# 血清斯钙素-1在稳定期慢性阻塞性肺病中的表达及意义

何淑娟,许家艳,贾　嫚,欧英炜,周　军,姚　欣*

南京医科大学第一附属医院呼吸与危重症医学科,江苏　南京　210029

[摘　要]　**目的:**探讨斯钙素-1(stanniocalcin-1,STC1)在稳定期慢性阻塞性肺病(chronic obstructive pulmonary disease,COPD)患者血清中的表达及意义。**方法:**收集55例稳定期COPD患者,根据肺功能和问卷评分进行相应分组,且以24例健康者作为对照。采用酶联免疫吸附法(ELISA)测定各研究对象的血清斯钙素-1表达情况,进行相关分析。**结果:**①与健康对照组相比,稳定期COPD患者血清斯钙素-1表达水平明显降低($P<0.05$)。②血清斯钙素-1在初筛COPD上具有一定价值($P$=0.025,AUC=0.659),最佳阈值为1 350 pg/mL(敏感度81.82%;特异度50.00%)。③血清斯钙素-1与稳定期COPD患者病情严重程度[包括GOLD分级、慢阻肺评估测试(COPD assessment test,CAT)评分、ABCD分组、肺功能]无明显相关性。**结论:**血清斯钙素-1在COPD中显著降低,可能对于COPD的诊治具有一定临床意义。

[关键词]　慢性阻塞性肺病;斯钙素-1

[中图分类号]　R563　　[文献标志码]　A　　[文章编号]　1007-4368(2018)10-1404-05

**doi:**10.7655/NYDXBNS20181015

## Expression and role of serum stanniocalcin-1 in chronic obstructive pulmonary disease

He Shujuan,Xu Jiayan,Jia Man,Ou Yingwei,Zhou Jun,Yao Xin*

*Department of Respiratory and Critical Care Medicine,the First Affiliated Hospital of NMU,Nanjing 210029,China*

[**Abstract**]　**Objective:** To investigate the serum level of stanniocalcin-1 (STC1) in patients with stable chronic obstructive pulmonary diseases(COPD) and to explore the relationship between STC1 and severity of the disease. **Method:** A total of 55 patients with definite stable COPD and 24 healthy controls were enrolled in this study. Serum STC1 was measured by enzyme-linked immunosorbent assay (ELISA), and the correlation between STC1 and COPD was analyzed. **Results:** ① Serum STC1 levels were significantly lower in patients with COPD than healthy controls ($P<0.05$). ② The receiver-operating characteristic (ROC) curve of serum SCT1 was used for threshold identification (AUC=0.659, $P$=0.025), the optimal cut-off point of serum STC1 was 1 350 pg/mL (sensitivity 81.82%, specificity 50.00%, respectively). ③Poor association of serum STC1 levels with stable COPD was found, including the GOLD classification, COPD assessment test (CAT) scores and lung functions. **Conclusion:** Serum STC1 levels were significantly decreased in COPD patients while it is poorly correlated with disease severity. STC1 might have clinical application in stable COPD.

[**Key words**]　chronic obstructive pulmonary disease(COPD);stanniocalcin-1(STC1)

[Acta Univ Med Nanjing,2018,38(10):1404-1408]

慢性阻塞性肺疾病(简称慢阻肺,chronic obstructive pulmonary disease,COPD)是一种以持续气流受限为特点的慢性气道炎症性疾病[1]。慢阻肺气道炎症由多种细胞和细胞因子共同参与[2],其具体机制至今仍是研究方向。目前认为,氧化应激在慢阻肺的发生发展过程中有重要作用[3]。吸烟引起的氧化应激过程,尤其是活性氧(reactive oxygen species,ROS)的生成,能够引起肺脏的损伤,与慢阻肺的进展有明显关系[4]。

斯钙素-1(stanniocalcin-1,STC1)是一种重要的分泌型蛋白,能够调节钙磷代谢[5]。近期研究已证实,它与氧化应激、细胞凋亡、细胞自噬等有关[6-7]。外源加入STC1重组蛋白,可明显改善小鼠肺部以及眼部的氧化应激程度[8-9],提示STC1可能参与慢阻肺的发生发展。既往临床研究发现,肺腺癌患者的

[基金项目]　国家自然科学基金(81470237)

*通信作者(Corresponding author),E-mail:yaoxin@njmu.edu.cn

血清STC1水平与疾病进展有显著相关性[10],但STC1与慢阻肺的关系尚未见报道。因此我们通过检测STC1在血清中的表达水平,探讨其与慢阻肺的关系。

## 1 对象和方法

### 1.1 对象

本研究通过南京医科大学第一附属医院伦理委员会批准,收集2012—2016年间稳定期慢阻肺患者55例,所有患者诊断均符合《全球慢阻肺防治创议》慢阻肺诊断标准[1],且所有受试者均已排除恶性肿瘤、活动性肺结核、肺间质纤维化、肺部手术史、哮喘或伴有严重的心、脑、肝、肾、内分泌、神经系统疾病等。慢阻肺患者独立填写慢阻肺评估测试(COPD assessment test,CAT)量表评分,并根据肺功能结果和量表评分,将患者进行相应分组。收集同期健康查体的对照组24例,确认其无心肺肾等相关疾病。

### 1.2 方法

#### 1.2.1 患者分组

分组1:基于患者肺功能结果中舒张后的1 s用力呼气容积(forced expiratory volume in 1 second,$FEV_1$%)占预计值的百分比(FEV%pred)可将患者分为4级:GOLD(Global initiative for chronic obstructive lung disease)1,$FEV_1$% pred > 80%;GOLD2,50%≤$FEV_1$pred < 80%;GOLD3,30%≤$FEV_1$%pred < 50%;GOLD4,$FEV_1$%pred < 30%。

分组2:基于患者填写的CAT问卷评分分为4组:0~10分为轻微影响;11~20分为中等影响;21~30分为严重影响;31~40分为非常严重影响。

分组3:结合患者过去1年的急性加重病史与CAT评分,根据GOLD评估标准,将其分为4组:A:CAT<10分,且过去1年急性加重次数≤1次;B:CAT≥10分,且过去1年急性加重次数≤1次;C:CAT<10分,且过去1年急性加重次数>1次;D:CAT≥10分,且过去1年急性加重次数>1次。

#### 1.2.2 血清测定

所有患者均空腹抽取静脉血4 mL,静置后1 000 r/min离心10 min,收集血清,置于-40 ℃冰箱保存。通过酶联免疫吸附法(ELISA)测定患者血清中STC1表达水平。操作步骤均按照ELISA试剂盒使用说明书(SEC874Hu,优尔生公司,武汉)进行。

### 1.3 统计学方法

数据均采用SPSS 20.0软件进行分析,结果以均值±标准差($\bar{x} \pm s$)表示。两组间差异比较采用成组$t$检验,多组间进行比较时采用单因素方差分析,相关性分析采用Pearson相关分析。$P \leqslant 0.05$差别有统计学意义。

## 2 结 果

### 2.1 研究对象基本资料

55例稳定期慢阻肺患者和24例健康对照者的基本情况均列于表1中。慢阻肺患者的平均年龄(70.02 ± 1.14)岁,BMI为(22.17 ± 0.38)kg/m$^2$,吸烟指数为(664.7 ± 87.02)年·支;健康对照平均年龄为(65.34 ± 1.26)岁,BMI为(23.90 ± 0.56)kg/m$^2$,吸烟指数为(13.64 ± 9.36)年·支。两组研究对象在年龄、BMI、吸烟指数、肺功能(包括$FEV_1$、$FEV_1$%预计值、$FEV_1$/FVC)上都具有差异性。

**表1 研究对象基本资料**

**Table 1 Basic information of the research object**

| 临床特征 | 健康对照组 | 慢阻肺组 |
|---|---|---|
| 例数(男/女) | 24(5/19) | 55(47/8) |
| 年龄(岁) | 65.34 ±1.26 | 70.02 ± 1.14*** |
| BMI(kg/m$^2$) | 23.90 ± 0.56 | 22.17 ± 0.38* |
| 吸烟指数(年·支) | 13.64 ± 9.36 | 664.70 ± 87.02*** |
| $FEV_1$(L) | 2.55 ± 0.14 | 1.36 ± 0.06*** |
| $FEV_1$% | 91.79 ± 2.01 | 53.56 ± 2.43*** |
| $FEV_1$/FVC | 77.51 ± 1.91 | 58.94 ± 1.35*** |

两组比较,*$P$ < 0.05,***$P$ < 0.001。

### 2.2 血清STC1在慢阻肺患者和健康对照者中的表达水平

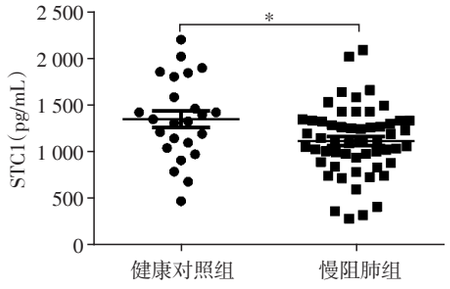
如图1所示,慢阻肺患者血清中STC1表达水平为(1 117 ± 49.81)pg/mL,健康对照组的血清STC1水平为(1 353 ± 89.24)pg/mL,两者进行对比分析发现,慢阻肺组的血清STC1水平显著低于健康对照组,差异有统计学意义($P$ < 0.05)。

### 2.3 慢阻肺患者血清STC1的ROC曲线

根据慢阻肺患者的血清STC1表达水平,绘制ROC曲线(图2)。ROC曲线结果显示,曲线下面积为0.659(95%CI:0.522~0.796;$P$=0.025),其最佳阈值为1 350 pg/mL,此时的敏感度为81.82%,特异度为50.00%。

### 2.4 慢阻肺不同分组下血清STC1的表达

根据不同分组要求,将慢阻肺患者不同分组情况下血清STC1表达水平与健康对照进行比较,并且进行组间两两比较。如图3A所示,GOLD分级下的血清STC1与健康对照组相比无明显差异,且GOLD分级各组间比较也无差异性。根据CAT分组后发现,与健康对照组相比,CAT评分各组患者STC1表




与健康对照组相比，*$P<0.05$。

**图1　血清斯钙素-1在慢阻肺患者和健康对照者中的表达水平**

**Figure 1　Expression level of serum STC1 in COPD patients and healthy controls**

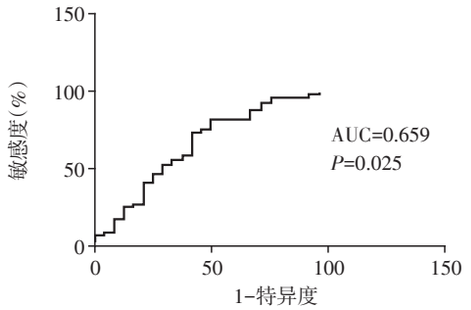



**图2　血清斯钙素-1的ROC曲线**

**Figure 2　The ROC curve of serum SCT1**

达未见明显差异，且CAT评分各组间比较亦未发现显著差异（图3B）。根据ABCD分组（图3C），D组的血清STC1水平与健康对照组相比明显降低，差异有统计学意义（$P<0.05$）。

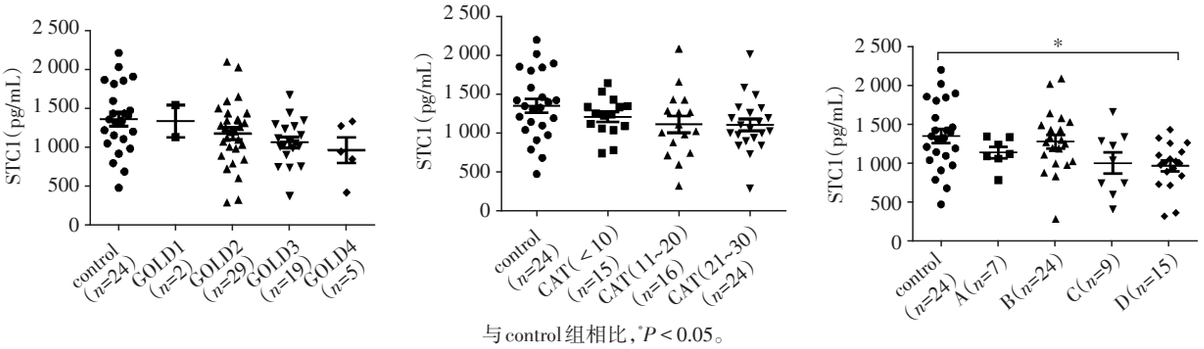
### 2.5　血清STC1与肺功能相关性

将血清STC1表达水平与慢阻肺患者$FEV_1$%和$FEV_1$/FVC进行比较，结果显示，慢阻肺患者血清中的STC1水平与其肺功能无明显相关性（图4）。

## 3　讨　论

慢阻肺的发病机制至今仍认为是复杂的[11]，这也造成了慢阻肺患者气道炎症的异质性。氧化应激过程在慢阻肺进程中发挥重大作用[12]。有研究表明，吸烟不但能将香烟中的多种氧化物引入肺部[13]，同时也可引起气道上皮细胞中的线粒体产生过多ROS[14]，从而导致肺损伤。对于慢阻肺中氧化应激产生的生物标志物研究一直是热点[15-16]。然而，至今仍无明确的标志物可以评估慢阻肺中的氧化应激。

本文中所研究的分泌型糖蛋白STC1，最开始发现于硬骨鱼肾脏中[5]，具有调控生物体内钙磷平衡的作用。近10年研究发现，STC1表达于多种组织，尤其是肿瘤组织。研究证实，STC1在多种肿瘤组织中




与control组相比，*$P<0.05$。

**图3　慢阻肺不同分组血清斯钙素-1的表达**

**Figure 3　Expression level of serum STC1 in different groups of COPD patients**

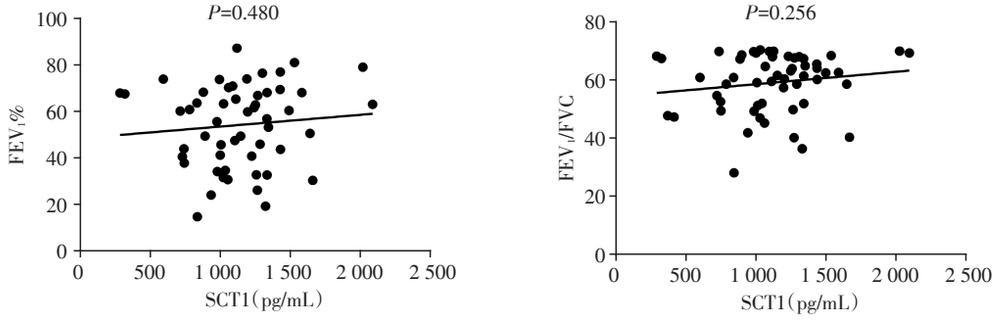



**图4　血清斯钙素-1与肺功能相关性**

**Figure 4　Correlation between serum STC1 and lung function**

表达升高,如乳腺癌[17]、结直肠癌[18]、卵巢癌[19]等。既往研究也发现,STC1在肺部也有所表达[20-21],如气道上皮细胞[14]。并且,STC1在氧化应激方面的作用也越来越得到重视。间充质干细胞(mesenchymal stromal cells,MSC)分泌的STC1可降低由ROS引起的肿瘤细胞凋亡[6-7],且STC1能改善博来霉素诱导的肺损伤中的氧化应激水平和气道炎症[8]。Tang等[22]发现,通过气道给予重组蛋白STC1,脂多糖诱导的小鼠气道炎症水平降低,氧化应激水平改善,细胞凋亡减少。Wang等[23]发现,STC1是通过诱导线粒体中的解偶连蛋白(uncoupling proteins,UCP2)活化来抑制氧化应激过程,具有解偶联蛋白依赖性。因此我们认为,在慢阻肺这种氧化应激参与其进程的疾病中,STC1可能发挥一定作用。

既往研究指出,STC1表达的调节机制包括:①在低氧环境中低氧诱导因子表达增加,从而导致STC1表达显著增高;②P53可促进STC1的表达,可能与STC1启动子上游存在P53结合元件有关;③曲古抑菌素(一种组蛋白乙酰化酶抑制剂)通过解除抑制性转录因子的抑制作用从而启动STC1的表达[24-25]。本研究发现,稳定期慢阻肺患者较健康对照组相比,STC1水平显著下降,差异有统计学意义。这可能与慢阻肺患者氧化应激程度较健康者明显有关。慢阻肺患者血清中STC1水平与肺功能无明显相关性,可能由于慢阻肺的异质性所致。尽管STC1与症状评估也无明显相关,但研究仍然发现,D组患者血清STC1水平较健康组明显下降,差别有统计学意义,这可能意味着,STC1在病情更加严重的慢阻肺患者中可能下降更为明显。

综上所述,STC1在慢阻肺的发生发展过程中可能发挥一定作用,通过检测其血清表达水平,可以作为一个辅助评估指标,具有一定临床意义。由于慢阻肺的异质性,本项目临床病例数目相对不多,进一步扩大样本量,获得相关亚组分析结果,将有助于进一步明确血清STC1水平在指导慢阻肺诊治中的作用。

**[参考文献]**

[1] Vogelmeier C, Criner G, Martinez F, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary[J]. Eur Respir J, 2017, 49(3): 1700214

[2] Barnes PJ, Burney PG, Silverman EK, et al. Chronic obstructive pulmonary disease[J]. Nat Rev Dis Primers, 2015, 1: 15076

[3] Kirkham PA, Barnes PJ. Oxidative stress in COPD[J]. Chest, 2013, 144(1): 266-273

[4] Barreiro E, Peinado V, Galdiz J, et al. Cigarette smoke-induced oxidative stress: A role in chronic obstructive pulmonary disease skeletal muscle dysfunction[J]. Am J Respir Crit Care Med, 2010, 182(4): 477-488

[5] Wagner G, Hampong M, Park C, et al. Purification, characterization, and bioassay of teleocalcin, a glycoprotein from salmon corpuscles of stannius[J]. Gen Comp Endocrinol, 1986, 63(3): 481-491

[6] Block G, Ohkouchi S, Fung F, et al. Multipotent stromal cells are activated to reduce apoptosis in part by upregulation and secretion of stanniocalcin-1[J]. Stem Cells, 2009, 27(3): 670-681

[7] Ohkouchi S, Block GJ, Katsha AM, et al. Mesenchymal stromal cells protect cancer cells from ROS-induced apoptosis and enhance the Warburg effect by secreting STC1[J]. Mol Ther, 2012, 20(2): 417-423

[8] Huang L, Zhang L, Ju H, et al. Stanniocalcin-1 inhibits thrombin-induced signaling and protects from bleomycin-induced lung injury[J]. Sci Rep, 2015, 5: 18117

[9] Kim SJ, Ko JH, Yun JH, et al. Stanniocalcin-1 protects retinal ganglion cells by inhibiting apoptosis and oxidative damage[J]. PLoS One, 2013, 8(5): e63749

[10] Du Y, Gu X, Cheng S, et al. The oncogenetic role of stanniocalcin 1 in lung adenocarcinoma: a promising serum candidate biomarker for tracking lung adenocarcinoma progression[J]. Tumour Biol, 2016, 37(4): 5633-5644

[11] Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease[J]. J Allergy Clin Immunol, 2016, 138(1): 16-27

[12] Loukides S, Bakakos P, Kostikas K. Oxidative stress in patients with COPD[J]. Curr Drug Targets, 2011, 12(4): 469-477

[13] Pryor WA, Dooley MM, Church DF. Mechanisms of cigarette smoke toxicity: the inactivation of human alpha-1-proteinase inhibitor by nitric oxide/isoprene mixtures in air[J]. Chem Biol Interact, 1985, 54(2): 171-183

[14] van der Toorn M, Rezayat D, Kauffman H, et al. Lipid-soluble components in cigarette smoke induce mitochondrial production of reactive oxygen species in lung epithelial cells[J]. Am J Physiol Lung Cell Mol Physiol, 2009, 297(1): L109-114

[15] Montuschi P, Collins JV, Ciabattoni G, et al. Exhaled 8-isoprostane as an in vivo biomarker of lung oxidative stress in patients with COPD and healthy smokers[J]. Am J Respir Crit Care Med, 2000, 162(3 Pt 1): 1175-1177

[16] Kostikas K, Papatheodorou G, Psathakis K, et al. Oxida-

tive stress in expired breath condensate of patients with COPD[J]. Chest,2003,124(4):1373-1380
[17] Chang A,Doherty J,Huschtscha L,et al. STC1 expression is associated with tumor growth and metastasis in breast cancer[J]. Clin Exp Metastasis,2015,32(1):15-27
[18] Peña C,Céspedes M,Lindh M,et al. STC1 expression by cancer-associated fibroblasts drives metastasis of colorectal cancer[J]. Cancer Res,2013,73(4):1287-1297
[19] Liu G,Yang G,Chang B,et al. Stanniocalcin 1 and ovarian tumorigenesis[J].J Natl Cancer Inst,2010,102(11):812-827
[20] Chang A,Janosi J,Hulsbeek M,et al. A novel human cDNA highly homologous to the fish hormone stanniocalcin [J]. Mol Cell Endocrinol,1995,112(2):241-247
[21] Varghese R,Wong C,Deol H,et al. Comparative analysis of mammalian stanniocalcin genes [J]. Endocrinology,1998,139(11):4714-4725
[22] Tang S,Wu C,Wu S,et al. Stanniocalcin-1 ameliorates lipopolysaccharide-induced pulmonary oxidative stress,inflammation,and apoptosis in mice[J]. Free Radic Biol Med,2014,71:321-331
[23] Wang Y,Huang L,Abdelrahim M,et al. Stanniocalcin-1 suppresses superoxide generation in macrophages through induction of mitochondrial UCP2[J].J Leukoc Biol,2009,86(4):981-988
[24] Ito Y,Zemans R,Correll K,et al. Stanniocalcin is induced by hypoxia inducible factor in rat alveolar epithelialcells [J]. Biochem Biophys Res Commun,2014,452:1091-1097
[25] Law AYS,Yeung BHY,Ching LY,et al. Spl is a transcription repressor to stanniocalcin-l expression in TSA-treated human colon cancer cells,HT29 [J]. J Cell Biochem,2011,112:2089-2096

[收稿日期] 2018-08-20

(上接第1360页)

而,介于ICI182780是非特异性雌激素受体拮抗剂,因此本实验不能区分E2是通过雌激素受体α亚型还是β亚型发挥抑制该信号通路的作用,需要进一步研究证实。

[参考文献]

[1] Shimizu I,Minamino T. Physiological and pathological cardiac hypertrophy[J]. J Mol Cell Cardiol,2016,97:245-262
[2] Jacot JG,Martin JC,Hunt DL. Mechanobiology of cardiomyocyte development[J]. J Biomech,2010,43(1):93-98
[3] Matter ML. Induction of VEGF secretion in cardiomyocytes by mechanical stretch[J]. Methods Mol Biol,2015,1332:67-74
[4] Israeli-Rosenberg S,Manso AM,Okada H,et al. Integrins and integrin-associated proteins in the cardiac myocyte [J]. Circ Res,2014,114(3):572-586
[5] Pentassuglia L,Sawyer DB. ErbB/integrin signaling interactions in regulation of myocardial cell-cell and cell-matrix interactions[J]. Biochim Biophys Acta,2013,1833(4):909-916
[6] 刁爱芹,阙玲俐,任丹阳,等. 17β-雌二醇对体外机械牵张诱导心肌细胞肥大的影响[J]. 南京医科大学学报(自然科学版),2011,31(7):976-980
[7] Chen-Izu Y,Izu LT. Mechano-chemo-transduction in cardiac myocytes[J]. J Physiol,2017,595(12):3949-3958
[8] Tan PM,Buchholz KS,Omens JH,et al. Predictive model identifies key network regulators of cardiomyocyte mechano-signaling [J]. PLoS Comput Biol,2017,13(11):e1005854
[9] Shradhanjali A,Riehl BD,Lee JS,et al. Enhanced cardiomyogenic induction of mouse pluripotent cells by cyclic mechanical stretch[J]. Biochem Biophys Res Commun,2017,488(4):590-595
[10] Hooper CL,Dash PR,Boateng SY. Lipoma preferred partner is a mechanosensitive protein regulated by nitric oxide in the heart[J]. FEBS Open Bio,2012,2:135-144
[11] Dhein S,Schreiber A,Steinbach S,et al. Mechanical control of cell biology. Effects of cyclic mechanical stretch on cardiomyocyte cellular organization[J]. Prog Biophys Mol Biol,2014,115(2-3):93-102
[12] Sun H,Tang J,Mou Y,et al. Carbon nanotube-composite hydrogels promote intercalated disc assembly in engineered cardiac tissues through β1-integrin mediated FAK and RhoA pathway[J]. Acta Biomater,2017,48:88-99
[13] Lal H,Verma SK,Smith M,et al. Stretch-induced MAP kinase activation in cardiac myocytes:differential regulation through beta1-integrin and focal adhesion kinase[J]. J Mol Cell Cardiol,2007,43(2):137-147
[14] 张潇伊,邹云增. 整合素在心肌肥大中的作用[J]. 临床心血管病杂志,2016,32(11):1164-1168
[15] Ross RS,Pham C,Shai SY,et al. Beta1 integrins participate in the hypertrophic response of rat ventricular myocytes[J]. Circ Res,1998,82(11):1160-1172

[收稿日期] 2018-03-20