·综　述　General review·

Pipeline™ 栓塞装置治疗颅内动脉瘤术后并发症研究进展

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【摘要】 近年来颅内动脉瘤血管内治疗发展迅速。新型血流导向装置——Pipeline™ 栓塞装置(PED)以重建载瘤动脉血流分布为创新，已广泛应用于临床，尤其是治疗颅内复杂动脉瘤取得了良好的临床效果。然而由于其金属覆盖率高，流量转移治疗后出现动脉瘤破裂、自发脑实质出血、分支动脉闭塞等并发症并不少见，且致残致死率较高，临床上须引起足够重视。该文就 PED 治疗颅内动脉瘤术后并发症研究进展作一综述。

【关键词】 Pipeline™ 栓塞装置；颅内动脉瘤；血流导向装置；并发症

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Progress in study on Pipeline embolization device treatment for postoperative complications of intracranial aneurysm

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【Abstract】 In recent years, endovascular treatment of intracranial aneurysms has been developed rapidly. Pipeline embolization device (PED), which is a novel blood flow guiding device, can creatively reconstruct the blood flow distribution of the aneurysm-bearing artery, and it has been widely employed in clinical practice. Satisfactory curative effect has been achieved by PED for intracranial aneurysms, especially for complex intracranial aneurysms. However, because of its high metal coverage rate, the complications such as aneurysm rupture, spontaneous cerebral parenchymal hemorrhage, branch artery occlusion, etc. are not uncommonly seen in patients after receiving flow divertion treatment, and the mortality rate is higher, to which sufficient attention should be paid by clinicians. This paper aims to make a review on the research progress concerning the postoperative complications of PED in the treatment of intracranial aneurysms. (J Intervent Radiol, 2017, 26: 760-764)

【Key words】 Pipeline embolization device; intracranial aneurysm; flow guiding device; complication

颅内动脉瘤发病率较高，破裂风险随时间增加而升高。动脉瘤一旦破裂造成蛛网膜下腔出血将严重危及生命，国外报道约有 40%动脉瘤破裂会导致致命性蛛网膜下腔出血，仅 1/3 患者预后良好[1]。传统治疗方法包括外科手术夹闭和血管内介入栓塞，ISUIA、ISAT、BRAT 等大型临床试验研究均证实这两种治疗方法对减少入瘤血流的有效性及安全性[2-4]，但对复杂颅内动脉瘤如大型/巨大、宽颈、串联多发或梭型动脉瘤，均无法取得令人满意的临床疗效。

近年来血管内治疗发展迅速，尤其是血流导向装置问世，使得颅内动脉瘤治疗迈上一新台阶[5-6]。区别于既往治疗理念，血流导向装置以载瘤动脉血运重建为创新点，通过降低入瘤血流流速、流量，促进动脉瘤腔内血栓形成及瘤颈处内膜生长，达到治疗动脉瘤目的[5]。北美和欧洲近期已展开多项关于 Pipeline™ 栓塞装置(PED，美国 ev3 公司/Covidien 公司)临床应用的多中心临床研究。Becske 等[7-8]报道北美多中心前瞻性临床试验研究(PUFS)结果，PED 治疗复杂颈内动脉颅内动脉瘤 180 d、1 年、3 年随访时完全闭塞率分别为 73.6%、86.8%、93.4%。O'Kelly 等[9]研究显示，PED 治疗复杂颅内动脉瘤 1 年随访时次全以上闭塞率为 90%。许多研究[8-11]均证实PED 治疗复杂颅内动脉瘤的有效性。

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随着 PED 治疗颅内动脉瘤越来越普及,手术相关并发症受到神经介入医师广泛关注。美国学者 Kallmes 等[12]研究分析 6 个国家 17 所临床中心接受 PED 治疗的 793 例患者,手术相关致残率为 8.4%,致死率为 3.8%;后循环动脉瘤发生率明显高于前循环。Brinjikji 等[13]meta 分析 29 项研究,PED 术后致残率约 5%,死亡率约 4%。如何防治 PED 手术相关并发症显得尤为重要。

PED 术中和术后并发症主要分为出血性和缺血性。出血性并发症主要有动脉瘤破裂和脑实质出血,缺血性并发症主要有分支动脉闭塞、支架内狭窄/闭塞等,其它相关并发症有术中血管壁损伤所致夹层、血管破裂及颈动脉海绵窦瘘等。

1 出血性并发症

1.1 术后动脉瘤破裂

PED 植入术后发生动脉瘤破裂较为少见,但破裂后往往会造成灾难性后果。相关报道显示,该并发症发生率约为 3%[13]。Kan 等[14]研究中 56 例患者 58 枚动脉瘤植入 PED,术后 2 例发生致命性动脉瘤破裂。Fox 等[15]报道 1 例患者 PED 植入术后 7 d 发生动脉瘤破裂致死, 开颅探查发现动脉瘤顶端撕裂,病理生理学检查显示破裂处瘤壁相比正常动脉瘤壁更加菲薄,导致变薄的瘤壁承受不住瘤腔内压而破裂。关于术后动脉瘤破裂机制研究较多,得到较多认同的有动脉瘤壁自溶学说和血流动力学改变学说。

有学者研究发现,PED 植入术后动脉瘤破裂常发生在 PED 置放并瘤腔内急性血栓形成后, 且大型、巨大动脉瘤风险较高,推测短期内大量血栓形成可能是动脉瘤壁不稳定的高危因素[16]。PED 置放并覆盖在瘤颈口处后,流至动脉瘤顶端的血流逐渐减缓,加速了血栓形成。一项关于腹主动脉瘤研究发现, 血栓形成同时其内白细胞可能分泌释放、激活一些蛋白酶,如基质金属蛋白酶(MMP)-2、MMP-9 及丝氨酸蛋白酶等;颅内动脉瘤形成血栓后可能同样产生这些高蛋白水解活性蛋白酶[17]。这些酶可能参与了动脉瘤壁结构成分降解,造成动脉瘤壁自溶或炎性反应,使瘤壁变得不稳定而诱发动脉瘤破裂[18-19]。动脉瘤越大,血栓化越迅速,可能产生的蛋白酶就越多,可加剧瘤壁削弱。最新动物实验研究表明,PED 植入显著增加了血液中前体 MMP-9 表达, 联合弹簧圈栓塞治疗动脉瘤可降低血液中 MMP-2、MMP-9 水平, 这可能是降低术后破裂风险的方法之一;环孢素治疗对预防术后破裂几乎无效果[20]。动脉瘤壁自溶学说仍需大型临床前研究加以验证。

血流动力学改变学说认为,PED 植入对动脉瘤内及载瘤动脉血流动力学影响毋庸置疑,可明显降低入瘤血流, 但有关研究发现入瘤血流虽有降低,瘤腔内瘤壁所受压力并未明显减小[21],原因可能是支架植入后动脉瘤内血液因 PED 作用淤滞,也可能是动脉瘤内短期血栓形成出现瘤腔临时性膨大,导致动脉瘤内压未发生明显变化,潜在地诱发动脉瘤破裂。

计算流体动力学模型可评估术前相关风险,如模拟支架置放后动脉瘤内压潜在变化[22]。计算流体动力学模型研究提示动脉瘤内压未明显降低,可能与治疗后动脉瘤壁削弱导致罕见破裂出血有关,其机制尚未完全阐明[16,23]。这项评估可能会成为一种预测患者 PED 植入后发生破裂出血事件风险的手段。

1.2 自发脑实质出血

与 PED 治疗动脉瘤后发生动脉瘤破裂相比,远端其它部位迟发性脑实质出血(intraparenchymal haemorrhage,IPH)更加难以解释。PED 植入血管内有血流动力学和动脉顺应性改变,术后数月双抗血小板药物维持治疗通常也会有稍高出血风险。术中医源性栓塞、内皮损伤或导管所致血管痉挛引起的缺血性卒中,也是潜在的出血转化风险。对这种不可预测、具有潜在毁灭性后果的并发症发生机制研究十分重要。多项研究发现大部分 IPH 发生于 PED 术后 1 个月内。有研究显示 PED 植入术后出现 IPH 概率约为 3%, 动脉瘤大小与部位均与 IPH 发生概率无关[13]。另一项研究中 7 所临床中心 449 例患者接受 PED 治疗后,有 11 例(2.4%)于 21 d 内出现 IPH,其中 1 例死亡,1 例出现严重残疾(改良Rankin 量表评分 5 分)[24]。

PED 植入术后自发性 IPH 原因尚未明确,一般认为可能与数种因素相关:①抗血小板药物作用。双抗血小板药物应用被认为是增加出血事件发生概率和脑实质血肿大小的危险因素[25],且高血压患者抗血小板药物治疗与 IPH 发生有关。既往多项研究认为,普通支架辅助栓塞动脉瘤相对 PED 植入术后出现 IPH 并发症较低[26-28]。然而近期研究发现,支架差异可能并非影响 IPH 发生的主要因素[29]。支架治疗后出血或缺血并发症发生分别与氯吡格雷高反应或抵抗有关[30-31]。血栓弹力图和抗血小板药物

基因测定可综合评估抗血小板药物抵抗程度,用于指导抗血小板药物应用策略调整。目前对如何调整用药策略尚未达成共识,仍需相关研究证实其预防 IPH 的有效性。②血流动力学改变。PED 网孔密度较高,对瘤腔及载瘤动脉有良好血流导向作用[32]。有研究认为术中术后血流动力学改变不仅涉及瘤腔及载瘤动脉,对远端血管及分支血管的影响也不可忽视[23]。PED 血流导向作用可能会提高载瘤动脉血压波动峰值,其变化传导至远端流域增加远端血管及其分支压力,可能会导致高灌注综合征,引发 IPH[33]。然而一项无载瘤动脉狭窄模型研究表明动脉瘤远端血管压力,并未随 PED 术后血流动力学改变有显著变化[34]。但动脉瘤远端血管血流动力学改变研究,对于预防 IPH 仍具有重要意义。③介入材料脱落。有研究对 3 例 PED 术后 IPH 死亡患者脑组织作组织病理学分析,镜下发现患者脑出血区域部分小血管均由某种异物材料堵塞,后经分析确定为聚乙烯吡咯烷酮(PVP)[35]。导管保护鞘等大部分介入器材的涂层中均含 PVP,术中操作可能会使之脱落进入血管,导致血管损伤;也有学者认为可能是远端小血管栓塞后缺血灶出血转化所致。然而 Brinjikji 等[36]研究表明,未发现既往认为与 IPH 密切相关的 Shuttle 指引导管,与 PED 术后 IPH 有明显关系;发现 PED 治疗破裂动脉瘤及植入 3 枚以上 PED 是发生 IPH 的高危因素。PED 术后 IPH 由多因素所致,介入材料涂层栓塞可能是导致 IPH 的因素之一。

2 缺血性并发症

缺血性并发症发生相对容易解释。PED 金属覆盖率为 35%,高于普通支架,且为了起到更好的血流导向作用,通常将其压缩得更致密。金属覆盖率越高,血栓形成及血管内膜增生可能会越旺盛。PED 植入所致缺血性并发症发生率为 6%,而后循环动脉瘤发生率更高[13]。一般认为缺血性并发症发生原因,主要包括植入多枚 PED、手术时间较长及治疗后循环动脉瘤等。Brinjikji 等[37]研究表明,793 例患者906 枚动脉瘤经 PED 治疗后 36 例患者(4.5%)出现急性缺血性卒中,其中 10 例死亡,26 例出现致残性并发症;发现梭形动脉瘤与术后缺血性并发症相关。术后载瘤动脉血栓形成及内膜增生可能导致以下缺血性并发症。

2.1 分支动脉闭塞

颈内动脉重要分支有眼动脉、脉络膜前动脉、大脑前动脉、后交通动脉等。植入 PED 后随着血管内血栓形成或内膜增生,载瘤动脉处细小分支动脉往往受累,表现为血管内血流减慢甚至闭塞。但由于颅内血管有 Willis 环及颈外动脉系统、脑膜支等代偿供血,即使影像学证实某些分支血管如眼动脉、大脑前动脉等闭塞,临床症状表现往往并不十分严重。相关文献报道 PED 术后半年随访中 DSA 证实被 PED 覆盖的眼动脉、后交通动脉闭塞率分别为 10.5%、10.7%,2 例被覆盖的大脑前动脉均闭塞,未发现被覆盖的脉络膜前动脉闭塞,闭塞患者均无临床症状[38]。但也因个体差异,对缺血程度耐受较差及代偿血管供血不足,均可能导致神经功能缺损。另有研究发现,早期识别急性血栓形成造影征象(分支血管闭塞和流动迟滞),早期应用血小板糖蛋白Ⅱb/Ⅲa 受体拮抗剂(如替罗非班、阿昔单抗),可有效防止严重缺血性并发症[39]。

此外,术前术后测定血小板功能并依据结果调整用药策略,可能会降低 PED 术后发生严重缺血并发症风险[39]。但一项回顾性分析抗血小板药物反应性研究显示,接受血小板功能测定患者并发症及致残、致死率均明显高于未接受血小板功能测定患者[40]。这一现象的根本原因尚不明确,血小板功能测定应用仍需进一步研究。

2.2 支架内狭窄/闭塞

PED 植入术中发生急性支架内狭窄或闭塞并不少见,主要原因为术中技术操作问题,导致支架内急性血栓形成。术中血栓形成风险随着技术不断成熟及改进逐渐降低。有研究表明,支架辅助栓塞颅内动脉瘤术中常规泵入替罗非班安全有效,可预防支架内急性血栓形成[41]。因此,推荐 PED 植入术中常规应用替罗非班,以减少术中缺血并发症发生。需要注意的是,手术当天泵入替罗非班需停止口服抗血小板药物,直至停止泵入前 2 h 泵入量减半,并改为双抗药物口服。

PED 植入术后出现迟发支架内狭窄或闭塞相对更为多见,一般认为是内膜过度增生所致。Chalouhi 等[42]报道 139 例患者 PED 植入术后半年造影随访显示,21 例(15.8%)出现载瘤动脉狭窄,其中 6 例狭窄程度较重(>75%),但大部分往往无症状。这些迟发的支架内狭窄或闭塞通常与停止服用抗血小板药物有关。PED 治疗颅内动脉瘤关键之一在于促进内膜增长,但如何防止内膜过度增长,仍需进一步研究。现有治疗手段主要有球囊扩张,包括药物洗脱球囊等新型器材。需要注意的是,扩张过程中一

旦发生血管夹层,一般需在 PED 装置内重叠置放自膨式支架,以保证血管通畅及夹层贴壁,防止进一步出现严重神经功能缺损。

3 其他并发症

PED 植入术后动脉瘤一般会因血流改变而缩小,但也有患者出现占位效应所致压迫症状,考虑可能与瘤腔内血栓形成增大有关。也有相关报道术中导丝头端断裂残留在载瘤动脉远端情况,但一般不会导致严重并发症。有文献报道术中出现 PED 迟发塌陷、短缩情况,可能与 PED 装置本身不足有关[43-44]。以上并发症发生较为罕见,但也应引起足够重视。

此外,操作过程中损伤血管壁可能会导致夹层形成、血管破裂或颈动脉海绵窦瘘,造成严重并发症。尽管血管壁损伤风险随着介入器械更新及操作熟练度提升越来越低, 但对管壁硬化严重患者,术中仍需格外谨慎操作。

4 结语

经过临床不断实践,PED 治疗颅内复杂动脉瘤的复发率相比传统血管内治疗低,但并发症发生率仍明显高于单纯弹簧圈栓塞及支架辅助栓塞。尤其是对巨大动脉瘤及超适应证应用于后循环动脉瘤,更应警惕相关并发症发生。PED 结合弹簧圈栓塞治疗动脉瘤可能会降低术后破裂风险,但直接证据尚未发现。抗血小板药物应用是防止缺血性并发症发生关键,但最佳给药方案和持续时间仍需进一步研究。总之,PED 并发症发生机制仍需相关临床研究和基础研究阐明。特别是对出血性并发症研究,重点应放在血流动力学改变及病理生理学等基础方面。相信随着相关机制进一步明确,PED 相关并发症发生率将会大大降低,从而提升 PED 治疗预后及临床疗效,并拓宽其适应证,解决更多临床难题。

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