainage tube time(d)	Total postoperative drainage(mL)
Observation group(n=30)	125.45 $\pm$ 8.86 [#]	4.49 $\pm$ 0.27 [#]	167.91 $\pm$ 19.47 [#]	2.61 $\pm$ 0.44 [#]	8.17 $\pm$ 1.71 [#]	5.03 $\pm$ 0.66 [#]	764.16 $\pm$ 240.62 [#]
Control group(n=30)	151.37 $\pm$ 11.75	11.01 $\pm$ 1.34	208.75 $\pm$ 31.07	3.92 $\pm$ 0.95	9.46 $\pm$ 2.15	6.75 $\pm$ 0.73	960.35 $\pm$ 306.16

Note: compared with the control group, [#] $P<0.05$.

2.2 两组治疗前后血清 EGFR、VEGF 水平的比较

治疗前,两组血清 EGFR、VEGF 水平比较差异无统计学意义($P>0.05$);治疗后,两组血清 EGFR、VEGF 水平均较治疗前显著降低,且观察组血清 EGFR、VEGF 水平明显低于对照组($P<0.05$),见表 2。

2.3 两组治疗前后免疫功能的比较

治疗前,两组 CD4⁺T、CD8⁺T、CD4⁺T/CD8⁺T、NK 水平比较差异无统计学意义($P>0.05$);治疗后,两组 CD4⁺T、CD8⁺T、CD4⁺T/CD8⁺T、NK 水平均较治疗前显著降低,而观察组 CD4⁺T、CD8⁺T、CD4⁺T/CD8⁺T、NK 水平均明显高于对照组($P<0.05$),见表 3。

05),见表3。

表2 两组治疗前后血清EGFR、VEGF水平的比较($\bar{x} \pm s$)Table 2 Comparison of the serumEGFR and VEGF levels between the two groups before and after treatment($\bar{x} \pm s$)

Groups		EGFR(pmol/L)	VEGF(ng/L)
Observation group(n=30)	Before treatment	97.64± 14.96	176.94± 66.28
	After treatment	52.69± 11.44* [#]	113.74± 33.67* [#]
Control group(n=30)	Before treatment	96.96± 15.09	174.86± 67.91
	After treatment	68.49± 14.78*	142.03± 42.07*

Note: Compared with before treatment, *P<0.05; compared with the control group, [#]P<0.05.

表3 两组治疗前后免疫功能的比较($\bar{x} \pm s$)Table 3 Comparison of the immune function between the two groups before and after treatment ($\bar{x} \pm s$)

Groups		CD4 ⁺ T(%)	CD8 ⁺ T(%)	CD4 ⁺ T/CD8 ⁺ T	NK(%)
Observation group(n=30)	Before treatment	36.76± 6.91	29.03± 5.76	1.27± 0.23	18.32± 5.57
	After treatment	33.47± 6.07* [#]	28.66± 5.51* [#]	1.17± 0.15* [#]	15.77± 5.39* [#]
Control group(n=30)	Before treatment	37.17± 7.04	29.06± 6.02	1.26± 0.24	18.63± 5.47
	After treatment	30.03± 5.73*	22.93± 5.17*	1.11± 0.08*	13.57± 5.31*

Note: Compared with before treatment, *P<0.05; compared with the control group, [#]P<0.05.

2.4 两组不良反应发生情况的比较

(16.7%, P<0.05),见表4。

观察组不良反应总发生率为6.7%，明显低于对照组

表4 两组不良反应发生情况的比较(例,%)

Table 4 Comparison of the incidence of adverse reactions between the two groups(n, %)

Groups	Atelectasis	Pulmonary infection	Incision infection	Arrhythmia	Shoulder movement disorders	Overall incidence(%)
Observation group(n=30)	0(0)	1(2)	0(0)	1(2)	0(0)	2(6.7) [#]
Control group(n=30)	1(2)	1(2)	1(2)	1(2)	1(2)	5(16.7)

Note: Compared with the control group, [#]P<0.05.

3 讨论

近年来,由于大气污染不断加重,全世界肺癌的发病率和致死率都呈直线增长态势。肺癌已成为目前全球发病率以及致死率增长速度最快的恶性肿瘤^[10]。其中,男性肺癌的发病及致死率占所有恶性肿瘤之首,女性肺癌发病及致死率占第二位^[11]。肺癌病因目前尚没有完全明确,但职业环境接触、日益严重的大气污染、电离辐射、吸烟等均被证实能诱发形成肺癌^[12]。肺癌患者平均5年的生存率不足10%,早期发现和治疗肺癌对于改善肺癌患者的预后具有重要意义。肺癌的临床表现根据患者肿瘤发生部位、类型及大小有所不同,其主要的临床症状肿瘤外侵和转移、局部与全身症状,包括气促、咳嗽、血痰等^[13,14]。治疗肺癌的临床方法主要是肺叶切除术,切除肺叶并且对淋巴结完成清扫。伴随着医学技术的不断进步,对肺癌的治疗方法已经开始从开胸手术进步为微创的胸腔镜根治术,且已在治疗肺癌的临床上广泛应用^[15]。

早期的胸腔镜根治术主要采用“三孔法”,即需要借助切口用作观察孔,还需要开两个孔,一个作为主操作孔,一个用作副操作孔。由于主治医师在通过操作孔进行体内切割缝合、血管闭合等操作时,需要借助副操作孔,其孔切口需通过背部肌群,而背部肌群层次多,血供丰富,在借助副操作孔时容易出血

且止血较难。后肋的间隙相比前肋来说更加细小,术中穿刺鞘的转动易导致肋间神经和血管的损伤,从而使患者愈加疼痛^[16]。2004年,Rocco第一次报道了单孔胸腔镜治疗肺癌的手术,该治疗的方法已由最开始切除肿块楔形逐步扩大到根治肺癌手术上^[17]。研究表明单孔胸腔镜较传统三孔法而言不但减少了切口数量和长度,其手术用时、术中的出血量、术后恢复等均得到了极大的改善,且单孔胸腔镜操作下进行的清扫淋巴结操作和传统三孔法并无明显差异,其根治肺癌切除肿瘤的目的同样达成,且更有效的提高了患者术后的生活质量。本研究中,采用单孔胸腔镜手术的患者其手术用时仅为125.45± 8.86(min),且切口长度仅为4.49± 0.27(cm)。

EGFR通过Ras-MAPK通路、PI3K-Akt通路和非经典的STAT通路等将各细胞信号传递至细胞核里,使得细胞的生长、分裂等正常生物反应得以调控。肿瘤细胞里存在的EGFR信号的传导通路有EGFR过度表达、EGFR突变等,会导致肿瘤细胞不断的增殖并促使其走向凋亡,进而使肿瘤细胞的生长调节失控。肿瘤组织能向血循环中释放出完整的肿瘤细胞和较多的EGFR蛋白,而被释放出来的肿瘤细胞又能过度释放EGFR蛋白,进而使血清中EGFR蛋白高表达,因而使得EGFR在肺癌患者的血清中表达升高。VEGF作为肿瘤诱导血管的生成的过程中主要的调节分子,可增加血管的通透性,促进血管

的形成和血管内皮细胞增生,和肿瘤的转移生长紧密相关。VEGF 于多种恶性肿瘤中具有高表达的性质,其表达越高就提示出新生的血管越丰富,肿瘤进展就更快,转移部位就更多^[18]。本研究中,采用两种胸腔镜手术的患者治疗后血清 EGFR、VEGF 水平均有不同程度的降低,采用单孔胸腔镜手术的患者治疗后的血清 EGFR 水平仅为 52.69 ± 11.44 (pmol/L),血清 VEGF 水平仅为 113.74 ± 33.67 (ng/L),降低效果相较于采用三孔法胸腔镜手术的患者更为明显。因此,血清 EGFR 和 VEGF 可能作为早期肺癌近期的疗效、转移及复发判断的重要指标,且单孔胸腔镜的手术效果更佳。

患者免疫功能的衰退密切影响着恶性肿瘤的发生和发展。大多数手术均会对人体免疫细胞产生影响^[19]。本研究比较了单操作孔电视胸腔镜肺叶切除术和三孔法胸腔镜手术对患者的淋巴细胞的影响,结果显示单孔胸腔镜手术对患者 CD4⁺T、CD8⁺T、CD4⁺T/CD8⁺T 及 NK 的影响均小于三孔法胸腔镜手术。在单孔胸腔镜组,患者 CD8⁺T 几乎没有受到影响,降低很少;但三孔法胸腔镜组的患者 CD8⁺T 术后降低极为明显^[20]。因此,单孔胸腔镜手术对患者的免疫功能影响较小,细胞毒作用影响更小。此外,本研究结果显示单孔胸腔镜组患者的不良反应总发生率仅为 6.7%,远低于三孔法胸腔镜组患者的 16.7%,提示单孔胸腔镜手术可有效减少患者术后不良反应的发生。

综上所述,单操作孔电视胸腔镜肺叶切除术治疗早期肺癌安全、可靠,可更快的降低患者疼痛,改善其生活质量,具有更好的临床疗效。

参考文献(References)

- [1] Liu Z, Yang R, Shao F, et al. Modified procedure of uniportal video-assisted thoracoscopic lobectomy with muscle sparing incision [J]. *Ann Transl Med*, 2016, 4(19): 367
- [2] Di Rienzo G, Surrente C, Lopez C, et al. Tips and tricks in video-assisted thoracoscopic surgery lobectomy [J]. *Future Oncol*, 2016, 12(23s): 35-38
- [3] Chen H, Xu G, Zheng B, et al. Initial experience of single-port video-assisted thoracoscopic surgery sleeve lobectomy and systematic mediastinal lymphadenectomy for non-small-cell lung cancer [J]. *J Thorac Dis*, 2016, 8(8): 2196-2202
- [4] Gonfiotti A, Bongiolatti S, Borgianni S, et al. Development of a video-assisted thoracoscopic lobectomy program in a single institution: results before and after completion of the learning curve [J]. *J Cardiothorac Surg*, 2016, 11(1): 130
- [5] Lin Y, Zheng W, Zhu Y, et al. Comparison of treatment outcomes between single-port video-assisted thoracoscopic anatomic segmentectomy and lobectomy for non-small cell lung cancer of early-stage: a retrospective observational study [J]. *J Thorac Dis*, 2016, 8(6): 1290-1296
- [6] Qiu B, Yan W, Chen K, et al. A multi-center evaluation of a powered surgical stapler in video-assisted thoracoscopic lung resection procedures in China [J]. *J Thorac Dis*, 2016, 8(5): 1007-1013
- [7] French DG, Thompson C, Gilbert S. Transition from multiple port to single port video-assisted thoracoscopic anatomic pulmonary resection: early experience and comparison of perioperative outcomes [J]. *Ann Cardiothorac Surg*, 2016, 5(2): 92-99
- [8] White A, Kucukak S, Lee DN, et al. Energy-Based Ligation of Pulmonary Vessels: A Six-Year Experience With Ultrasonic Shears in Video-Assisted Thoracoscopic Lobectomy and Segmentectomy [J]. *Ann Thorac Surg*, 2016, 101(4): 1334-1337
- [9] Yang C, Mo L, Ma Y, et al. A comparative analysis of lung cancer patients treated with lobectomy via three-dimensional video-assisted thoracoscopic surgery versus two-dimensional resection [J]. *J Thorac Dis*, 2015, 7(10): 1798-1805
- [10] Maeda H, Kanzaki M, Sakamoto K, et al. Video-assisted thoracoscopic surgery after renal transplantation: A single-institution experience [J]. *Asian J Endosc Surg*, 2016, 9(1): 37-43
- [11] Iwata H, Shirahashi K, Yamamoto H, et al. Propensity score-matching analysis of hybrid video-assisted thoracoscopic surgery and thoracoscopic lobectomy for clinical stage I lung cancer [J]. *Eur J Cardiothorac Surg*, 2016, 49(4): 1063-1067
- [12] Ocakcioglu I, Sayir F, Dinc M. A 3-cm Single-port Video-assisted Thoracoscopic Lobectomy for Lung Cancer [J]. *Surg Laparosc Endosc Percutan Tech*, 2015, 25(4): 351-353
- [13] Acharya MN, Haqzad YS, Rao JN, et al. Uniportal thoracoscopic management of middle lobe torsion after upper lobectomy [J]. *Asian Cardiovasc Thorac Ann*, 2015, 23(9): 1129-1131
- [14] Xie HY, Xu K, Tang JX, et al. A prospective randomized, controlled trial deems a drainage of 300 ml/day safe before removal of the last chest drain after video-assisted thoracoscopic surgery lobectomy [J]. *Interact Cardiovasc Thorac Surg*, 2015, 21(2): 200-205
- [15] Fukui Y, Kohno T, Fujimori S, et al. Three-port thoracoscopic middle lobectomy in a patient after left pneumonectomy [J]. *Ann Thorac Surg*, 2015, 99(4): 1422-1425
- [16] Rothenberg SS, Middlesworth W, Kadanne-Chiwehe A, et al. Two decades of experience with thoracoscopic lobectomy in infants and children: standardizing techniques for advanced thoracoscopic surgery [J]. *J Laparoendosc Adv Surg Tech A*, 2015, 25(5): 423-428
- [17] Kara HV, Balderson SS, D'Amico TA. Modified uniportal video-assisted thoracoscopic lobectomy: Duke approach [J]. *Ann Thorac Surg*, 2014, 98(6): 2239-2241
- [18] Reichert M, Kerber S, Amati AL, et al. Total video-assisted thoracoscopic (VATS) resection of a left-sided sulcus superior tumor after induction radiochemotherapy: video and review [J]. *Surg Endosc*, 2015, 29(8): 2407-2409
- [19] Xu C, Ma H, Ni B, et al. Analysis of single-operation-hole thoracoscopic lobectomy in 113 clinical cases [J]. *Zhongguo Fei Ai Za Zhi*, 2014, 17(5): 424-427
- [20] Yang Y, Bao F, He Z, et al. Single-port video-assisted thoracoscopic right upper lobectomy using a flexible videoscope [J]. *Eur J Cardiothorac Surg*, 2014, 46(3): 496-497
- [21] Crisci R, Droghetti A, Migliore M, et al. Video-assisted thoracic lobectomy for lung cancer in Italy: the 'VATS Group' Project [J]. *Future Oncol*, 2016, 12(23s): 9-11
- [22] Wang T, Ma S, Yan T, et al. Clinical Study of Surgical Treatment of Non-small Cell Lung Cancer 10 mm or Less in Diameter Under Video-assisted Thoracoscopy [J]. *Zhongguo Fei Ai Za Zhi*, 2016, 19(4): 9-216

- [20] Van H L, Hamdani N, Falcao-Pires I, et al. Low myocardial protein kinase G activity in heart failure with preserved ejection fraction[J]. *Circulation*, 2012, 126(7): 830-839
- [21] Wang Y, Li Z C, Zhang P, et al. Nitric Oxide-cGMP-PKG Pathway Acts on Orail to Inhibit the Hypertrophy of Human Embryonic Stem Cell-Derived Cardiomyocytes [J]. *Stem Cells*, 2015, 33 (10): 2973-2984
- [22] Takimoto E, Koitabashi N, Hsu S, et al. Regulator of G protein signaling 2 mediates cardiac compensation to pressure overload and antihypertrophic effects of PDE5 inhibition in mice [J]. *J Clin Invest*, 2009, 119(2): 408-420
- [23] Koitabashi N, Aiba T, Hesketh G G, et al. Cyclic GMP/PKG-dependent inhibition of TRPC6 channel activity and expression negatively regulates cardiomyocyte NFAT activation novel mechanism of cardiac stress modulation by PDE5 inhibition[J]. *J Mol Cell Cardiol*, 2010, 48(4): 713-724
- [24] Lee D I, Zhu G, Sasaki T, et al. Phosphodiesterase 9A controls nitric-oxide-independent cGMP and hypertrophic heart disease [J]. *Nature*, 2015, 519(7544): 472-476
- [25] Al-Rasheed N M, Al-Oteibi M M, Al-Manee R Z, et al. Simvastatin prevents isoproterenol-induced cardiac hypertrophy through modulation of the JAK/STAT pathway [J]. *Drug Des Devel Ther*, 2015, 9: 3217-3229
- [26] Fu Z, Jiang L, Li D, et al. Effect of Shenfu injection on JAK-STAT signaling pathway in rats with chronic heart failure [J]. *Chinese Journal of Critical Care Medicine*, 2014
- [27] Feng H J, Ouyang W, Liu J H, et al. Global microRNA profiles and signaling pathways in the development of cardiac hypertrophy [J]. *Braz J Med Biol Res*, 2014, 47(5): 361-368
- [28] Karakikes I, Chaanine A H, Kang S, et al. Therapeutic cardiac-targeted delivery of miR-1 reverses pressure overload-induced cardiac hypertrophy and attenuates pathological remodeling [J]. *J Am Heart Assoc*, 2013, 2(2): e000078
- [29] Wei L, Yuan M, Zhou R, et al. MicroRNA-101 inhibits rat cardiac hypertrophy by targeting Rab1a [J]. *J Cardiovasc Pharmacol*, 2015, 65 (4): 357-363
- [30] Wang J, Liew O W, Richards A M, et al. Overview of MicroRNAs in Cardiac Hypertrophy, Fibrosis, and Apoptosis[J]. *Int J Mol Sci*, 2016, 17(5)
- [31] Janssen R, Zuidwijk M J, Kuster D W D, et al. Thyroid Hormone-Regulated Cardiac microRNAs are Predicted to Suppress Pathological Hypertrophic Signaling[J]. *Frontiers in Endocrinology*, 2014, 5: 171
- [32] Kim, Ty T, Dyck, et al. Is AMPK the savior of the failing heart ?[J]. *Trends Endocrinol Metab*, 2015, 26(1): 40-48
- [33] Traister A, Aafaqi S, Masse S, et al. ILK induces cardiomyogenesis in the human heart[J]. *Plos One*, 2012, 7(5): e37802
- [34] Gu R, Bai J, Ling L, et al. Increased expression of integrin-linked kinase improves cardiac function and decreases mortality in dilated cardiomyopathy model of rats[J]. *Plos One*, 2012, 7(2): e31279

(上接第 728 页)

- [23] Lee PC, Kamel M, Nasar A, et al. Lobectomy for Non-Small Cell Lung Cancer by Video-Assisted Thoracic Surgery: Effects of Cumulative Institutional Experience on Adequacy of Lymphadenectomy[J]. *Ann Thorac Surg*, 2016, 101(3): 22-1116
- [24] Liu C, Guo C, Lin F, et al. Long term outcomes of patients with stage I lung cancer treated by single-direction video-assisted thoracoscopic surgery lobectomy or segmentectomy [J]. *Zhonghua Wai Ke Za Zhi*, 2015, 53(10): 6-742
- [25] Ghaly G, Kamel M, Nasar A, et al. Video-Assisted Thoracoscopic Surgery Is a Safe and Effective Alternative to Thoracotomy for Anatomical Segmentectomy in Patients with Clinical Stage I Non-Small Cell Lung Cancer[J]. *Ann Thorac Surg*, 2016, 101(2): 72-465
- [26] Reichert M, Steiner D, Kerber S, et al. A standardized technique of systematic mediastinal lymph node dissection by video-assisted thoracoscopic surgery (VATS) leads to a high rate of nodal upstaging in early-stage non-small cell lung cancer [J]. *Surg Endosc*, 2016, 30 (3): 25-1119
- [27] Radkani P, Joshi D, Barot T, et al. Robotic video-assisted thoracoscopic lung resection for lung tumors: a community tertiary care center experience over four years [J]. *Surg Endosc*, 2016, 30(2): 24-619
- [28] Zhang L, Ren Y, Liu Y. Comparison of the Effects of Lobectomy on Immunologic Function Between Video-Assisted Thoracoscopic Surgery and Traditional Open Surgery for Non-Small-Cell Lung Cancer[J]. *Am J Ther*, 2016, 23(6): e1406-e1413
- [29] Murakawa T, Ichinose J, Hino H, et al. Long-term outcomes of open and video-assisted thoracoscopic lung lobectomy for the treatment of early stage non-small cell lung cancer are similar: a propensity-matched study[J]. *World J Surg*, 2015, 39(5): 91-1084
- [30] Yamashita S, Goto T, Mori T, et al. Video-assisted thoracic surgery for lung cancer: republication of a systematic review and a proposal by the guidelines committee of the Japanese Association for Chest Surgery 2014[J]. *Gen Thorac Cardiovasc Surg*, 2014, 62(12): 5-701