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不同剂量瑞舒伐他汀用于急诊 PCI 患者的疗效及 对 Lp-PLA2、IL-6、TNF- α 的影响 *

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摘要 目的:探讨不同剂量瑞舒伐他汀对急诊经皮冠状动脉介入术(PCI)患者疗效及脂蛋白相关磷脂酶 A2(Lp-PLA2)、白介素(IL)-6、肿瘤坏死因子(TNF)- α 的影响。**方法:**选择2014年2月至2016年2月我院接诊的120例急性冠状动脉综合征(ACS)患者,均急诊行PCI,以随机数表分为A组(n=40)、B组(n=40)和C组(n=40),三组PCI术后均给予常规治疗,在此基础上,A组瑞舒伐他汀剂量10 mg,B组20 mg,C组30 mg,均1次/d,睡前服用,连续用药7 d。比较三组治疗前后心率(HR)、心功能以及Lp-PLA2、IL-6、TNF- α 的变化,并随访一年,记录心血管不良事件发生率。**结果:**治疗后,三组HR、心功能指标、Lp-PLA2、IL-6、TNF- α 较治疗前均显著改善($P<0.05$);在HR中,C组<B组<A组,组间比较均具有显著差异($P<0.05$);在左室舒张期末内径(LVEDD)、左室收缩期末内径(LVESD)、左室舒张末期容积(LVEDV)、左室收缩末期容积(LVESV)、左室射血分数(LVEF)结果中,C组改善程度明显优于B组和A组,组间比较均具有显著差异($P<0.05$);在Lp-PLA2、IL-6、TNF- α 中,C组<B组<A组,组间比较均具有显著差异($P<0.05$);随访结果显示,C组再狭窄发生率明显低于B组和A组,A组心肌梗死明显高于C组($P<0.05$),三组心源性休克、死亡率比较无显著差异($P>0.05$)。**结论:**在急诊PCI患者术后应用40 mg的瑞舒伐他汀效果显著,其有助于改善心功能,降低不良心血管事件发生率,其内在机制可能和降低Lp-PLA2、IL-6、TNF- α 的表达相关。

关键词:急性冠状动脉综合征;经皮冠状动脉介入术;瑞舒伐他汀;脂蛋白相关磷脂酶A2;白介素-6;肿瘤坏死因子- α

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Curative Efficacy of Different Doses of Rosuvastatin in Treatment of Primary PCI and Its Effects on Lp-PLA2, IL-6 and TNF- α Levels*

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ABSTRACT Objective: To study Curative efficacy of different doses of rosuvastatin in treatment of primary percutaneous coronary intervention(PCI) and its effects on lipoprotein associated phospholipase A2(Lp-PLA2), interleukin(IL)-6 and tumor necrosis factor(TNF)- α levels levels. **Methods:** 120 patients of acute coronary syndromes(ACS) who received therapy from February 2014 to February 2016 in our hospital were selected, all emergency departments were PCI. According to random number table, those patients were divided into the A group(n=40), B group(n=48) and C group(n=40). The three groups received routine treatment after PCI, on this basis, A group rosuvastatin dose of 10 mg, A group rosuvastatin dose of 20 mg, C group rosuvastatin dose of 40 mg, 1 times /d, take before going to bed, continuous medication 7 d. The changes of heart rate (HR), heart function and Lp-PLA2, IL-6 and TNF- α the three groups were compared before and after treatment, the incidence of adverse cardiovascular events was recorded for a year following up. **Results:** After treatment, the HR, cardiac function index, Lp-PLA2, IL-6, TNF- α in three groups were significantly improved compared with before treatment($P<0.05$); in the HR, C group < B group < A group, there were significant differences between groups($P<0.05$); in the left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricular ejection fraction (LVEF) results, the improvement degree of C group was better than that of B group and A group, there were significant differences between groups($P<0.05$); in the Lp-PLA2, IL-6 and TNF- α , C group < B group < A group, there were significant differences between groups ($P<0.05$); follow up showed, the restenosis rate in the C group was significantly lower than that of the B group and A group, the myocardial infarction in the A group was significantly higher than that of the C group($P<0.05$), there was no significant difference in cardiogenic shock and mortality between the three groups($P>0.05$). **Conclusion:** 40mg of rosuvastatin is well for after primary PCI, it's can improve heart function, and it's intrinsic mechanism may be related to the reduction of Lp-PLA2, IL-6 and TNF- α expression.

Key words: Acute coronary syndromes; Percutaneous coronary intervention; Rosuvastatin; Lipoprotein associated phospholipase

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前言

急诊 PCI 目前已在急性冠脉综合征(ACS)中普遍应用,相关数据显示,其可将 30%左右的住院死亡率降低到 4%,有利于提高预后^[1]。但也有较多报道指出,在 PCI 术后可加重局部炎症反应,增加术后再狭窄、血栓形成、缺血事件等的发生率,对心肌造成损伤^[2-3]。他汀类药物具有降脂、稳定斑块、抗炎等效果,在降低缺血事件发生率中效果显著,而其中瑞舒伐他汀作为强效的新型他汀类药物,羟基二甲甲基二酰辅 A(HMG-CoA)还原酶抑制剂,不仅具有明显的调脂效果,还可产生抗氧化、抗血小板聚集、抗动脉粥样硬化、改善免疫功能及内皮功能等作用,其安全性、耐受性均优于同类药物^[4-5]。但在急诊 PCI 术后,使用何种剂量的瑞舒伐他汀可达到最明显的效果临床上仍处于讨论阶段。较多国内外学者指出,对脂蛋白相关磷脂酶 A2(Lp-PLA2)、白介素(IL)-6、肿瘤坏死因子(TNF)- α 等炎症因子

指标的观察,有助于进一步判断患者预后^[6,7]。本次研究旨在探讨在急诊 PCI 患者术后应用不同剂量瑞舒伐他汀的效果,并观察其对 Lp-PLA2、IL-6、TNF- α 的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择 2014 年 2 月至 2016 年 2 月我院接诊的 120 例 ACS 患者。纳入标准^[8]:①符合 ACS 诊断标准,均存在不同程度的心前区不适、疼痛等,并通过心电图、心肌标志物等检查得以确诊;②急诊行 PCI;③患者及家属知情同意此次研究。排除标准^[9]:①近期曾有降脂类药物、免疫抑制剂、肾上腺皮质激素等服用;②合并其余心血管疾病、自身免疫性疾病、恶性肿瘤等;③肝、肾功能障碍;④瑞舒伐他汀过敏;⑤近期有外科手术史、重大外伤等。以随机数表法分为 3 组,每组 40 例。三组一般资料、急诊 PCI 情况比较均无显著差异($P>0.05$),见表 1,具有可比性。

表 1 三组一般资料、急诊 PCI 情况比较($\bar{x} \pm s$)

Table 1 Comparison of the general information and emergency PCI among three groups($\bar{x} \pm s$)

Groups	Gender[n(%)]		Age(years)	Operation time (min)	The amount of bleeding(mL)	Length of stay(d)
	Male	Female				
A group(n=40)	23(57.50)	17(42.50)	62.73 $\pm$ 4.12	46.85 $\pm$ 3.41	57.84 $\pm$ 4.52	7.84 $\pm$ 1.32
B group(n=40)	25(62.50)	15(37.50)	63.19 $\pm$ 3.95	47.08 $\pm$ 3.22	56.95 $\pm$ 4.99	7.49 $\pm$ 1.46
C group(n=40)	21(52.50)	19(47.50)	62.48 $\pm$ 4.26	46.16 $\pm$ 3.75	58.03 $\pm$ 4.13	7.65 $\pm$ 1.37

1.2 方法

三组 PCI 术后均给予常规氯吡格雷、低分子肝素、阿司匹林、 β 受体阻滞剂等的应。

在此基础上,三组均给予不同剂量瑞舒伐他汀(规格 10 mg,厂家:南京先声东元制药有限公司,国药准字 H20113246)口服,A 组 10 mg,B 组 20 mg,C 组 40 mg,均 1 次/d,睡前服用。连续用药 7d。

1.3 观察指标

1.3.1 心率(HR) 令患者处于安静、清醒状态下,以鱼跃 YX301 指夹式血氧仪进行检测,每次 1 min,进行 3 次测量后,记录平均值。

1.3.2 心功能 采用 Philips IE33 彩色多普勒超声诊断仪,检测左心室舒张期末内径(LVEDD)、左心室收缩期末内径(LVESD)、左心室舒张末期容积(LVEDV)、左心室收缩末期容积(LVESV)、左室射血分数(LVEF)。

1.3.3 实验室指标 抽取 3 mL 空腹静脉血,以酶联免疫吸附法检测 Lp-PLA2、IL-6、TNF- α ,试剂盒均购于津康尔克生物科技有限公司。

1.3.4 随访 随访一年,记录不良心血管事件发生率。

1.4 统计学分析

以 SPSS18.0 软件包处理,计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)

表示,组间两两比较 t 检验,多组间比较以方差分析,计数资料 χ^2 检验, $P<0.05$ 表示差异显著。

2 结果

2.1 三组 HR 比较

三组治疗前 HR 比较无显著差异($P>0.05$);治疗后,三组 HR 较治疗前均显著改善($P<0.05$),且 C 组 $<$ B 组 $<$ A 组,组间比较均具有显著差异($P<0.05$),见表 1。

表 2 三组 HR 比较($\bar{x} \pm s$, 次/min)

Table 2 Comparison of the HR among three groups($\bar{x} \pm s$, time/min)

Groups	HR	
A group(n=40)	Before treatment	128.34 $\pm$ 4.95
	After treatment	112.73 $\pm$ 3.49*
B group(n=40)	Before treatment	128.76 $\pm$ 4.53
	After treatment	93.42 $\pm$ 3.40* [#]
C group(n=40)	Before treatment	128.59 $\pm$ 4.72
	After treatment	83.58 $\pm$ 3.15* [#]

Note: Vs with the before treatment, * $P<0.05$; vs the A group, [#] $P<0.05$; vs the B group, [△] $P<0.05$.

2.2 三组心功能比较

治疗前,三组心功能各指标比较无显著差异($P>0.05$);治疗后,三组 LVEDD、LVESD、LVEDV、LVESV 较治疗前均显著

降低,LVEF 显著升高($P<0.05$),其中 C 组改善程度明显优于 B 组和 C 组,组间比较均具有显著差异($P<0.05$),见表 2。

表 3 三组心功能比较($\bar{x}\pm s$)

Table 3 Comparison of the heart function among three groups($\bar{x}\pm s$)

Groups		LVEDD(mm)	LVESD(mm)	LVEDV(mL)	LVESV(mL)	LVEF(%)
A group(n=40)	Before treatment	112.73 $\pm$ 4.92	67.34 $\pm$ 5.34	103.42 $\pm$ 5.73	68.34 $\pm$ 4.83	41.82 $\pm$ 3.84
	After treatment	76.82 $\pm$ 3.84*	45.93 $\pm$ 3.72*	81.73 $\pm$ 3.89*	53.92 $\pm$ 3.04*	49.15 $\pm$ 4.06*
B group(n=40)	Before treatment	113.02 $\pm$ 4.37	67.83 $\pm$ 5.14	103.14 $\pm$ 5.85	67.98 $\pm$ 5.02	42.02 $\pm$ 3.42
	After treatment	65.83 $\pm$ 3.52**	39.47 $\pm$ 3.48**	75.88 $\pm$ 3.14**	46.73 $\pm$ 2.76**	55.83 $\pm$ 4.10**
C group(n=40)	Before treatment	112.95 $\pm$ 4.68	67.62 $\pm$ 5.20	103.29 $\pm$ 5.79	68.14 $\pm$ 4.92	41.95 $\pm$ 3.75
	After treatment	56.73 $\pm$ 3.40***	31.84 $\pm$ 3.12***	69.84 $\pm$ 3.05***	41.72 $\pm$ 2.43***	63.84 $\pm$ 4.24***

Note: Vs with the before treatment, * $P<0.05$; vs the A group, ** $P<0.05$; vs the B group, *** $P<0.05$.

2.3 三组 Lp-PLA2、IL-6、TNF- α 比较

治疗前,三组 Lp-PLA2、IL-6、TNF- α 比较均无显著差异($P>0.05$);治疗后,三组 Lp-PLA2、IL-6、TNF- α 较治疗前均显

著降低($P<0.05$),其中 C 组<B 组<A 组,组间比较均具有显著差异($P<0.05$),见表 3。

表 4 三组 Lp-PLA2、IL-6、TNF- α 比较($\bar{x}\pm s$)

Table 4 Comparison of the Lp-PLA2, IL-6 and TNF- α among three groups($\bar{x}\pm s$)

Groups		Lp-PLA2(ng/mL)	IL-6(ng/L)	TNF- α (ng/L)
A group(n=40)	Before treatment	287.45 $\pm$ 34.52	12.73 $\pm$ 2.16	28.74 $\pm$ 3.42
	After treatment	241.67 $\pm$ 25.82*	8.12 $\pm$ 0.73*	16.83 $\pm$ 1.53*
B group(n=40)	Before treatment	288.12 $\pm$ 34.12	13.02 $\pm$ 2.05	28.94 $\pm$ 3.27
	After treatment	213.23 $\pm$ 23.50**	6.83 $\pm$ 0.56**	12.42 $\pm$ 1.16**
C group(n=40)	Before treatment	287.94 $\pm$ 34.27	12.93 $\pm$ 2.10	29.02 $\pm$ 3.16
	After treatment	189.74 $\pm$ 21.58***	3.48 $\pm$ 0.42***	8.44 $\pm$ 0.92***

Note: Vs with the before treatment, * $P<0.05$; vs the A group, ** $P<0.05$; vs the B group, *** $P<0.05$.

2.4 三组心血管不良事件比较

三组再狭窄发生比较具有显著差异,A 组心肌梗死明显高

于 C 组($P<0.05$),三组心源性休克、死亡率比较无显著差异($P>0.05$),见表 4。

表 5 三组心血管不良事件比较(例,%)

Table 5 Comparison of the adverse cardiovascular events among three groups(n, %)

Groups	Restenosis	Miocardial infarction	Cardiogenic shock	Death
A group(n=40)	16(40.00)	7(17.50)	2(5.00)	5(12.50)
B group(n=40)	8(20.00)*	3(7.50)	1(2.50)	2(5.00)
C group(n=40)	2(5.00)**	1(2.50)*	0(0.00)	1(2.50)

Note: vs the A group, * $P<0.05$; vs the B group, ** $P<0.05$.

3 讨论

急诊 PCI 有助于实现 ACS 患者冠状动脉血运重建,可在短时间内再通阻塞血管,缓解临床症状。但此过程中所造成的心肌缺血再灌注损伤、斑块破裂等,会增加细胞代谢功能障碍及结果破坏,致使心肌收缩失调、心肌细胞损伤等,对预后造成影响^[10,11]。

他汀类药物的调脂作用已在临床上得到证实,切还具有改

善内皮功能、缓解炎症反应、稳定斑块、抗氧化等作用^[12]。并且在最新的治疗指南中提出,在 PCI 术后应持续给予一段时间的降脂治疗,其主要目的是抗炎、防血栓等,可提高远期生存率^[13]。瑞舒伐他汀是第一个可稳定逆转粥样硬化斑块、缩小斑块体积的他汀类调脂药物。H A 等^[14]报道称,在急性心肌梗死行 PCI 术后应用负荷量的瑞舒伐他汀有助改善冠脉微循环。Jiao Y 等^[15]研究也指出,瑞舒伐他汀可明显减少 PCI 术后的心肌细胞坏死数量,有助于促进心功能的改善。本研究显示,经过

治疗后, 三组患者 HR、LVEDD、LVESD、LVEDV、LVESV、LVEF 均得到明显改善, 且呈剂量依赖性, 使用剂量越高的患者改善程度越佳; 且在随访结果中显示, 使用 40 mg 瑞舒伐他汀的患者再狭窄发生率明显比使用 20 mg 和 10 mg 的患者低, 且心肌梗死发生率明显低于使用 10 mg 瑞舒伐他汀的患者, 进一步显示出使用大剂量的瑞舒伐他汀在改善心脏功能中具有积极意义, 有助于减少 PCI 术后心血管不良事件发生率。

在急性行 PCI 时, 支架作为异物, 可直接对局部组织产生较大刺激, 诱导炎症因子释放, 而球囊扩张、支架置入机械损伤会对血管内皮造成损伤, 造成斑块破裂, 从而激活炎症的表达^[16]。有学者发现, 在冠心病患者中, Lp-PLA2 的表达明显比正常人群高, 且可作为预测心血管事件的独立危险因素^[17]。Haraguchi Y 等^[18]分析中指出, 在冠脉易损、破裂斑块周围, 均可检测到高表达的 Lp-PLA2, 在水解脂质后, 其产物可吸引循环中的单核细胞, 并在巨噬细胞的活化中进行参与, 可作为斑块形成、斑块破裂过程中的特殊标志物。IL-6 可对肝脏 C-反应蛋白(CRP)的合成和肝脏急性期的反应进行调节, 对肝脏产生诱导作用, 令其生成血浆凝血因子 I, 形成血栓, 使中性粒细胞、心肌细胞的粘附程度增加, 引发中性粒细胞大量释放氧自由基, 进而损伤到心肌细胞^[19]。而 TNF- α 在动脉粥样硬化中也发挥着重要的作用, 其可诱导血小板粘附, 令白细胞的趋化作用和血管细胞增殖迁移情况增加, 对内皮细胞造成直接损伤, 并诱导 CRP 的形成^[20]。国内外均有学者指出, 在急诊 PCI 操作过程中, 由于会对机体及心肌造成一定损伤, 引发大量炎症因子的释放, 例如 Lp-PLA2、IL-6、TNF- α 的等, 而降低此类因子的高表达, 有助于缓解心肌细胞损伤, 在提高预后中具有积极意义。本研究显示, 使用 40 mg 瑞舒伐他汀的患者 Lp-PLA2、IL-6、TNF- α 的降低程度明显优于使用 20 mg 及 10 mg 的患者, 提示早期采用大剂量的瑞舒伐他汀在抑制 PCI 术后炎症反应中效果更具有优势, 这也可能是应用大剂量瑞舒伐他汀患者心功能改善程度更佳、不良心血管事件发生率更低的内在机制之一。

综上所述, 在急诊 PCI 患者术后应用 40 mg 的瑞舒伐他汀效果显著, 其有助于改善心功能, 降低不良心血管事件发生率, 其内在机制可能和降低 Lp-PLA2、IL-6、TNF- α 的表达相关。

参考文献(References)

- [1] Shah R, Mattox A, Khan MR, et al. Contrast use in relation to the arterial access site for percutaneous coronary intervention: A comprehensive meta-analysis of randomized trials [J]. World J Cardiol, 2017, 9 (4): 378-383
- [2] Song L, Maehara A, Finn MT, et al. Intravascular Ultrasound Analysis of Intraplaque Versus Subintimal Tracking in Percutaneous Intervention for Coronary Chronic Total Occlusions and Association With Procedural Outcomes [J]. JACC Cardiovasc Interv, 2017, 10 (10): 1011-1021
- [3] Cuevas C, Ryan N, Quirós A, et al. Determinants of percutaneous coronary intervention success in repeat chronic total occlusion procedures following an initial failed attempt [J]. World J Cardiol, 2017, 9 (4): 355-362
- [4] Takayama T, Komatsu S, Ueda Y, et al. Comparison of the Effect of Rosuvastatin 2.5 mg vs 20 mg on Coronary Plaque Determined by Angioscopy and Intravascular Ultrasound in Japanese With Stable Angina Pectoris (from the Aggressive Lipid-Lowering Treatment Approach Using Intensive Rosuvastatin for Vulnerable Coronary Artery Plaque [ALTAIR] Randomized Trial)[J]. Am J Cardiol, 2016, 117(8): 1206-1212
- [5] Jiao Y, Hu F, Zhang Z, et al. Efficacy and Safety of Loading-Dose Rosuvastatin Therapy in Elderly Patients with Acute Coronary Syndromes Undergoing Elective Percutaneous Coronary Intervention[J]. Clin Drug Investig, 2015, 35(12): 777-784
- [6] Gajos G, Zalewski J, Mostowik M, et al. Polyunsaturated omega-3 fatty acids reduce lipoprotein-associated phospholipase A (2) in patients with stable angina [J]. Nutr Metab Cardiovasc Dis, 2014, 24 (4): 434-439
- [7] Leibundgut G, Lee JH, Strauss BH, et al. Acute and long-term effect of percutaneous coronary intervention on serially-measured oxidative, inflammatory, and coagulation biomarkers in patients with stable angina[J]. J Thromb Thrombolysis, 2016, 41(4): 569-580
- [8] Sinha SK, Mishra V, Jha MJ, et al. Primary Percutaneous Coronary Intervention Using Balloon-Assisted Sliding and Tracking (BLAST) of Diagnostic Catheter to Negotiate Double Hairpin Loop of Radial Artery[J]. Cardiol Res, 2017, 8(2): 81-85
- [9] Xie W, Li P, Wang Z, et al. Rosuvastatin may reduce the incidence of cardiovascular events in patients with acute coronary syndromes receiving percutaneous coronary intervention by suppressing miR-155/SHIP-1 signaling pathway[J]. Cardiovasc Ther, 2014, 32(6): 276-282
- [10] Sinha SK, Mishra V, Abdali N, et al. Primary Percutaneous Coronary Intervention Angioplasty of Occluded Twin Circumflex Coronary Artery in a Patient of Acute Inferior Wall Myocardial Infarction: A Rare Anomaly[J]. Cardiol Res, 2017, 8(2): 52-56
- [11] Przywara-Chowaniec B, Puzio A, Czamecki Ł, et al. Common origin of all three coronary arteries from the right sinus of Valsalva - first case study accompanied by mitral valve prolapse and vein anomaly, second case study followed by successful percutaneous coronary intervention of right coronary artery stenosis [J]. Kardiologia i Torakochirurgia Pol, 2017, 14(1): 66-70
- [12] Masuda J, Tanigawa T, Yamada T, et al. Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease[J]. Int Heart J, 2015, 56(3): 278-285
- [13] Leoncini M, Toso A, Maioli M, et al. Early high-dose rosuvastatin and cardioprotection in the protective effect of rosuvastatin and antiplatelet therapy on contrast-induced acute kidney injury and myocardial damage in patients with acute coronary syndrome (PRATO-ACS) study[J]. Am Heart J, 2014, 168(5): 792-797
- [14] H A, N E, S A, et al. The Effect of High Dose Cilostazol and Rosuvastatin on Periprocedural Myocardial Injury in Patients with Elective Percutaneous Coronary Intervention [J]. Acta Cardiol Sin, 2015, 31 (4): 292-300
- [15] Jiao Y, Hu F, Zhang Z, et al. Effect of rosuvastatin dose-loading on serum sLox-1, hs-CRP, and postoperative prognosis in diabetic patients with acute coronary syndromes undergoing selected percutaneous coronary intervention (PCI)[J]. Int J Clin Exp Med, 2015, 8 (11): 21565-21571

- [15] Luckoff A, Caramoy A, Scholz R, et al. Interferon-beta signaling in retinal mononuclear phagocytes attenuates pathological neovascularization[J]. *EMBO Mol Med*, 2016, 8(6): 670-678
- [16] Folkman J. Tumor angiogenesis: therapeutic implications [J]. *N Engl J Med*, 1971, 285(21): 1182-1186
- [17] Fan F, Schimming A, Jaeger D, et al. Targeting the tumor microenvironment: focus on angiogenesis[J]. *J Oncol*, 2012, 2012: 281261
- [18] Shahneh FZ, Baradaran B, Zamani F et al. Tumor angiogenesis and anti-angiogenic therapies[J]. *Hum Antibodies*, 2013, 22(1-2): 15-19
- [19] Kobayashi K, Maeda K, Takefuji M, et al. Dynamics of angiogenesis in ischemic areas of the infarcted heart[J]. *Sci Rep*, 2017, 7(1): 7156
- [20] Koole D, Heyligers J, Moll FL, et al. Intraplaque neovascularization and hemorrhage: markers for cardiovascular risk stratification and therapeutic monitoring[J]. *J Cardiovasc Med (Hagerstown)*, 2012, 13(10): 635-639
- [21] Xiao W, Jia Z, Zhang Q, et al. Inflammation and oxidative stress, rather than hypoxia, are predominant factors promoting angiogenesis in the initial phases of atherosclerosis [J]. *Mol Med Rep*, 2015, 12(3): 3315-3322
- [22] Kodama T, Narula N, Agozzino M, et al. Pathology of plaque haemorrhage and neovascularization of coronary artery[J]. *J Cardiovasc Med (Hagerstown)*, 2012, 13(10): 620-627
- [23] Michel JB, Martin-Ventura JL, Nicoletti A, et al. Pathology of human plaque vulnerability: mechanisms and consequences of intraplaque haemorrhages[J]. *Atherosclerosis*, 2014, 234(2): 311-319
- [24] Batty JA, Subba S, Luke P et al. Intracoronary Imaging in the Detection of Vulnerable Plaques[J]. *Curr Cardiol Rep*, 2016, 18(3): 28
- [25] Chistiakov DA, Orekhov AN, Bobryshev YV. Contribution of neovascularization and intraplaque haemorrhage to atherosclerotic plaque progression and instability [J]. *Acta Physiol (Oxf)*, 2015, 213(3): 539-553
- [26] Corliss BA, Azimi MS, Munson J, et al. Macrophages: An Inflammatory Link between Angiogenesis and Lymphangiogenesis [J]. *Microcirculation (New York, NY : 1994)*, 2016, 23(2): 95-121
- [27] Foster WS, Suen CM, Stewart DJ. Regenerative cell and tissue-based therapies for pulmonary arterial hypertension[J]. *Can J Cardiol*, 2014, 30(11): 1350-1360
- [28] Peplow PV. Growth factor- and cytokine-stimulated endothelial progenitor cells in post-ischemic cerebral neovascularization [J]. *Neural Regen Res*, 2014, 9(15): 1425-1429
- [29] Nabeebaccus A, Zheng S, Shah AM. Heart failure-potential new targets for therapy[J]. *Br Med Bull*, 2016, 119(1): 99-110
- [30] Mahecha AM, Wang H. The influence of vascular endothelial growth factor-A and matrix metalloproteinase-2 and -9 in angiogenesis, metastasis, and prognosis of endometrial cancer [J]. *Oncotargets Ther*, 2017, 10: 4617-4624
- [31] Schmidt DE, Manca M, Hoefer IE. Circulating endothelial cells in coronary artery disease and acute coronary syndrome [J]. *Trends Cardiovasc Med*, 2015, 25(7): 578-587
- [32] Itoh N, Ohta H, Nakayama Y, et al. Roles of FGF Signals in Heart Development, Health, and Disease [J]. *Front Cell Dev Biol*, 2016, 4: 110
- [33] Wang X, Ma W, Han S, et al. TGF-beta participates choroid neovascularization through Smad2/3-VEGF/TNF-alpha signaling in mice with Laser-induced wet age-related macular degeneration[J]. *Sci Rep*, 2017, 7(1): 9672
- [34] Marsiglia M, Boddu S, Chen CY, et al. Correlation between neovascular lesion type and clinical characteristics of nonneovascular fellow eyes in patients with unilateral, neovascular age-related macular degeneration[J]. *Retina*, 2015, 35(5): 966-974
- [35] Barquet LA. Role of VEGF in diseases of the retina[J]. *Arch Soc Esp Oftalmol*, 2015, 90 Suppl 1(3-5)
- [36] Lim LS, Mitchell P, Seddon JM, et al. Age-related macular degeneration[J]. *Lancet*, 2012, 379(9827): 1728-1738
- [37] Ramjiawan RR, Griffioen AW, Duda DG. Anti-angiogenesis for cancer revisited: Is there a role for combinations with immunotherapy? [J]. *Angiogenesis*, 2017, 20(2): 185-204
- [38] Tarallo V, De Falco S. The vascular endothelial growth factors and receptors family: Up to now the only target for anti-angiogenesis therapy[J]. *Int J Biochem Cell Biol*, 2015, 64: 185-189
- [39] Potz BA, Parulkar AB, Abid RM, et al. Novel molecular targets for coronary angiogenesis and ischemic heart disease [J]. *Coron Artery Dis*, 2017, 28(7): 605-613
- [40] Lu X, Sun X. Profile of conbercept in the treatment of neovascular age-related macular degeneration [J]. *Drug Des Devel Ther*, 2015, 9: 2311-2320
- [41] Paulus YM, Sodhi A. Anti-angiogenic Therapy for Retinal Disease [J]. *Handb Exp Pharmacol*, 2017, 242: 271-307
- [42] Ribatti D. Tumor refractoriness to anti-VEGF therapy [J]. *Cotarget*, 2016, 7(29): 46668-46677
- [43] Maj E, Papiernik D, Wietrzyk J. Antiangiogenic cancer treatment: The great discovery and greater complexity (Review)[J]. *Int J Oncol*, 2016, 49(5): 1773-1784

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- [16] Ganyukov VI, Tarasov RS, Neverova YN, et al. Long-term results of different approaches to revascularization in non-ST-segment elevation acute coronary syndrome and multiple coronary atherosclerosis[J]. *Ter Arkh*, 2017, 89(4): 29-34
- [17] Wu X, Zhang Y, Wu Z, et al. Plasma Lipoprotein-Associated Phospholipase A2 Level Is an Independent Predictor of High Thrombus Burden in Patients With Acute ST-segment Elevation Myocardial Infarction[J]. *Int Heart J*, 2016, 57(6): 689-696
- [18] Haraguchi Y, Toh R, Hasokawa M, et al. Serum myeloperoxidase/paraoxonase 1 ratio as potential indicator of dysfunctional high-density lipoprotein and risk stratification in coronary artery disease[J]. *Atherosclerosis*, 2014, 234(2): 288-294
- [19] Meng S, Wang LS, Huang ZQ, et al. Berberine ameliorates inflammation in patients with acute coronary syndrome following percutaneous coronary intervention [J]. *Clin Exp Pharmacol Physiol*, 2012, 39(5): 406-411
- [20] Balta S, Celik T, Ozturk C, et al. The relation between monocyte to HDL ratio and no-reflow phenomenon in the patients with acute ST-segment elevation myocardial infarction [J]. *Am J Emerg Med*, 2016, 34(8): 1542-1547