DOI:10.16781/j.0258-879x.2021.09.0988

·论　著·

# 抗血小板药物替格瑞洛临床相关呼吸困难的危险因素分析

曾倩倩，徐琛华，严健华，焦昆立，蔺艳军，徐全福*，孟　舒*
上海交通大学医学院附属新华医院心血管内科，上海 200092

［摘要］ **目的**　探讨经皮冠状动脉介入（PCI）治疗的急性冠状动脉综合征（ACS）患者服用抗血小板药物替格瑞洛后出现呼吸困难的危险因素。**方法**　采用回顾性研究和前瞻性研究相结合的方法。回顾性纳入2016年1月至2019年11月上海交通大学附属新华医院心血管内科收治的418例接受PCI治疗后服用替格瑞洛的ACS患者，根据呼吸困难发生情况将患者分为替格瑞洛相关呼吸困难组和未发生呼吸困难组，收集并比较两组患者的临床及实验室检查资料。在前瞻性研究中选择2020年1月至8月上海交通大学附属新华医院心血管内科收治的PCI术后服用替格瑞洛的ACS患者367例，根据回顾性研究结果并参照临床指南将患者分为低密度脂蛋白胆固醇（LDL-C）组（LDL-C＜2.6 mmol/L）和高LDL-C组（LDL-C≥2.6 mmol/L），比较两组患者资料，并采用多因素logistic回归分析替格瑞洛相关呼吸困难的危险因素。**结果**　回顾性研究的418例ACS患者中71例（17.0%）发生替格瑞洛相关呼吸困难。与未发生呼吸困难组相比，替格瑞洛相关呼吸困难组的出血事件更多［23.9%（17/71）vs 10.1%（35/347），$P$=0.001］、LDL-C水平更高［（2.54±0.88）mmol/L vs（2.32±0.81）mmol/L，$P$=0.045］。多因素logistic回归分析结果显示出血事件（$OR$=3.128，95% $CI$ 1.613～6.065，$P$=0.001）、LDL-C升高（$OR$=1.451，95% $CI$ 1.071～1.964，$P$=0.016）是PCI术后ACS患者发生替格瑞洛相关呼吸困难的危险因素。前瞻性研究的367例ACS患者中64例（17.4%）发生替格瑞洛相关呼吸困难。高LDL-C组患者替格瑞洛相关呼吸困难的发生率高于低LDL-C组［23.4%（33/141）vs 13.7%（31/226），$P$=0.018］，同时两组在吸烟史、PCI史、心肌梗死史、超敏CRP、空腹血糖、总胆固醇、总甘油三酯、高密度脂蛋白胆固醇、左心室射血分数、植入支架数目方面的差异均有统计学意义（$P$均＜0.05）。经多因素logistic回归分析发现吸烟史是PCI术后ACS患者发生替格瑞洛相关呼吸困难的独立预测因素（$OR$=2.695，95% $CI$ 1.236～5.878，$P$=0.013）。**结论**　PCI术后服用替格瑞洛的ACS患者呼吸困难的发生率为17.4%（64/367），血清LDL-C≥2.6 mmol/L的PCI术后ACS患者服用替格瑞洛后呼吸困难发生率更高，吸烟史是替格瑞洛相关呼吸困难的独立预测因素。

［关键词］ 替格瑞洛；呼吸困难；急性冠状动脉综合征；低密度脂蛋白胆固醇；危险因素
［中图分类号］ R 972.7　　［文献标志码］ A　　［文章编号］ 0258-879X(2021)09-0988-09

## Analysis of risk factors for clinical dyspnea related to antiplatelet drug ticagrelor

ZENG Qian-qian, XU Chen-hua, YAN Jian-hua, JIAO Kun-li, LIN Yan-jun, XU Quan-fu*, MENG Shu*
Department of Cardiovasology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

［**Abstract**］ **Objective**　To investigate the risk factors of dyspnea in acute coronary syndrome (ACS) patients taking antiplatelet drug ticagrelor after percutaneous coronary intervention (PCI). **Methods**　A combination of retrospective and prospective studies was used. A total of 418 ACS patients taking ticagrelor after PCI in the Department of Cardiovasology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from Jan. 2016 to Nov. 2019 were retrospectively included. According to the incidence of dyspnea, the patients were divided into ticagrelor-related dyspnea group and non-dyspnea group. The clinical and laboratory data were collected and compared. In the prospective study, 367 ACS patients taking ticagrelor after PCI in the Department of Cardiovasology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from Jan. to Aug. 2020 were selected. Based on the results of retrospective study and guidelines, the patients were divided into low low-density lipoprotein-cholesterol (LDL-C) group (LDL-C＜2.6 mmol/L) and

［收稿日期］ 2021-01-05　　［接受日期］ 2021-03-31
［基金项目］ 上海市卫生健康委员会科研课题［ZT（2018-2020）-FWTX-3027］，上海交通大学医学院科研课题（TM201811）. Supported by Scientific Research Project of Shanghai Municipal Health Commission (ZT［2018-2020］-FWTX-3027) and Scientific Research Project of Shanghai Jiao Tong University School of Medicine (TM201811).
［作者简介］ 曾倩倩，主治医师. E-mail: drzengqianqian@163.com
* 通信作者（Corresponding authors）. Tel: 021-25077275, E-mail: xqf710@163.com; Tel: 021-25077307, E-mail: msdoctor@126.com

high LDL-C group (LDL-C≥2.6 mmol/L), The clinical data were compared, and the risk factors of ticagrelor-related dyspnea were further analyzed using multiple logistic regression. **Results** Of the 418 ACS patients in the retrospective study, 71 (17.0%) had ticagrelor-related dyspnea. The ticagrelor-related dyspnea group had more bleeding events (23.9% ［17/71］ vs 10.1% ［35/347］, $P$=0.001) and higher LDL-C level (［2.54±0.88］ mmol/L vs ［2.32±0.81］ mmol/L, $P$=0.045) compared with the non-dyspnea group. Multiple logistic regression analysis showed that bleeding events (odds ratio ［$OR$］= 3.128, 95% confidence interval ［$CI$］1.613-6.065, $P$=0.001) and elevated LDL-C ($OR$=1.451, 95% $CI$ 1.071-1.964, $P$= 0.016) were the risk factors of ticagrelor-related dyspnea. Of the 367 ACS patients in the prospective study, 64 (17.4%) had ticagrelor-related dyspnea. The incidence of ticagrelor-related dyspnea was higher in the high LDL-C group than that in the low LDL-C group (23.4% ［33/141］ vs 13.7% ［31/226］, $P$=0.018). At the same time, there were significant differences in the history of smoking, PCI and myocardial infarction, the levels of hypersensitive C reactive protein, fasting blood glucose, total cholesterol, total triglyceride, high-density lipoprotein-cholesterol, left ventricular ejection fraction, and the number of stent implantation between the 2 groups (all $P$<0.05). Multiple logistic regression analysis showed that smoking history was an independent predictor of ticagrelor-related dyspnea ($OR$=2.695, 95% $CI$ 1.236-5.878, $P$=0.013). **Conclusion** The incidence of dyspnea in ACS patients taking ticagrelor after PCI is 17.4% (64/367). The ACS patients after PCI with serum LDL-C≥ 2.6 mmol/L are prone to ticagrelor-related dyspnea. Smoking history is an independent predictor of ticagrelor-related dyspnea.

［**Key words**］ ticagrelor; dyspnea; acute coronary syndrome; low-density lipoprotein-cholesterol; risk factors

［Acad J Sec Mil Med Univ, 2021, 42(9): 988-996］

$P2Y_{12}$ 受体拮抗剂联合阿司匹林的双联抗血小板治疗是急性冠状动脉综合征（acute coronary syndrome, ACS）患者经皮冠状动脉介入（percutaneous coronary intervention，PCI）术后的基础药物治疗方案[1]，是有效降低 PCI 术后血栓事件的重要措施[2-5]。新型的第三代 $P2Y_{12}$ 受体拮抗剂替格瑞洛为非前体药物，无须肝酶激活，原药（活性代谢物）即可直接起效，其与 $P2Y_{12}$ 受体可逆性结合，停药后血小板功能恢复较快，并且其抗血小板作用不受具有多态性的药物转运体和代谢酶基因型影响[6-9]。因此，替格瑞洛抗血小板作用起效迅速、强效、个体效应差异性小。国内外指南均推荐替格瑞洛作为 ACS 首选抗血小板治疗药物[1-2,10-11]。研究发现呼吸困难是替格瑞洛的常见不良反应，替格瑞洛相关呼吸困难的发生率达 10% 以上[2,12-14]，远高于氯吡格雷及其他抗血小板药物所致呼吸困难的发生率[15-16]。目前替格瑞洛相关呼吸困难的临床危险因素尚不清楚。本研究采用回顾性和前瞻性 2 种方法，对 ACS 患者接受 PCI 治疗并服用替格瑞洛后呼吸困难的发生率及危险因素进行分析，以利于精准个体化治疗方案的制订。

## 1 资料和方法

1.1 *研究对象* 回顾性纳入 2016 年 1 月至 2019 年 11 月上海交通大学附属新华医院心血管内科收治的 PCI 术后服用替格瑞洛抗血小板治疗的 ACS 患者 418 例，前瞻性选择 2020 年 1 月至 8 月上海交通大学附属新华医院心血管内科收治的 PCI 术后服用替格瑞洛抗血小板治疗的 ACS 患者 367 例。

回顾性研究纳入标准：接受 PCI 治疗并服用替格瑞洛（180 mg 负荷剂量或 90 mg 每天 2 次维持剂量）抗血小板治疗的 ACS 患者。回顾性研究排除标准：（1）年龄≤18 岁或≥85 岁；（2）对替格瑞洛过敏或不能耐受；（3）存在呼吸系统疾病，如慢性阻塞性肺疾病、支气管哮喘、肺栓塞、急性呼吸窘迫综合征；（4）心功能不全［左心室射血分数（left ventricular ejection fraction，LVEF）＜40% 或 NYHA 心功能分级 Ⅲ 级及以上］、心动过缓（心率＜60 $min^{-1}$）、病态窦房结综合征、房室传导阻滞；（5）严重肝肾功能异常［丙氨酸转氨酶或天冬氨酸转氨酶检测值大于正常值上限 2 倍，估算的肾小球滤过率（estimated glomerular filtration rate，eGFR）＜30 mL/（min • 1.73 $m^2$）］；（6）活动性消化性溃疡或胃肠道出血；（7）近 6 个月内有出血性脑卒中史；（8）患有虽经积极治疗但仍无法控制的高血压和糖尿病；（9）依从性差，未按照研究方案的规定剂量或疗程用药者。前瞻性研究与回顾性研究的纳入、排除标准相同。本研究通过上海交通大学附属新华医院伦理委员会审批（XHEC-D-2020-184），患者个人信息均为匿名。

1.2 *研究方法* 所有入组 ACS 患者均在接受 PCI 治疗前后服用替格瑞洛进行抗血小板治疗。对患

者的医疗记录进行系统性回顾，了解患者人口统计学特征、生化指标、药物使用情况等。信息收集采用标准化记录格式，项目如下：性别、年龄、BMI、吸烟史、高血压、糖尿病、心肌梗死史；血常规包括血红蛋白、红细胞分布宽度、血小板分布宽度；超敏C反应蛋白（hypersensitive C reactive protein，hs-CRP）；血生化指标包括空腹血糖、总胆固醇（total cholesterol，TC）、总甘油三酯（total triglyceride，TG）、高密度脂蛋白胆固醇（high-density lipoprotein-cholesterol，HDL-C）、低密度脂蛋白胆固醇（low-density lipoprotein-cholesterol，LDL-C）、血尿素氮、血肌酐、eGFR；脑钠肽前体；LVEF；服用药物、急诊PCI、既往PCI史、冠状动脉旁路移植术史等。

在回顾性研究中，根据呼吸困难发生情况将患者分为替格瑞洛相关呼吸困难组和未发生呼吸困难组，比较两组患者的临床及实验室检查资料，并进行电话随访或门诊随访，记录呼吸困难发生情况。出血事件是指符合心肌梗死溶栓（thrombolysis in myocardial infarction，TIMI）出血分级标准[17]的任何出血事件，即满足如下条件中的任意1条：（1）主要出血，颅内出血或临床可见出血，伴血红蛋白浓度下降≥0.5 g/L；（2）小出血，临床可见出血（包括影像学诊断），伴血红蛋白浓度下降0.3～＜0.5 g/L；（3）轻微出血，临床可见出血（包括影像学诊断），血红蛋白浓度下降＜0.3 g/L。替格瑞洛相关呼吸困难指在服用替格瑞洛治疗后出现的呼吸困难或出现与先前症状、频率及严重程度均不同的呼吸困难，且患者的呼吸困难症状在3 d内未能自发改善，虽给予适当安慰和咨询，患者对呼吸困难仍不能耐受，停药或换药后呼吸困难症状改善。呼吸困难的临床诊断由2名副主任以上职称医师共同确认，意见不一致时再次讨论至判断一致后录入数据库。

在前瞻性研究中，参照回顾性研究中ROC曲线分析结果并结合临床指南[11]，根据血清LDL-C水平将患者分为低LDL-C组（LDL-C＜2.6 mmol/L）和高LDL-C组（LDL-C≥2.6 mmol/L），比较两组患者替格瑞洛相关呼吸困难的发生情况及基线资料，并分析LDL-C水平与替格瑞洛相关呼吸困难之间的关系。

1.3　统计学处理　应用SPSS 24.0软件进行统计学分析。呈正态分布的计量资料以$\bar{x}\pm s$表示，两组间比较采用独立样本$t$检验；呈偏态分布的计量资料以中位数（下四分位数，上四分位数）表示，两组间比较采用Mann-Whitney $U$检验；计数资料以例数和百分数表示，两组间比较采用$\chi^2$检验或Fisher确切概率法。采用多因素logistic回归分析替格瑞洛相关呼吸困难发生的独立危险因素。绘制ROC曲线，分析血清LDL-C水平对替格瑞洛相关呼吸困难的诊断效能。检验水准（$\alpha$）为0.05。

## 2　结　果

### 2.1　回顾性研究结果

2.1.1　替格瑞洛相关呼吸困难组和未发生呼吸困难组ACS患者基线资料比较　418例PCI术后服用替格瑞洛的ACS患者中71例[17.0%（71/418）]发生替格瑞洛相关呼吸困难。替格瑞洛相关呼吸困难组出血事件发生率为23.9%（17/71），未发生呼吸困难组出血事件发生率为10.1%（35/347），两组比较差异有统计学意义（$P$=0.001）。替格瑞洛相关呼吸困难组的血清LDL-C水平高于未发生呼吸困难组，差异有统计学意义[（2.54±0.88）mmol/L vs（2.32±0.81）mmol/L，$P$=0.045]。其他基线资料在两组间的差异均无统计学意义（$P$均＞0.05）。见表1。

2.1.2　替格瑞洛相关呼吸困难影响因素的多因素logistic回归分析结果　将单因素分析中差异有统计学意义的变量纳入多因素logistic回归，分析结果显示出血事件（$OR$=3.128，95% $CI$ 1.613～6.065，$P$=0.001）、血清LDL-C升高（$OR$=1.451，95% $CI$ 1.071～1.964，$P$=0.016）是血清PCI术后ACS患者发生替格瑞洛相关呼吸困难的危险因素。绘制血清LDL-C判断替格瑞洛相关呼吸困难的ROC曲线，以灵敏度＋特异度－1为最大值时所对应的数值作为最佳诊断界值，结果显示血清LDL-C的诊断界值为2.535 mmol/L。

### 2.2　前瞻性研究结果

2.2.1　低LDL-C组与高LDL-C组ACS患者基线资料比较　367例PCI术后服用替格瑞洛的ACS患者中64例（17.4%）发生替格瑞洛相关呼吸困难。226例低LDL-C患者中31例（13.7%）发生替格瑞洛相关呼吸困难，141例高LDL-C患者中33例（23.4%）发生替格瑞洛相关呼吸困难，高LDL-C组替格瑞洛相关呼吸困难的发生率高于低LDL-C组，差异有统计学意义（$P$=0.018）。两组在吸烟

史、急性心肌梗死、陈旧性心肌梗死、hs-CRP、空腹血糖、TC、TG、HDL-C、LVEF、植入支架数目、急诊 PCI、既往 PCI 史的差异均有统计学意义（$P$ 均＜0.05）。两组的性别、年龄、BMI 及其他基线资料比较差异均无统计学意义（$P$ 均＞0.05）。见表 2。

**表 1　替格瑞洛相关呼吸困难组和未发生呼吸困难组 ACS 患者的基线资料比较**

**Tab 1　Comparison of baseline data of ACS patients in ticagrelor-related dyspnea group and non-dyspnea group**

| Index | Non-dyspnea $N$=347 | Dyspnea $N$=71 | Statistic | $P$ value |
|---|---|---|---|---|
| Demographic data | | | | |
| Male, $n$ (%) | 260 (74.9) | 56 (78.9) | $\chi^2$=0.497 | 0.481 |
| Age/year, $\bar{x}\pm s$ | 63.62±7.89 | 64.31±7.44 | $t$=−2.038 | 0.558 |
| BMI/(kg•m$^{-2}$), $\bar{x}\pm s$ | 24.73±3.02 | 24.53±2.78 | $t$=0.494 | 0.644 |
| Smoking, $n$ (%) | 154 (44.4) | 36 (50.7) | $\chi^2$=0.951 | 0.330 |
| Medical history, $n$ (%) | | | | |
| Hypertension | 229 (66.0) | 50 (70.4) | $\chi^2$=0.521 | 0.471 |
| Diabetes | 100 (28.8) | 16 (22.5) | $\chi^2$=1.161 | 0.282 |
| Acute myocardial infarction | 122 (35.2) | 32 (45.1) | $\chi^2$=2.489 | 0.115 |
| Prior myocardial infarction | 45 (13.0) | 8 (11.3) | $\chi^2$=0.154 | 0.695 |
| Laboratory examination | | | | |
| HGB/(g•L$^{-1}$), $\bar{x}\pm s$ | 138.19±13.47 | 139.00±15.63 | $t$=−0.450 | 0.495 |
| RDW/%, $M$ ($Q_L$, $Q_U$) | 13.10 (12.70, 13.60) | 13.20 (12.70, 13.90) | $Z$=−0.453 | 0.651 |
| PDW/%, $\bar{x}\pm s$ | 15.85±1.87 | 15.88±1.67 | $t$=−0.122 | 0.896 |
| hs-CRP/(mg•L$^{-1}$), $M$ ($Q_L$, $Q_U$) | 1.50 (0.55, 4.62) | 2.18 (0.76, 4.67) | $Z$=−1.172 | 0.241 |
| FBG/(mmol•L$^{-1}$), $\bar{x}\pm s$ | 6.23±2.00 | 5.35±1.91 | $t$=−0.448 | 0.196 |
| TC/(mmol•L$^{-1}$), $\bar{x}\pm s$ | 4.15±1.12 | 4.25±1.03 | $t$=−0.710 | 0.296 |
| TG/(mmol•L$^{-1}$), $M$ ($Q_L$, $Q_U$) | 1.44 (1.05, 2.09) | 1.51 (1.15, 2.25) | $Z$=−0.982 | 0.326 |
| HDL-C/(mmol•L$^{-1}$), $M$ ($Q_L$, $Q_U$) | 1.11 (0.96, 1.30) | 1.15 (0.99, 1.27) | $Z$=−0.356 | 0.722 |
| LDL-C/(mmol•L$^{-1}$), $\bar{x}\pm s$ | 2.32±0.81 | 2.54±0.88 | $t$=−2.038 | 0.045 |
| BUN/(mmol•L$^{-1}$), $\bar{x}\pm s$ | 5.36±1.67 | 5.49±1.95 | $t$=−0.495 | 0.946 |
| SCr/(μmol•L$^{-1}$), $\bar{x}\pm s$ | 74.56±24.60 | 74.57±22.42 | $t$=−0.001 | 0.663 |
| eGFR/(mL•min$^{-1}$•[1.73 m$^2$]$^{-1}$), $\bar{x}\pm s$ | 92.75±23.41 | 94.20±27.58 | $t$=−0.460 | 0.687 |
| proBNP/(pg•mL$^{-1}$), $M$ ($Q_L$, $Q_U$) | 117.15 (48.15, 398.23) | 179.10 (64.46, 538.20) | $Z$=−0.923 | 0.058 |
| LVEF/%, $\bar{x}\pm s$ | 63.12±5.97 | 61.88±6.68 | $t$=1.567 | 0.165 |
| Medication, $n$ (%) | | | | |
| ACEI/ARB | 192 (55.3) | 39 (54.9) | $\chi^2$=0.004 | 0.951 |
| β-blockade | 303 (87.3) | 58 (81.7) | $\chi^2$=1.586 | 0.208 |
| Statin | 327 (94.2) | 67 (94.4) | $\chi^2$=0.002 | 0.966 |
| CCB | 96 (27.7) | 16 (22.5) | $\chi^2$=0.791 | 0.374 |
| Metformin | 51 (14.7) | 9 (12.7) | $\chi^2$=0.196 | 0.658 |
| Other hypoglycemic agents or RI | 110 (31.7) | 16 (22.5) | $\chi^2$=2.351 | 0.126 |
| Coronary lesion and surgical condition | | | | |
| Single vessel lesion, $n$ (%) | 175 (50.4) | 31 (43.7) | $\chi^2$=1.081 | 0.299 |
| Multi-vessel lesion, $n$ (%) | 172 (49.6) | 40 (56.3) | $\chi^2$=1.081 | 0.299 |
| Stent number, $\bar{x}\pm s$ | 1.34±0.75 | 1.42±0.77 | $t$=−0.809 | 0.395 |
| Urgent PCI, $n$ (%) | 54 (15.6) | 15 (21.1) | $\chi^2$=1.324 | 0.250 |
| Prior PCI, $n$ (%) | 98 (28.2) | 27 (38.0) | $\chi^2$=2.693 | 0.101 |
| Prior CABG, $n$ (%) | 1 (0.3) | 0 | $\chi^2$=0.205 | 0.651 |
| Adverse reaction | | | | |
| Bleeding event, $n$ (%) | 35 (10.1) | 17 (23.9) | $\chi^2$=10.390 | 0.001 |

ACS: Acute coronary syndrome; BMI: Body mass index; HGB: Hemoglobin; RDW: Red blood cell distribution width; PDW: Platelet distribution width; hs-CRP: Hypersensitive C reactive protein; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Total triglyceride; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; BUN: Blood urea nitrogen; SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate; proBNP: Pro-brain natriuretic peptide; LVEF: Left ventricular ejection fraction; ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin Ⅱ receptor blocker; CCB: Calcium channel blocker; RI: Regular insulin; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; $M$ ($Q_L$, $Q_U$): Median (lower quartile, upper quartile).

**表 2　低 LDL-C 组和高 LDL-C 组 ACS 患者的基线资料比较**

**Tab 2　Comparison of baseline data of ACS patients in low and high LDL-C groups**

| Index | Low LDL-C $N$=226 | High LDL-C $N$=141 | Statistic | $P$ value |
|---|---|---|---|---|
| Demographic data | | | | |
| Male, $n$ (%) | 179 (79.2) | 111 (78.7) | $\chi^2$=0.012 | 0.913 |
| Age/year, $\bar{x}\pm s$ | 63.21±8.14 | 61.95±9.43 | $t$=1.354 | 0.243 |
| BMI/(kg•m$^{-2}$), $\bar{x}\pm s$ | 24.64±2.97 | 24.91±3.08 | $t$=−0.832 | 0.326 |
| Smoking, $n$ (%) | 65 (28.8) | 61 (43.3) | $\chi^2$=8.099 | 0.004 |
| Medical history, $n$ (%) | | | | |
| Hypertension | 146 (64.6) | 85 (60.3) | $\chi^2$=0.694 | 0.405 |
| Diabetes | 65 (28.8) | 38 (27.0) | $\chi^2$=0.141 | 0.708 |
| Acute myocardial infarction | 35 (15.5) | 62 (44.0) | $\chi^2$=36.232 | 0.001 |
| Prior myocardial infarction | 54 (23.9) | 16 (11.3) | $\chi^2$=8.855 | 0.003 |
| Laboratory examination | | | | |
| HGB/(g•L$^{-1}$), $\bar{x}\pm s$ | 138.89±15.39 | 141.06±12.08 | $t$=−1.423 | 0.322 |
| RDW/%, $\bar{x}\pm s$ | 12.78±0.67 | 12.81±0.74 | $t$=−0.431 | 0.739 |
| PDW/%, $\bar{x}\pm s$ | 15.41±1.90 | 15.28±2.02 | $t$=0.614 | 0.906 |
| hs-CRP/(mg•L$^{-1}$), $M$ ($Q_L$, $Q_U$) | 1.31 (0.47, 3.02) | 2.81 (1.20, 6.41) | $Z$=−3.611 | 0.001 |
| FBG/(mmol•L$^{-1}$), $\bar{x}\pm s$ | 6.01±1.97 | 6.44±2.32 | $t$=−1.899 | 0.026 |
| TC/(mmol•L$^{-1}$), $M$ ($Q_L$, $Q_U$) | 3.43 (3.05, 3.80) | 4.81 (4.40, 5.40) | $Z$=−15.602 | 0.001 |
| TG/(mmol•L$^{-1}$), $M$ ($Q_L$, $Q_U$) | 1.33 (0.98, 1.92) | 1.82 (1.29, 2.52) | $Z$=−4.753 | 0.001 |
| HDL-C/(mmol•L$^{-1}$), $\bar{x}\pm s$ | 1.05±0.29 | 1.14±0.38 | $t$=−2.585 | 0.011 |
| BUN/(mmol•L$^{-1}$), $\bar{x}\pm s$ | 5.38±1.65 | 5.58±1.56 | $t$=−1.134 | 0.120 |
| SCr/(μmol•L$^{-1}$), $\bar{x}\pm s$ | 74.05±18.87 | 73.28±17.72 | $t$=0.388 | 0.922 |
| eGFR/(mL•min$^{-1}$•[1.73 m$^2$]$^{-1}$), $\bar{x}\pm s$ | 92.47±21.91 | 94.72±24.07 | $t$=0.919 | 0.641 |
| proBNP/(pg•mL$^{-1}$), $M$ ($Q_L$, $Q_U$) | 79.57 (41.02, 220.90) | 81.22 (33.44, 337.25) | $Z$=−0.343 | 0.732 |
| LVEF/%, $\bar{x}\pm s$ | 61.98±5.50 | 60.59±5.59 | $t$=2.227 | 0.016 |
| Medication, $n$ (%) | | | | |
| ACEI/ARB | 113 (50.0) | 82 (58.2) | $\chi^2$=2.319 | 0.128 |
| β-blockade | 186 (82.3) | 117 (83.0) | $\chi^2$=0.028 | 0.868 |
| Statin | 212 (93.8) | 133 (94.3) | $\chi^2$=0.042 | 0.838 |
| CCB | 51 (22.6) | 36 (25.5) | $\chi^2$=0.442 | 0.516 |
| Metformin | 40 (17.7) | 18 (12.8) | $\chi^2$=1.588 | 0.208 |
| Other hypoglycemic agents or RI | 56 (24.8) | 34 (24.1) | $\chi^2$=0.021 | 0.886 |
| Coronary lesion and surgical condition | | | | |
| Single vessel lesion, $n$ (%) | 102 (45.1) | 58 (4.1) | $\chi^2$=0.564 | 0.453 |
| Multi-vessel lesion, $n$ (%) | 119 (52.7) | 83 (58.9) | $\chi^2$=1.353 | 0.245 |
| Stent number, $\bar{x}\pm s$ | 1.06±0.87 | 1.33±0.70 | $t$=22.723 | 0.001 |
| Urgent PCI, $n$ (%) | 12 (5.3) | 32 (22.7) | $\chi^2$=24.872 | 0.001 |
| Prior PCI, $n$ (%) | 128 (56.6) | 25 (17.7) | $\chi^2$=54.068 | 0.001 |
| Prior CABG, $n$ (%) | 3 (1.3) | 1 (0.7) | $\chi^2$=0.308 | 0.580 |
| Adverse reaction, $n$ (%) | | | | |
| Ticagrelor-related dyspnea | 31 (13.7) | 33 (23.4) | $\chi^2$=5.660 | 0.018 |
| Bleeding event | 27 (11.9) | 22 (15.6) | $\chi^2$=1.003 | 0.317 |

Low LDL-C group: LDL-C＜2.6 mmol/L; High LDL-C group: LDL-C≥2.6 mmol/L. LDL-C: Low-density lipoprotein-cholesterol; ACS: Acute coronary syndrome; BMI: Body mass index; HGB: Hemoglobin; RDW: Red blood cell distribution width; PDW: Platelet distribution width; hs-CRP: Hypersensitive C reactive protein; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Total triglyceride; HDL-C: High-density lipoprotein-cholesterol; BUN: Blood urea nitrogen; SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate; proBNP: Pro-brain natriuretic peptide; LVEF: Left ventricular ejection fraction; ACEI/ARB: Angiotensin-converting enzyme inhibitor/angiotensin Ⅱ receptor blocker; CCB: Calcium channel blocker; RI: Regular insulin; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; $M$ ($Q_L$, $Q_U$): Median (lower quartile, upper quartile).

2.2.2 替格瑞洛相关呼吸困难预测因素的多因素 logistic 回归分析结果 多因素 logistic 回归分析结果（表 3）显示吸烟史是 PCI 术后 ACS 患者发生替格瑞洛相关呼吸困难的预测因素（*OR*＝2.695，95% *CI* 1.236～5.878，*P*＝0.013），见表 3。

**表 3 ACS 患者替格瑞洛相关呼吸困难危险因素的多因素 logistic 回归分析**

**Tab 3 Multiple logistic regression analysis of risk factors for ticagrelor-related dyspnea in ACS patients**

| Variable | *OR* (95% *CI*) | *P* value |
|---|---|---|
| Smoking | 2.695 (1.236, 5.878) | 0.013 |
| AMI | 1.667 (0.508, 5.468) | 0.399 |
| PMI | 0.561 (0.153, 2.050) | 0.382 |
| hs-CRP | 0.991 (0.971, 1.013) | 0.430 |
| FBG | 0.954 (0.756, 1.203) | 0.691 |
| TC | 0.958 (0.503, 1.825) | 0.897 |
| TG | 0.869 (0.552, 1.368) | 0.869 |
| HDL-C | 0.702 (0.155, 3.190) | 0.647 |
| LDL-C | 1.963 (0.589, 6.545) | 0.272 |
| LVEF | 0.998 (0.949, 1.084) | 0.959 |
| Stent number | 0.915 (0.494, 1.695) | 0.778 |
| Urgent PCI | 0.537 (0.139, 2.071) | 0.366 |
| Prior PCI | 0.977 (0.346, 2.755) | 0.964 |

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; PMI: Prior myocardial infarction; hs-CRP: Hypersensitive C reactive protein; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Total triglyceride; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; LVEF: Left ventricular ejection fraction; PCI: Percutaneous coronary intervention; *OR*: Odds ratio; *CI*: Confidence interval.

## 3 讨 论

既往研究证实临床较常见的抗血小板治疗药物如氯吡格雷、普拉格雷、替格瑞洛等服用后患者均可出现呼吸困难症状，且替格瑞洛相关呼吸困难的发生率最高[15-16]。PLATO（PLATelet Inhibition and Patient Outcomes）研究显示服用替格瑞洛患者在 1 年随访期内有 1 339 例出现呼吸困难，发生率为 14.5%[14]。Bonaca 等[18] 在 PEGASUS-TIMI 54（Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54）研究中纳入陈旧性心肌梗死病史 1 年以上的稳定型冠心病患者 21 162 例，随访 33 个月发现标准剂量下替格瑞洛（90 mg，每天 2 次）相关呼吸困难发生率为 18.93%。本研究中回顾性分析结果提示行 PCI 治疗并服用替格瑞洛的 ACS 患者呼吸困难发生率为 17.0%（71/418），而前瞻性分析结果显示替格瑞洛相关呼吸困难的发生率为 17.4%（64/367），均与上述研究结果接近。

本研究回顾性分析发现，与无出血事件的 ACS 患者相比，发生过出血事件的 ACS 患者呼吸困难发生率较高［23.9%（17/71）vs 10.1%（35/347），*P*＝0.001］，且多因素 logistic 回归分析证明出血事件是 ACS 患者发生替格瑞洛相关呼吸困难的危险因素（*OR*＝3.128，95% *CI* 1.613～6.065，*P*＝0.001）。本研究还发现血清 LDL-C 升高与替格瑞洛相关呼吸困难的发生有关，也是 ACS 患者发生替格瑞洛相关呼吸困难的危险因素（*OR*＝1.451，95% *CI* 1.071～1.964，*P*＝0.016）。GRAPE（GReek AntiPlatElet）注册研究显示，服用替格瑞洛期间有出血事件的患者更易发生呼吸困难（*OR*＝2.21，*P*＜0.001）[15]。国内亦有研究发现，出血事件与替格瑞洛相关呼吸困难的发生有关（*OR*＝2.925，95% *CI* 1.386～6.175，*P*＝0.005）[16]。虽然多项研究表明出血事件与替格瑞洛相关呼吸困难的发生有关[14,16,19]，但 PLATO 研究也表明出血本身可通过多种机制（包括缺血、贫血和心力衰竭）促进呼吸困难的发展[14]。本研究未精确记录出血和呼吸困难发生的具体时间，尚难以确定出血事件和呼吸困难之间的关系。因此，本研究仅选取血清 LDL-C 为暴露因素进行前瞻性研究，以进一步验证 LDL-C 对替格瑞洛相关呼吸困难的影响。

我们在回顾性研究中绘制了血清 LDL-C 对替格瑞洛相关呼吸困难的 ROC 曲线，将约登指数最大值时的数值 2.535 mmol/L 作为最佳诊断界点，结合《中国成人血脂异常防治指南（2016 年修订版）》[20] 中血清 LDL-C 理想目标值（＜2.6 mmol/L），选定 2.6 mmol/L 作为 LDL-C 值分界点。在前瞻性研究中将 ACS 患者分为低 LDL-C 组（LDL-C＜2.6 mmol/L）和高 LDL-C 组（LDL-C≥2.6 mmol/L），单因素分析结果显示两组呼吸困难发生率有显著差异，低 LDL-C 组替格瑞洛相关呼吸困难发生率为 13.7%（31/226），而高 LDL-C 组替格瑞洛相关呼吸困难发生率为 23.4%（33/141），差异具有统计学意义（*P*＝0.018）。进一步多因素 logistic 回归分析结果显示吸烟史是替格瑞洛相关呼吸困难发生

的独立预测因素（*OR*＝2.695，95% *CI* 1.236～5.878，*P*＝0.013）。吸烟与血清LDL-C水平的相关性已被多项研究[21-23]证实，本研究也发现与低LDL-C组相比，高LDL-C组有吸烟史患者的比例更高，分别为43.3%（61/141）和28.8%（65/226），差异有统计学意义（*P*＝0.004）。一项药代动力学研究发现，吸烟习惯可使替格瑞洛的清除率降低22%（95% *CI* 19%～25%）[24]，而有关替格瑞洛代谢的研究表明吸烟患者血浆中的替格瑞洛向其活性代谢物的转化率更高（4.2%，95% *CI* 0.2%～8.3%，*P*＝0.04）[25]。吸烟者血浆中替格瑞洛向活性代谢物转化加速，加之体内替格瑞洛药物本身清除率降低，使得血药浓度也相应增加。Storey等[14]报道呼吸困难可能与替格瑞洛血药浓度有关，故解释了吸烟患者表现出更高的呼吸困难发生率。

目前被广泛接受的替格瑞洛相关呼吸困难的机制主要有2种：一种与细胞外腺苷水平升高有关，另一种与$P2Y_{12}$受体有关[26-27]。这2种机制假说各有优劣，目前暂时没有一种机制被完全证实或推翻[28]。腺苷假说认为，替格瑞洛能够促进腺苷生成、抑制腺苷被红细胞再摄取，从而引起血液中腺苷浓度增加[14]。腺苷一方面刺激迷走性C纤维引起呼吸困难的感觉[29-30]，另一方面可诱导支气管平滑肌细胞的收缩，导致支气管痉挛[31-33]。还有研究显示LDL-C可以通过影响血管外腺苷脱氨酶水平促进腺苷生成[34]。替格瑞洛和LDL-C均能增加腺苷浓度，这可能解释了本研究中血清LDL-C水平偏高的ACS患者在服用替格瑞洛后更容易发生呼吸困难，LDL-C水平升高是替格瑞洛相关呼吸困难的危险因素。

$P2Y_{12}$受体假说提出，替格瑞洛作为可逆性$P2Y_{12}$受体拮抗剂，不断与神经元或神经胶质细胞中新产生的$P2Y_{12}$受体结合[28]，刺激中央化学反射系统和引发潮式呼吸[35-36]。这可能也是本研究中接受替格瑞洛治疗后LDL-C水平偏高ACS患者呼吸困难发生率更高的原因之一。一项将LDL-C充当药物载体并调节体内药物运输和代谢的体外实验研究认为，LDL受体过表达显著增加了与LDL-C相关的$P2Y_{12}$受体拮抗剂的吸收，即高水平LDL-C可促进体内替格瑞洛的吸收[37]。

总之，PCI术后服用替格瑞洛的ACS患者中替格瑞洛所致呼吸困难较为常见。本研究认为血清LDL-C水平偏高的ACS患者更容易发生替格瑞洛相关呼吸困难，而吸烟史是替格瑞洛相关呼吸困难发生的独立预测因素。这一结果有助于我们在开始替格瑞洛治疗前筛选易发生呼吸困难的患者，从而有利于精准个体化治疗方案的制订。

本研究存在以下局限性：对呼吸困难症状的界定仍然基于随访过程的主观互动，受访者的自身直观感受可能会影响试验结果，而真实世界中对于呼吸困难的物理刺激来源很难被准确界定和衡量[38]。如在住院或门诊随访期间，医疗人员对患者就替格瑞洛可能带来的呼吸困难会提前警示。这可能造成一部分患者会因自我暗示，将自身某些症状联想为呼吸困难；也可能会使一部分患者忽略已出现的轻微呼吸困难症状。虽然在本次研究前，通过排除肺部疾病、严重心功能不全及谨慎设计随访问题等手段最大限度地避免其他因素引起的呼吸困难所带来的干扰[39]，但并不能完全避免上述情况的发生。此外，本研究为单中心研究，样本量仍然较小，研究对象仅限于上海交通大学医学院附属新华医院的住院患者，未能纳入更大范围的人群资料，不能排除由于地域、治疗条件等因素造成的选择偏倚，因此研究结果有待于大样本、多中心研究进一步验证。

## ［参 考 文 献］


［1］ VALGIMIGLI M, BUENO H, BYRNE R A, COLLET J P, COSTA F, JEPPSSON A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS[J]. Eur J Cardiothorac Surg, 2018, 53: 34-78.

［2］ AMSTERDAM E A, WENGER N K, BRINDIS R G, CASEY D E Jr, GANIATS T G, HOLMES D R Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines[J/OL]. J Am Coll Cardiol, 2014, 64: e139-e228. DOI: 10.1016/j.jacc.2014.09.017.

［3］ ROFFI M, PATRONO C, COLLET J P, MUELLER C, VALGIMIGLI M, ANDREOTTI F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)[J]. Eur Heart J, 2016, 37: 267-315.

[4] BASSAND J P, HAMM C W, ARDISSINO D, BOERSMA E, BUDAJ A, FERNANDEZ-AVILES F, et al. [Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes][J]. Rev Port Cardiol, 2008, 27: 1063-1143.

[5] MEMBERS A F, VAN DE WERF F, BAX J, BETRIU A, BLOMSTROM-LUNDQVIST C, CREA F, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology[J]. Eur Heart J, 2008, 29: 2909-2945.

[6] WALLENTIN L, BECKER R C, BUDAJ A, CANNON C P, EMANUELSSON H, HELD C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes[J]. N Engl J Med, 2009, 361: 1045-1057.

[7] VAN GIEZEN J J, NILSSON L, BERNTSSON P, WISSING B M, GIORDANETTO F, TOMLINSON W, et al. Ticagrelor binds to human $P2Y_{12}$ independently from ADP but antagonizes ADP-induced receptor signaling and platelet aggregation[J]. J Thromb Haemost, 2009, 7: 1556-1565.

[8] BLIDEN K P, TANTRY U S, STOREY R F, JEONG Y H, GESHEFF M, WEI C, et al. The effect of ticagrelor versus clopidogrel on high on-treatment platelet reactivity: combined analysis of the ONSET/OFFSET and RESPOND studies[J]. Am Heart J, 2011, 162: 160-165.

[9] 李慕鹏，熊艳，陈小平. 抗血小板药物替格瑞洛药代药效动力学及遗传药理学研究进展[J]. 中国临床药理学与治疗学，2014，19：214-222.

[10] TANGUAY J F, BELL A D, ACKMAN M L, BAUER R D, CARTIER R, CHAN W S, et al. Focused 2012 update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy[J]. Can J Cardiol, 2013, 29: 1334-1345.

[11] 中华医学会心血管病学分会介入心脏病学组，中国医师协会心血管内科医师分会血栓防治专业委员会，中华心血管病杂志编辑委员会. 中国经皮冠状动脉介入治疗指南（2016）[J]. 中华心血管病杂志，2016，44：382-400.

[12] GURBEL P A, BLIDEN K P, BUTLER K, TANTRY U S, GESHEFF T, WEI C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study[J]. Circulation, 2009, 120: 2577-2585.

[13] STOREY R F, BECKER R C, HARRINGTON R A, HUSTED S, JAMES S K, COOLS F, et al. Pulmonary function in patients with acute coronary syndrome treated with ticagrelor or clopidogrel (from the Platelet Inhibition and Patient Outcomes [PLATO] pulmonary function substudy)[J]. Am J Cardiol, 2011, 108: 1542-1546.

[14] STOREY R F, BECKER R C, HARRINGTON R A, HUSTED S, JAMES S K, COOLS F, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes[J]. Eur Heart J, 2011, 32: 2945-2953.

[15] ALEXOPOULOS D, XANTHOPOULOU I, PERPERIS A, GOUDEVENOS J, HAMILOS M, SITAFIDIS G, et al. Dyspnea in patients treated with $P2Y_{12}$ receptor antagonists: insights from the GReek AntiPlatElet (GRAPE) registry[J]. Platelets, 2017, 28: 691-697.

[16] 李海玲，侯攀，郭显，唐文栋，柳俊梅，赵仙先，等. 急性冠状动脉综合征患者替格瑞洛相关呼吸困难的危险因素分析[J]. 第二军医大学学报，2020，41：11-17.
LI H L, HOU P, GUO X, TANG W D, LIU J M, ZHAO X X, et al. Risk factors of ticagrelor-associated dyspnea in patients with acute coronary syndrome[J]. Acad J Sec Mil Med Univ, 2020, 41: 11-17.

[17] RAO A K, PRATT C, BERKE A, JAFFE A, OCKENE I, SCHREIBER T L, et al. Thrombolysis in myocardial infarction (TIMI) trial—phase Ⅰ[J/OL]. Dimens Crit Care Nurs, 1990, 9: 29. DOI: 10.1097/00003465-199001000-00008.

[18] BONACA M P, BHATT D L, COHEN M, STEG P G, STOREY R F, JENSEN E C, et al. Long-term use of ticagrelor in patients with prior myocardial infarction[J]. N Engl J Med, 2015, 372: 1791-1800.

[19] 董加建，宋爽，马心超，陈愿，崔留义，赵子明. 冠心病患者替格瑞洛相关呼吸困难预测因素的分析[J]. 临床心血管病杂志，2018，34：990-992.

[20] 中国成人血脂异常防治指南修订联合委员会. 中国成人血脂异常防治指南（2016 年修订版）[J]. 中华健康管理学杂志，2017，11：7-28.

[21] 钟毓瑜，马静，陈志锦，夏敏，朱旭雯. 吸烟与中年男性血脂及氧化低密度脂蛋白的关系[J]. 广东医学，2005，26：1268-1270.

[22] 高金库，万丽梅，孙晓鸥. 中老年吸烟与不吸烟者对血脂的影响：1 ∶ 1 配对比较[J]. 中国临床康复，2005，9：191.

[23] CHELLAND CAMPBELL S, MOFFATT R J, STAMFORD B A. Smoking and smoking cessation—the relationship between cardiovascular disease and lipoprotein metabolism: a review[J]. Atherosclerosis, 2008, 201: 225-235.

[24] LI J G, TANG W F, STOREY R F, HUSTED S, TENG R L. Population pharmacokinetics of ticagrelor in patients with acute coronary syndromes[J]. Int J Clin Pharmacol Ther, 2016, 54: 666-674.

[25] ADAMSKI P, BUSZKO K, SIKORA J, NIEZGODA P, BARAŃSKA M, OSTROWSKA M, et al. Metabolism of ticagrelor in patients with acute coronary syndromes[J/OL].

Sci Rep, 2018, 8: 11746. DOI: 10.1038/s41598-018-29619-9.

[26] ARORA S, SHEMISA K, VADUGANATHAN M, QAMAR A, GUPTA A, GARG S K, et al. Premature ticagrelor discontinuation in secondary prevention of atherosclerotic CVD: JACC review topic of the week[J]. J Am Coll Cardiol, 2019, 73: 2454-2464.

[27] PARODI G, STOREY R F. Dyspnoea management in acute coronary syndrome patients treated with ticagrelor[J]. Eur Heart J Acute Cardiovasc Care, 2015, 4: 555-560.

[28] KRAKOWIAK A, KULETA J, PLECH I, ZARĘBIŃSKI M, WOJCIECHOWSKA M, WRETOWSKI D, et al. Ticagrelor-related severe dyspnoea: mechanisms, characteristic features, differential diagnosis and treatment[J/OL]. Clin Med Insights Case Rep, 2020, 13: 1179547620956634. DOI: 10.1177/1179547620956634.

[29] BONELLO L, LAINE M, KIPSON N, MANCINI J, HELAL O, FROMONOT J, et al. Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome[J]. J Am Coll Cardiol, 2014, 63: 872-877.

[30] WITTFELDT A, EMANUELSSON H, BRANDRUP-WOGNSEN G, VAN GIEZEN J J, JONASSON J, NYLANDER S, et al. Ticagrelor enhances adenosine-induced coronary vasodilatory responses in humans[J]. J Am Coll Cardiol, 2013, 61: 723-727.

[31] BROWN R A, SPINA D, PAGE C P. Adenosine receptors and asthma[J]. Br J Pharmacol, 2008, 153(Suppl 1): S446-S456.

[32] WILSON C N, NADEEM A, SPINA D, BROWN R, PAGE C P, MUSTAFA S J. Adenosine receptors and asthma[J]. Handb Exp Pharmacol, 2009: 329-362.

[33] MORROW A, FORD T J, BROGAN R. Incidence of acute bronchospasm during systemic adenosine administration for coronary angiography[J]. J R Coll Physicians Edinb, 2019, 49: 204-206.

[34] KUTRYB-ZAJAC B, MIERZEJEWSKA P, SUCAJTYS-SZULC E, BULINSKA A, ZABIELSKA M A, JABLONSKA P, et al. Inhibition of LPS-stimulated ecto-adenosine deaminase attenuates endothelial cell activation[J]. J Mol Cell Cardiol, 2019, 128: 62-76.

[35] CATTANEO M, FAIONI E M. Why does ticagrelor induce dyspnea?[J]. Thromb Haemost, 2012, 108: 1031-1036.

[36] GIANNONI A, EMDIN M, PASSINO C. Cheyne-stokes respiration, chemoreflex, and ticagrelor-related dyspnea[J]. N Engl J Med, 2016, 375: 1004-1006.

[37] YAMAMOTO H, TAKADA T, YAMANASHI Y, OGURA M, MASUO Y, HARADA-SHIBA M, et al. VLDL/LDL acts as a drug carrier and regulates the transport and metabolism of drugs in the body[J/OL]. Sci Rep, 2017, 7: 633. DOI: 10.1038/s41598-017-00685-9.

[38] MANNING H L, SCHWARTZSTEIN R M. Pathophysiology of dyspnea[J]. N Engl J Med, 1995, 333: 1547-1553.

[39] SEREBRUANY V L, STEBBING J, ATAR D. Dyspnoea after antiplatelet agents: the AZD6140 controversy[J]. Int J Clin Pract, 2007, 61: 529-533.

［本文编辑］　商素芳