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血流导向装置治疗颅内动脉瘤的研究进展

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摘 要

颅内动脉瘤(IAs)的血管内治疗在过去几十年中有了长足的发展。弹簧圈栓塞无法治疗所有动脉瘤，发生动脉瘤的载瘤动脉亦需要治疗，以及常规介入在治疗复杂动脉瘤的局限性推进了技术进步。颅内支架最初是为栓塞宽颈动脉瘤时支持弹簧圈而研发的。早期对支架状管状编织结构的研究孕育出了一种更复杂的结构，后来被称为分流器(flow diverter, FD)，并进入临床应用。FDs最初用于治疗宽颈大或巨大的颈内动脉瘤。随后，我们见证了FDs应用的爆发式增长，并对其不断进行改进，引来了其在血管内治疗中的广泛应用。本文中，我们将从其作用机制及在不同场景下使用的优缺点做一综述。

关键词

颅内动脉瘤，血流导向装置，蛛网膜下腔出血

Research Progress on the Treatment of Intracranial Aneurysms with Flow Diverters

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Abstract

Endovascular treatment of intracranial aneurysms (IAs) has evolved considerably over the past decades. The technological advances have been driven by the experience that coils fail to completely exclude all IAs from the blood circulation, the need to treat the diseased parent vessel segment leading to the aneurysm formation, and expansion of endovascular therapy to treat more complex IAs. Stents were initially developed to support the placement of coils inside wide neck

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aneurysms. However, early work on stent-like tubular braided structure led to a more sophisticated construct that then later was coined as a flow diverter (FD) and found its way into clinical application. FDs were initially used to treat wide-neck large and giant internal carotid artery aneurysms. We have witnessed an explosion in the application of FDs and subsequently their modifications leading to their ubiquitous use in endovascular therapy.

Keywords

Intracranial Aneurysm, Flow Diverters, Subarachnoid Hemorrhage

1. 背景

随着 Guido Guglielmi 在 20 世纪 90 年代早期引入可拆卸线圈[1]，并增加了辅助装置(颅内支架、球囊、预成形和可成形微导管)，血管内治疗成为了治疗破裂和(或)未破裂颅内动脉瘤(intracranial aneurysm, IA)手术的替代方法[2] [3]。然而，治疗后完全闭塞率占接受治疗患者的三分之一，复发率占五分之一[4]。如遇到较大的宽颈动脉瘤，由于其形态复杂、瘤颈宽大等原因，复发率可能更高。在一项针对破裂动脉瘤的国际研究中，动脉瘤栓塞术后完全闭塞率只有 55%，24%的动脉瘤部分闭塞，而 18%的动脉瘤无法治疗。动脉瘤栓塞的主要缺点在于高达 40%的病例中难以将弹簧圈致密地置入到动脉瘤腔内，从而导致动脉瘤再通复发，尤其在大、巨大动脉瘤中更常见[5]。血流导向装置的出现，弥补了动脉瘤栓塞上述的不足[6] [7]。在这个过程中 Wakhlo 和 Lieber 等人推动了用于血管重建的腔内支架的开发，并将其称为“分流器”(flow diverters, FDs) [8]。本文将对血流导向装置治疗颅内动脉瘤的研究进展做一综述。

2. 定义

FDs 的主要目的是阻断载瘤动脉与动脉瘤体之间的血流，同时为血管提供血管内支架，以修复因动脉瘤形成的血管损伤。其治疗效果取决于血流导向装置本身与载瘤动脉、动脉瘤大小、侧支循环和穿支血管间的相互作用，其中最关键的是血流导向装置的空隙率和孔密度[9] [10]。孔隙率是指孔隙面积与装置总面积之比，孔密度是指单位面积内孔的总数。

$$孔隙率(\%) = (总表面积 - 金属表面积)/总表面积 \times 100\%$$

研究表明，最大至 70%的孔隙率和最小值 18 孔/平方毫米的孔密度是最理想的参数[9] [11] [12]，在这个参属下可实现最理想的动脉瘤闭塞率的同时保持被 FDs 覆盖的侧支血管长达 3~6 个月的血液供应[9] [10]。这是血流导向装置的一大特点。

血流导向装置另一个特点在于其释放过程当中的可预测性。即释放过程中 FDs 在血管内缩短的程度是可预测的，通过判断其缩短程度可选择合适的大小而避免误判[13] [14]。与此同时，随着虚拟仿真仪器的引用，术中可在术前即可预测 FDs 的变形特点，这些仪器的应用有助于缩短 FDs 产品参数与实际使用情况间的误差[13] [14]。

3. 作用机制

FDs 的作用机制可分为三个阶段：血流动力学改变、血栓形成和内皮化[15]。血流动力学改变在放置

FDs 后立即发生。网孔产生的阻力限制血液流入动脉瘤，尽管造影时瘤体内可见造影剂显影，但是瘤体内的血流速度和相对压力随即明显降低[12]。随后通过复杂的途径立即激活血小板，在数天至数周内逐渐形成稳定的血栓(即血栓形成阶段)。动脉瘤内血栓的形成取决于动脉瘤及瘤颈的大小，血流导向装置的参数，患者自身血小板以及抗血小板药物的相互作用。在此过程中占位效应和(或)炎症可能会进一步加重，导致术前症状进一步加重(如有术前症状)。内皮化阶段可持续数月至数年，此过程中，无定形血栓最终转化为胶原蛋白，同时 CD34+内皮祖细胞驱使 FDs 内皮化[16]。FDs 支撑血管重塑并内皮化，同时胶原蛋白最终使动脉瘤变小。FDs 的出现与发展为难以完成动脉瘤栓塞或显微手术的患者带来了另一种选择。

4. 抗血小板聚集

由于 FDs 是金属材质，需要双重抗血小板聚集治疗(dual antiplatelet therapy, DAPT)来降低血栓栓塞的风险。阿司匹林和氯吡格雷是最常用的抗血小板药物。在颅内未破裂动脉瘤治疗中使用抗血小板药物可降低围手术期血栓栓塞发生率[17] [18] [19]，抗血小板药物诱导颅内出血时有发生，如何把出血及血栓形成的发生率都降到最低，是困扰临床医生的难题。

5. FDs 在 Willis 环及远端动脉瘤中的应用

由于 Willis 环及末端血管解剖特点，用 FDs 治疗远端的动脉瘤比较困难。载瘤动脉直径 ≤ 3 mm，而且常伴有重要分支血管和穿支血管，导致 FDs 治疗时缺血性并发症发生概率更高[20] [21] [22]。尽管远端动脉瘤中使用 FDs 达到了 82%的动脉瘤闭塞率，仍发生了多达数十种并发症。在一项单中心研究指出，使用 PED 治疗 A1 段动脉瘤患者中 8.3%患者发生了缺血性卒中[18]。在另一项研究中，PED 治疗更远端的 A2，M2，P2 段动脉瘤，观察到 7.7%患者发生了缺血性和(或)出血性并发症，其中 4.6%位于 M2 段动脉瘤[22]。事实上，大脑中动脉动脉瘤发生缺血性并发症的风险较高[23]。

另一方面，远端血管弯曲度大，容易导致释放 FDs 时缩短明显[24]。再者，归因于前期 FDs 输送系统体积大、柔韧性不足，导致 FDs 难以准确释放，需要用多个 FD 来充分覆盖动脉瘤颈，从而增加缺血性并发症的发生[25]。部分专家建议遇到过于迂曲的血管时选择略微过大的装置来应对 FDs 的缩短[24]。然而这样会导致 FDs 过长，增加孔隙率，降低金属覆盖率，从而影响治疗效果。Cagnazzo 等人使用前几代 FDs 治疗远端动脉瘤的荟萃分析中观察到，在 484 个治疗过的动脉瘤中，使用多个 FDs 比使用单个 FD 的闭塞趋势更高(OR 2.3，95% CI 0.8 至 7.2；$p = 0.08$)，可能与装置尺寸过大有关[23]。

如 FRED Jr., p48MW，SVB 等新一代 FDs 的问世解决了前几代 FDs 在远端血管上遇到的技术难题。它们娇小的外形和可输送性有助于它们在弯曲的小血管中输送，以治疗具有挑战性的远端位置的动脉瘤，以至于能够以单个 FDs 实现前几代多个 FDs 才能达到的遮挡率[20] [24] [26] [27]。与此同时，体积的缩小也有可能随之带来了以 FDs 辅助弹簧圈栓塞来即时永久闭塞动脉瘤同时保护远端血管的可能性。Mario 等人进行的一项 Silk Vista Baby (SVB)分流装置治疗颅内动脉瘤的研究中，报道了 13 例破裂动脉瘤患者行 SVB 辅助弹簧圈栓塞治疗，术后复查提示 13 例患者动脉瘤均完全闭塞，未发生缺血性并发症[26]。当然上述可能性仍需进一步仔细研究。

6. FDs 在治疗破裂的颅内动脉瘤中的应用

如前面所提到，治疗急性破裂出血的复杂动脉瘤时，FDs 可作为除介入栓塞及显微夹闭之外的第三种选择。血泡样动脉瘤的动脉瘤壁薄而脆弱，夹层动脉瘤和梭形动脉瘤没有真正意义上的动脉瘤颈，阔颈动脉瘤和位于血管分叉处的动脉瘤置入的弹簧圈稳定性不足，使得这些病变难以用常规显微夹闭术或栓塞术来治疗[28]。抗血小板药物的抗凝作用，以及 FD 置入后不会立即形成血栓闭塞动脉瘤，FDs 治疗急性蛛网膜下出血时再出血风险依然高，因此 FDs 治疗急性蛛网膜下出血仍存在争议。最近一项 meta

分析中，评估了 223 例接受 FD 治疗动脉瘤破裂导致急性 SAH 患者。结果显示平均 9.6 个月的影像学随访中，动脉瘤即时闭塞率为 32%，长期闭塞率为 88.9%。总体而言，缺血性和出血性并发症分别为 8%和 7%，在后循环动脉瘤中和(或)置入多个 FDs 后并发症发生率更高[25]。

虽然还没有相关对照研究，新一代药物涂层装置(如 Pipeline Shield，p48_HPC，Derivo 等)配 SAPT 作为次选替代方案[29] [30]。Pipeline Shield 配 SAPT 治疗急性动脉瘤破裂的一项研究共报道 14 例患者，其中 2 例发生动脉瘤再破裂出血，其中 1 例死亡。每日口服阿司匹林+注射肝素的治疗组出血事件和缺血事件发生率最高，发生率均为 14.3%。而单用阿司匹林的治疗组缺血事件发生率仅为 7.1%。每日两次服用阿司匹林组未发生并发症。aSAH 发生 7 天后完全闭塞率为 85.7% [26]。p48_HPC 配 SAPT 治疗的一项研究共报道 8 例急性动脉瘤破裂患者，4 例术中幸好曾血栓，其中 2 例死于严重的脑血管痉挛。未发生术后再破裂出血。平均 6 个月的随访中，6 例患者中 5 例动脉瘤完全闭塞[30]。

7. FDs 在后循环动脉瘤中的应用

FDs 治疗后循环动脉瘤的致死致残率均较高[31] [32] [33]。其中部分原因是由于 FDs 置入后后循环众多穿支血管或者装置内形成血栓从而导致严重脑梗。在一项单中心研究者，12 例椎基底动脉瘤患者接受 PED 治疗，平均 14.5 个月的随访中，10 例显示动脉瘤完全闭塞，1 例出现缺血性并发症[34]。Bender 等人的研究中，55 例后循环动脉瘤患者接受 PED 治疗，术后 6 个月和 12 个月时的完全比赛率分别为 68%和 78%。5 例(9%)发生严重的缺血性卒中，2 例死亡。研究者建议后循环 FDs 置入患者术后 24 小时全身肝素化并终身使用双抗，以降低缺血性并发症发生的风险[29]。我们认为，FDs 治疗后循环动脉瘤仍需要更多研究。

8. 结论

FDs 已成为血管内治疗大部分颅内动脉瘤的新趋势。FDs 的广泛应用、所总结的经验、科学技术的迅速发展在脑血管病治疗领域中开辟了新的道路。我们应该更加谨慎的进一步研究其有效性和安全性。此外，可用的设备种类繁多，需要神经介入医生至少精通其中的一种，同时进一步了解其他设备优势及局限性。随着 FDs 在多种临床场景中使用的增加，需要针对特定动脉瘤解剖结构、位置和形态进行设计定制，以涵盖更广泛的临床适应症。

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