

· 综 述 General review ·

弹性蛋白酶诱导的兔颈总动脉瘤模型在颅内动脉瘤介入治疗中的应用和进展

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【摘要】 颅内动脉瘤介入治疗中出现的新材料和新技术需要在临床应用前进行可靠性动物实验,这不仅能有效地预测和降低临床应用中不良事件发生,而且能指导和开发新材料。弹性蛋白酶诱导的兔颈总动脉瘤模型是测试介入新材料安全性和有效性的最常用模型之一。该文主要就颅内动脉瘤介入治疗历史,弹性蛋白酶诱导的兔颈总动脉瘤模型发展,该模型相较其他动物模型的优势,用于新材料临床前实验的优势,如组织病理学、自然史、形态学和血流动力学特征,该模型弱点及发展方向等作一综述。

【关键词】 颅内动脉瘤; 弹性蛋白酶; 兔; 颈总动脉瘤模型

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【Abstract】 New materials and technologies emerging in the endovascular treatment of intracranial aneurysms require reliable animal experiments before clinical application, which can not only effectively predict and reduce the occurrence of adverse events in clinical application, but also definitely guide and develop updated materials. The elastase-induced carotid aneurysm rabbit model is one of the most commonly used experimental models for testing the safety and effectiveness of newly-developed interventional materials. This paper aims to make a comprehensive review, focusing on the history of endovascular treatment of intracranial aneurysms, the development of elastase-induced carotid aneurysm model in rabbits, the superiority of this model to other animal models and its advantages in using new materials for preclinical trials, including histopathology, natural history, morphology, hemodynamic features, etc. The disadvantages of this model and its future development direction are also discussed. (J Intervent Radiol, 2020, 29: 323-327)

【Key words】 intracranial aneurysm; elastase; rabbit; common carotid aneurysm model

颅内动脉瘤是自发性蛛网膜下腔出血最主要病因,其破裂出血后自然死亡率和致残率极高,全球范围内每年将近有 50 万人遭受动脉瘤性蛛网膜下腔出血,严重威胁人体健康^[1]。随着神经介入治疗新材料和新技术不断发展,建立血流动力学和组织病理学接近于人的颅内动脉瘤的动物模型显得十分重要。弹性蛋白酶诱导的兔颈总动脉瘤模型是近年来应用广泛、比较可靠的颅内动脉瘤动物模型。

1 颅内动脉瘤介入治疗史

随着新技术和新材料发展,血管内介入治疗术已成为颅内动脉瘤主要治疗方法。其发展历经 70 余年,概括为 4 个阶段。20 世纪 40 年代开始的电凝技术致颅内动脉瘤瘤腔内血栓形成第 1 阶段^[2],70 年代球囊栓塞颅内动脉瘤应用为第 2 阶段^[3],90 年代后电解脱弹簧圈栓塞颅内动脉瘤(介入治疗技术里程碑^[4])为第 3 阶段,近 10 余年来颅内血管支架、覆膜支架、血流转向装置和动脉瘤腔内血

流阻断装置临床应用(开拓了颅内动脉瘤治疗新方向^[5-8])为第 4 阶段。近年生物可降解覆膜支架/吸收支架、载药覆膜支架/弹簧圈等新材料和技术,成为探索和研究热点^[9-11]。

颅内动脉瘤介入治疗发展归功于新材料不断推出。神经介入新材料不断发展的同时,需要进行临床前实验,以更好地检测新材料安全性和有效性,为临床应用提供客观的实验数据,并证明其治疗效果,预测可能存在的并发症。其中弹性蛋白酶诱导的兔颈总动脉瘤模型是目前检测介入新材料最常用模型之一。其最初应用于检测弹簧圈^[12],后来逐渐用于检测支架^[13]、血流转向装置^[14]和覆膜支架^[15]等。许多经临床前实验证实的新材料应用于临床治疗颅内动脉瘤取得了类似结果,并起到很好的指导作用,有效降低了临床应用并发症。

2 弹性蛋白酶诱导的兔颈总动脉瘤模型发展历程

弹性蛋白酶诱导的兔颈总动脉瘤模型构建始于 20 世纪 90 年代末。Altes 等^[16]创立外科联合介入球囊方法制作兔颈总动脉起始段动脉瘤模型。具体过程是暴露右颈总动脉主干后,逆血流插入 4 F/5 F 导管鞘,DSA 透视下通过导管鞘将一 2 F/3 F 球囊导管置于右颈总动脉起始处并临时阻断颈总动脉,将 100 U 弹性蛋白酶注入右颈总动脉近端残腔并保持 20 min,最后近段结扎颈总动脉,复制出兔头臂干弯曲部动脉瘤模型。随后的研究也证实该模型长期通畅率可达 100%^[17]。血管造影和组织病理学检查显示,这种动脉瘤在形态学和血流动力学参数上与人颅内动脉瘤非常相似,具有内弹力层变薄或消失等人颅内动脉瘤组织病理学特点,类似于人颈内动脉眼动脉段动脉瘤。

很多研究报道对上述动脉瘤模型制作过程进行改进。Krings 等^[18]提议将弹性蛋白酶注入动脉瘤瘤颈区域而非右颈总动脉中部,并在 DSA 监测下防止弹性蛋白酶漏出至气管分支血管导致气管出血性坏死,同时减少弹性蛋白酶用量至 20 U,这样既可减少右颈总动脉外周组织对弹性蛋白酶吸收,又减轻实验动物术后早期疼痛。考虑到导管鞘和球囊会损伤血管, Hoh 等^[19]采用直形临时动脉瘤夹夹闭右颈总动脉根部,再以 24 G 留置针穿刺入右颈总动脉近端死腔,注入足量弹性蛋白酶保留 20 min,最后在穿刺点上方结扎,撤出动脉瘤夹。Wang 等^[20]在此基础上又进行改进,采用 C 形动脉瘤瘤夹夹闭颈总动脉根部及部分锁骨下动脉和头臂干,成功构建宽

颈动脉瘤模型。这种方法具有明显优势:① C 形动脉瘤瘤夹较直形瘤夹可减少手术空间,更易于操作;②瘤夹夹闭部分锁骨下动脉和头臂干,使得动脉瘤瘤颈充分暴露于弹性蛋白酶下。因此,动脉瘤夹放置位置对于宽颈动脉瘤形成至关重要。Ding 等^[21]回顾性研究 72 例弹性蛋白酶诱导的兔颈总动脉瘤模型,结果发现动脉瘤瘤颈宽度与闭塞球囊放置位置相关,球囊位置越高、瘤颈越窄,瘤体长度-瘤颈宽度比值越大。Onizuka 等^[22]回顾性分析 30 例弹性蛋白酶诱导的兔颈总动脉瘤模型,发现宽颈动脉瘤瘤颈中轴与头臂干夹角与瘤体长度成正比,这可能与动脉瘤内局部血流动力学有关。

3 弹性蛋白酶诱导兔颈总动脉瘤模型优势

理想的弹性蛋白酶诱导的兔颈总动脉瘤模型应具备以下特征:①动脉瘤大小形态、组织病理学、血流动力学和瘤周环境与人动脉瘤相同或相似;②动脉瘤稳定性好,未经治疗时可保持长期通畅;③形成周期短,制作过程快捷;④费用低,可重复性好。但目前所能制作的动脉瘤模型均不具备以上所有特征。目前构建动脉瘤模型常用实验动物有大鼠、兔、犬、猪和猴等。这些动物椎动脉系统相较颈动脉系统发达,制作动脉瘤模型时不会因暂时阻断前循环或切断单侧颈总动脉发生脑梗死。

大鼠繁殖快、价格低,颈总动脉易暴露,动脉搏动快、不易形成血栓,且不易受机械刺激发生血管痉挛。但大鼠颈总动脉直径与人类相差甚远,且术后死亡率较高,不适宜用于治疗方面研究。目前大鼠作为实验动物主要用于动脉瘤发生和发展过程和机制研究,以及可能的药物治疗研究^[23]。犬在动物模型构建中应用率较高,其优点在于麻醉和手术耐受性强,死亡率和术后并发症均低于其他实验动物。犬动脉直径和血流动力学特征与人类非常接近,也便于导管置入和血管内操作,适合用于血管内治疗研究^[24]。但犬凝血系统和纤溶系统远比其他动物活跃,这一特点又使得犬动脉瘤模型难以在临床推广或用于远期疗效评价。猪一直是医学实验中常用动物,除了具有犬的优点外,凝血倾向也较高。其血栓和新生内膜形成倾向尤其适用于评估动脉瘤治疗装置植入后再狭窄^[25]。但由于价格较高,不易管理,尚未广泛应用。同样,猴和猩猩等灵长动物是制作人颅内动脉瘤模型的理想对象^[26],但来源较少、价格昂贵、不易管理,因此也难以在实验中广泛应用。

兔子性情温和、适应能力强、费用相对较低且操

作简单。兔颈总动脉口径与人脑中动脉近端非常相似,非常适合栓塞材料,尤其是支架研究。超过 80% 兔双侧颈总动脉共同起源于头臂干,制作分叉型动脉瘤较为理想,且兔是非灵长类中血栓形成和纤溶过程与人类最为相似的一种动物,用于评估栓塞材料、栓塞效果,观察血栓事件十分可靠,并可长期存活。弹性蛋白酶诱导的兔颈总动脉瘤模型的局限性主要包括耐受手术能力较差,且操作时易损伤喉返神经,对手术人员要求比较高,但不影响模型广泛应用。

4 用于新材料临床前试验优势

弹性蛋白酶诱导的兔颈总动脉瘤模型组织病理学与人颅内动脉瘤有许多相似之处,为颅内动脉瘤瘤壁进展性变化研究提供了机会。弹性蛋白酶诱导的兔颅内动脉瘤模型瘤壁部分内皮细胞不连续或完全缺失,内弹力层消失,中层平滑肌细胞排列紊乱,这些大体病理特征与人动脉瘤很接近。Wang 等^[27]在病理组织学基础上将人颅内动脉瘤分成 4 亚型, A 型瘤壁内皮化伴平滑肌细胞线性排列, B 型瘤壁增厚伴平滑肌细胞排列紊乱, C 型厚壁和胶原化瘤壁伴或不伴机化的血栓形成, D 型极薄壁和少细胞动脉瘤壁;实验 2 周和 12 周组织病理学检查证实弹性蛋白酶诱导的兔颈总动脉瘤模型具有以上人动脉瘤所有亚型之特征。

弹性蛋白酶诱导的兔颈总动脉瘤模型另一特点是其自然史,其瘤体未经处理时可长期保持通畅。一项研究对 25 例弹性蛋白酶诱导的兔颈总动脉瘤进行长达 5 年随访,期间除 13 例发生与动脉瘤无关的死亡外,余 12 例动脉瘤模型均保持良好^[17]。这种长期稳定性在模拟人颅内未破裂动脉瘤特征上可起到重要作用。

弹性蛋白酶诱导的兔颈总动脉瘤模型形态学特征也是其优势之一。瘤体平均直径、高度分别为 4.5 mm、7.5 mm,与人颅内动脉瘤相似^[16]。此外,载瘤动脉直径(平均 4.3 mm)与人颅内动脉直径相似^[28]。血流动力学因素在动脉瘤形成、生长和血管内介入治疗后再通等研究方面发挥着重要作用。Zeng 等^[29]研究 51 例弹性蛋白酶诱导的兔右颈总动脉瘤模型,发现动脉瘤内压力、瘤壁应切力和剪切指数均在人颅内动脉瘤范围内,这主要得益于兔动脉瘤模型与人颅内动脉瘤在大小和载瘤血管曲度上高度相似。人颅内动脉瘤大多位于血管分叉部或血管弯曲处,承受较高的血流冲击,导致动脉瘤生长和再

通。兔右颈总动脉瘤载瘤血管曲度使之能承受很强的血流冲击,因而在颅内动脉瘤复发等关键问题研究中相比其他动脉瘤模型更具优势^[30]。

Ding 等^[31]采用弹性蛋白酶诱导的兔颈总动脉瘤模型比较普通弹簧圈、Hydroycoil 弹簧圈和 Matrix 弹簧圈的栓塞效果,结果表明 Hydroycoil 弹簧圈组动脉瘤平均栓塞密度为 76%,显著高于普通弹簧圈组(31%)和 Matrix 弹簧圈组(23%),且有较高的远期闭塞率。有临床研究也证实生物圈栓塞优势^[32]。Adibi 等^[33]采用间充质干细胞辅助弹簧圈栓塞治疗弹性蛋白酶诱导的兔动脉瘤模型,结果表明间充质干细胞辅助弹簧圈组较裸弹簧圈组组织病理学有明显改善。间充质干细胞可分化为平滑肌细胞并抑制促炎性细胞因子白细胞介素-1 β 、基质金属蛋白酶-2、基质金属蛋白酶-9 及肿瘤坏死因子。这些因素均在颅内动脉瘤发病机制中起着重要作用。

血流导向装置是一种创新且具有广阔前景的新材料器械,但在早期临床应用中发生治疗失败及未预料的术后动脉瘤迟发性破裂、分支动脉闭塞、支架内狭窄和自发性脑实质出血等并发症^[34]。血流导向装置如 Pipeline、Silk、Surpass、Tubridge 和 Fred 等临床前实验研究最常应用弹性蛋白酶诱导的兔动脉瘤模型^[35-39]。该模型已被公认为是检测颅内支架的标准化动脉瘤模型。大多数实验研究表明血流导向装置可对该模型实现完全闭塞,但若受孔隙率和孔隙密度影响治疗失败,表明这种新型器械尚需进一步改进。

Holcomb 等^[40]采用 RNA 测序技术分离弹性蛋白酶诱导的兔动脉瘤模型瘤体和左颈总动脉信使 RNA 和 miRNA,结果显示瘤体侧与左颈总动脉相比有 143 个基因表达上调,471 个基因表达下调,同时伴有 5 个 miRNA 表达上调,3 个 miRNA 表达下调,一些关键信号转导通路如炎症反应和抗原呈递等也存在差异表达;表明该模型在动脉瘤生长、愈合和破裂中发挥重要作用,支持该模型可作为基础性实验动物模型。

5 发展方向

目前制作的弹性蛋白酶诱导的兔颈总动脉瘤模型并不能完全体现颅内动脉瘤病变过程,其瘤周围环境与人颅内动脉瘤存在较大差异,且难以形成自发性破裂出血。有研究发现动脉瘤患者常伴有 I 型或 III 型胶原纤维基因突变,因此胶原纤维可能在动脉瘤自然生长中起着重要作用^[41]。Kang 等^[42]报道

在弹力酶处理基础上结合胶原酶处理瘤段,理论上可增加动脉瘤自发破裂机会。经弹性蛋白酶和胶原酶处理构建兔颈总动脉瘤模型在形态结构、组织结构、自然发展史和血流动力学特点上与人颅内动脉瘤更接近,可能具有广阔的研究前景。

Kainth 等^[43]研究提出通过血管外途径对动脉瘤模型制作进行改进,即以精致细尖刷将高浓度弹性蛋白酶涂布于动脉瘤瘤顶,可大大减少弹性蛋白酶用量,且经实验证明足以诱导动脉瘤形成;Verhoeff-VanGieson(VVG)染色证实此方法诱导的动脉瘤模型组织病理学特征与血管内途径制作方法完全相同。Fahed 等^[44]质疑兔颈总动脉瘤模型是否具有足够挑战性用于血流导向装置测试,因为高孔隙率支架已实现对其完全闭塞,不具挑战性的动脉瘤模型将导致对新器械材料性能高估,为此构建梭形动脉瘤模型,以测试血流导向装置和新材料不同性能;血管造影结果显示梭形动脉瘤明显大于囊状动脉瘤,且复杂梭形动脉瘤模型在植入血流导向装置后闭塞率明显高于植入双枚高孔隙率支架和单枚高孔隙率支架,因此初步认为复杂梭形动脉瘤模型是一种更大、更复杂和更具挑战性的动脉瘤模型,可用于检测新材料不同性能并探索治疗失败潜在原因。本中心近期在 Wang 等^[20]报道基础上对动脉瘤模型进行改进,尝试采用 2 个 C 型动脉瘤夹分别夹闭头臂干远端和右锁骨下动脉近端,具体效果还需更多动物模型和影像学检查加以证实。该方法优点是使动脉瘤颈暴露得更完全,以获得相对较宽颈动脉瘤模型,且在很大程度上降低实验操作难度。

[参 考 文 献]

- [1] Hughes JD, Bond KM, Mekary RA, et al. Estimating the global incidence of aneurysmal subarachnoid hemorrhage: a systematic review for central nervous system vascular lesions and meta-analysis of ruptured aneurysms[J]. *World Neurosurg*, 2018, 115: 430-447.
- [2] Guglielmi G, Vinuela F, Dion J, et al. Electrothrombosis of saccular aneurysms via endovascular approach. Part 2: Preliminary clinical experience[J]. *J Neurosurg*, 1991, 75: 8-14.
- [3] Serbinenko FA. Balloon catheterization and occlusion of major cerebral vessels[J]. *J Neurosurg*, 1974, 41: 125-145.
- [4] Guglielmi G, Vinuela F, Duckwiler G, et al. Endovascular treatment of posterior circulation aneurysms by electrothrombosis using electrically detachable coils[J]. *J Neurosurg*, 1992, 77: 515-524.
- [5] Ma L, Xu JC, Yan S, et al. A single-center experience in the endovascular treatment of carotid siphon aneurysms using the Willis covered stent: a retrospective analysis[J]. *J Neurointerv Surg*, 2018, 10: 1197-1202.
- [6] Gu Y, Gu B, Li Y, et al. Endovascular treatment of blood blister-like aneurysms in the internal carotid artery using a Willis covered stent[J]. *J Intervent Med*, 2018, 1: 157-163.
- [7] Fiorella D, Lylyk P, Szikora I, et al. Curative cerebrovascular reconstruction with the pipeline embolization device: the emergence of definitive endovascular therapy for intracranial aneurysms[J]. *J Neurointerv Surg*, 2009, 1: 56-65.
- [8] Pierot L, Costalat V, Moret J, et al. Safety and efficacy of aneurysm treatment with WEB: results of the WEBCAST study[J]. *J Neurosurg*, 2016, 124: 1250-1256.
- [9] Wang W, Wang YL, Chen M, et al. Magnesium alloy covered stent for treatment of a lateral aneurysm model in rabbit common carotid artery: an in vivo study[J]. *Sci Rep*, 2016, 6: 37401.
- [10] Arat A, Daglioglu E, Akmangit I, et al. Bioresorbable vascular scaffolds in interventional neuroradiology[J]. *Clin Neuroradiol*, 2018, 28: 585-592.
- [11] Wang J, An Q, Li D, et al. Heparin and vascular endothelial growth factor loaded poly (l-lactide-co-caprolactone) nanofiber covered stent-graft for aneurysm treatment[J]. *J Biomed Nanotechnol*, 2015, 11: 1947-1960.
- [12] Kallmes DF, Helm GA, Hudson SB, et al. Histologic evaluation of platinum coil embolization in an aneurysm model in rabbits[J]. *Radiology*, 1999, 213: 217-222.
- [13] Hans FJ, Krings T, Moller-Hartmann W, et al. Endovascular treatment of experimentally induced aneurysms in rabbits using stents: a feasibility study[J]. *Neuroradiology*, 2003, 45: 430-434.
- [14] Kim BM, Kim DJ, Kim DI. A new flow-diverter (the FloWise): in-vivo evaluation in an elastase-induced rabbit aneurysm model[J]. *Korean J Radiol*, 2016, 17: 151-158.
- [15] Nishi S, Nakayama Y, Ishibashi-Ueda H, et al. Treatment of rabbit carotid aneurysms by hybrid stents (microporous thin polyurethane-covered stents): preservation of side-branches[J]. *J Biomater Appl*, 2014, 28: 1097-1104.
- [16] Altes TA, Cloft HJ, Short JG, et al. 1999 ARRS Executive Council Award. Creation of saccular aneurysms in the rabbit: a model suitable for testing endovascular devices. American Roentgen Ray Society[J]. *AJR Am J Roentgenol*, 2000, 174: 349-354.
- [17] Ding Y, Dai D, Kadirvel R, et al. Five-year follow-up in elastase-induced aneurysms in rabbits[J]. *AJNR Am J Neuroradiol*, 2010, 31: 1236-1239.
- [18] Krings T, Moller-Hartmann W, Hans FJ, et al. A refined method for creating saccular aneurysms in the rabbit[J]. *Neuroradiology*, 2003, 45: 423-429.
- [19] Hoh BL, Rabinov JD, Pryor JC, et al. A modified technique for using elastase to create saccular aneurysms in animals that histologically and hemodynamically resemble aneurysms in human[J]. *Acta Neurochir (Wien)*, 2004, 146: 705-711.
- [20] Wang K, Huang Q, Hong B, et al. Neck injury is critical to elastase-induced aneurysm model[J]. *AJNR Am J Neuroradiol*, 2009, 30: 1685-1687.
- [21] Ding YH, Dai D, Lewis DA, et al. Can neck size in elastase-induced aneurysms be controlled? A retrospective study[J]. *AJNR Am J*

- Neuroradiol, 2006, 27: 1681-1684.
- [22] Onizuka M, Miskolczi L, Gounis MJ, et al. Elastase-induced aneurysms in rabbits: effect of postconstruction geometry on final size[J]. AJNR Am J Neuroradiol, 2006, 27: 1129-1131.
- [23] Wang Y, Emeto TI, Lee J, et al. Mouse models of intracranial aneurysm[J]. Brain pathology (Zurich, Switzerland), 2015, 25: 237-247.
- [24] Fahed R, Gentric JC, Salazkin I, et al. Flow diversion of bifurcation aneurysms is more effective when the jailed branch is occluded: an experimental study in a novel canine model[J]. J Neurointerv Surg, 2017, 9: 311-315.
- [25] Matsuda Y, Chung J, Lopes DK. Analysis of neointima development in flow diverters using optical coherence tomography imaging[J]. J Neurointerv Surg, 2018, 10: 162-167.
- [26] Hashimoto N, Kim C, Kikuchi H, et al. Experimental induction of cerebral aneurysms in monkeys[J]. J Neurosurg, 1987, 67: 903-905.
- [27] Wang S, Dai D, Kolumam Parameswaran P, et al. Rabbit aneurysm models mimic histologic wall types identified in human intracranial aneurysms[J]. J Neurointerv Surg, 2018, 10: 411-415.
- [28] Short JG, Fujiwara NH, Marx WF, et al. Elastase-induced saccular aneurysms in rabbits: comparison of geometric features with those of human aneurysms[J]. AJNR Am J Neuroradiol, 2001, 22: 1833-1837.
- [29] Zeng Z, Kallmes DF, Durka MJ, et al. Hemodynamics and anatomy of elastase-induced rabbit aneurysm models: similarity to human cerebral aneurysms?[J]. AJNR Am J Neuroradiol, 2011, 32: 595-601.
- [30] Meng H, Wang Z, Kim M, et al. Saccular aneurysms on straight and curved vessels are subject to different hemodynamics: implications of intravascular stenting[J]. AJNR Am J Neuroradiol, 2006, 27: 1861-1865.
- [31] Ding YH, Dai D, Lewis DA, et al. Angiographic and histologic analysis of experimental aneurysms embolized with platinum coils, Matrix, and HydroCoil[J]. AJNR Am J Neuroradiol, 2005, 26: 1757-1763.
- [32] White PM, Lewis SC, Gholkar A, et al. Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial[J]. Lancet (London, England), 2011, 377: 1655-1662.
- [33] Adibi A, Eesa M, Wong JH, et al. Combined endovascular coiling and intra-aneurysmal allogeneic mesenchymal stromal cell therapy for intracranial aneurysms in a rabbit model: a proof-of-concept study[J]. J Neurointerv Surg, 2017, 9: 707-712.
- [34] Zhou G, Su M, Yin YL, et al. Complications associated with the use of flow-diverting devices for cerebral aneurysms: a systematic review and meta-analysis[J]. Neurosurg focus, 2017, 42: E17.
- [35] Fahed R, Raymond J, Ducroux C, et al. Testing flow diversion in animal models: a systematic review[J]. Neuroradiology, 2016, 58: 375-382.
- [36] Fahed R, Darsaut TE, Gentric J, et al. Flow diversion: what can clinicians learn from animal models?[J]. Neuroradiology, 2017, 59: 255-261.
- [37] Kolumam Parameswaran P, Dai D, Ding YH, et al. Downstream vascular changes after flow-diverting device deployment in a rabbit model[J]. J Neurointerv Surg, 2019, 11: 523-527.
- [38] Mallik AS, Nuss K, Kronen PW, et al. A new-generation, low-permeability flow diverting device for treatment of saccular aneurysms[J]. Eur Radiol, 2014, 24: 12-18.
- [39] Li Z, Zhao R, Fang X, et al. AMD3100 accelerates reendothelialization of neointima in rabbit saccular aneurysm after flow diverter treatment[J]. World Neurosurg, 2017, 107: 416-423.
- [40] Holcomb M, Ding YH, Dai D, et al. RNA-sequencing analysis of messenger rna/microrna in a rabbit aneurysm model identifies pathways and genes of interest[J]. AJNR Am J Neuroradiol, 2015, 36: 1710-1715.
- [41] Meng Q, Hao Q, Zhao C. The association between collagen gene polymorphisms and intracranial aneurysms: a meta-analysis[J]. Neurosurg Rev, 2019, 42: 243-253.
- [42] Kang W, Connor J, Yan X, et al. A modified technique improved histology similarity to human intracranial aneurysm in rabbit aneurysm model[J]. Neuroradiol J, 2010, 23: 616-621.
- [43] Kainth D, Salazar P, Safinia C, et al. A modified method for creating elastase-induced aneurysms by ligation of common carotid arteries in rabbits and its effect on surrounding arteries[J]. J Vasc Interv Neurol, 2017, 9: 26-35.
- [44] Fahed R, Darsaut TE, Salazkin I, et al. Testing stenting and flow diversion using a surgical elastase-induced complex fusiform aneurysm model[J]. AJNR Am J Neuroradiol, 2017, 38: 317-322.

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