

·综述 General review·

颅内动脉瘤血管内治疗现状与进展

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【摘要】 颅内动脉瘤破裂出血具有极高的致残率和致死率。随着技术方法、材料发展及神经介入医师经验积累,血管内治疗已成为降低破裂颅内动脉瘤再出血率和死亡率的首选治疗方法。血管内治疗主要历经载瘤动脉和动脉瘤闭塞、动脉瘤瘤腔内栓塞和载瘤动脉重建等3个研究阶段,其中应用最广泛的是瘤腔内栓塞治疗,包括单纯弹簧圈、液体栓塞剂、瘤腔内栓塞装置、球囊/支架辅助技术等。载瘤动脉重建(覆膜支架和血流导向装置)也是近期研究热点。尽管新材料和新技术发展,但难治性动脉瘤如宽颈动脉瘤血管内治疗复发率仍较高。为了完全隔绝颅内动脉瘤或实现瘤颈完全内皮化,载药弹簧圈/支架、生物可降解支架等正在研究中。

【关键词】 颅内动脉瘤; 血管内治疗; 弹簧圈; 支架; 蛛网膜下腔出血

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[Abstract] Ruptured intracranial aneurysm with bleeding has high morbidity and mortality. With the advancement of technology, the development of materials and the accumulation of experience of neuro-interventional physicians, endovascular therapy has become the first choice for reducing the rate of re-bleeding and mortality of ruptured intracranial aneurysms. Endovascular therapy has mainly gone through three stages of research, including, in chronological order, the occlusion of the parent artery of aneurysm and the aneurysm itself in the first stage, the embolization of aneurysmal cavity in the second stage, and the reconstruction of the parent artery of aneurysm in the third stage. The most widely used treatment among the above therapies is the embolization of aneurysmal cavity with various embolization materials or techniques, which include simple spring coil, liquid embolizing agent, embolization device for aneurysmal cavity, balloon/stent-assisted technique, etc. The reconstruction of the parent artery of aneurysm (covered stent and flow diverter device) is a hot spot of recent researches. Despite the development of new materials and technologies, the recurrence rate of intractable aneurysms, such as wide-necked aneurysms, is still very high. In order to completely isolate intracranial aneurysm or to achieve complete endothelialization of the aneurysmal neck, the new kind of stent and new materials of stent such as drug-eluting coils and stents, biodegradable stents, etc. are being studied at present.(J Intervent Radiol, 2018, 27: 592-597)

[Key words] intracranial aneurysm; endovascular treatment; spring coil; stent; subarachnoid hemorrhage

颅内动脉瘤是颅内动脉管壁病理性突起,发病率为5%~10%,MRA研究表明我国35~75岁成年人未破裂动脉瘤发病率约为7.0%^[1]。虽然颅内动脉瘤破裂引起的蛛网膜下腔出血约占脑卒中5%,但

首次破裂死亡率为20%~30%,再次破裂死亡率高达60%。随着技术方法、材料发展及神经介入医师经验积累,血管内治疗已成为颅内动脉瘤首选治疗方法,有助于明显降低破裂动脉瘤再出血率及死亡率。根据颅内动脉瘤性状、大小和部位等特点,血管内治疗主要历经载瘤动脉和动脉瘤闭塞、动脉瘤瘤腔内栓塞和载瘤动脉重建等3个研究阶段。

1 颅内载瘤动脉和动脉瘤闭塞

苏联神经外科医师 Serbinenko 发明可脱式球囊, 继成功治愈 1 例外伤性颈内动脉海绵窦瘘后率先治疗 1 例基底动脉顶端动脉瘤和 1 例后交通动脉动脉瘤^[2]。可脱式球囊在 20 世纪 70 年代和 80 年代风靡一时, 目前仍用于闭塞巨大动脉瘤载瘤动脉, 是颅内动脉瘤治疗重要辅助技术。同时闭塞载瘤动脉和动脉瘤的血管内治疗类似于外科孤置(trapping)技术, 虽能阻断载瘤动脉血流并中止动脉瘤瘤腔内血流, 但明显影响颅内血流动力学, 远期增加了脑缺血发生率。有学者认为同时闭塞载瘤动脉和动脉瘤疗法仍是治疗难治性动脉瘤的一种选择, 尤其是对大/巨大动脉瘤或后循环椎动脉夹层动脉瘤及其附属分支远段夹层动脉瘤, 目前主要应用弹簧圈或液体胶闭塞载瘤动脉和动脉瘤。

2 颅内动脉瘤瘤腔内栓塞

颅内动脉瘤瘤腔内栓塞治疗起源于外科电凝技术, 最初在瘤腔内电凝形成血凝块。受此启发, Guglielmi 等率先设计电解脱弹簧圈(GDC)填塞动脉瘤瘤腔, 其基于电凝和电解脱原理, 阳极可吸附血流中白细胞、红细胞、血小板和纤维蛋白原等负电荷成分, 形成血栓即电凝, 同时通过惰性金属铂制成的弹簧圈与不锈钢传输线连接即形成电解脱。弹簧圈自最初的裸圈发展至表面修饰弹簧圈、放射性弹簧圈以及液体胶和瘤腔内栓塞装置, 旨在更加致密地填塞动脉瘤, 降低复发率和再出血率, 促进瘤颈内皮化。

2.1 单纯弹簧圈栓塞

20 世纪 80 年代末就有学者采用弹簧圈治疗大动脉瘤模型和颅内动脉瘤, 证明弹簧圈可治疗某些特定动脉瘤, GDC 治疗颅内动脉瘤具可行性、有效性和安全性。随后 GDC 便迅速广泛应用于临床, 尤其是 1995 年美国食品药品监督管理局(FDA)认证后, 成为血管内治疗颅内动脉瘤的重大创新。2002 年一项“国际蛛网膜下腔出血动脉瘤临床试验(ISAT)”研究首次报道迄今最大病例组(2 143 例)颅内破裂动脉瘤患者治疗结果, 术后 1 年随访显示弹簧圈栓塞组患者($n=801$)死亡率(23.7%)低于外科夹闭组($n=793$)(30.6%)^[3]; 并于 2005 年、2009 年和 2015 年陆续报道随访结果, 进一步证实血管内弹簧圈栓塞破裂颅内动脉瘤安全有效, 可降低早期再出血率和远期致死率^[4]。但远期复发率和再出血率仍高于外科夹闭术, 究其原因主要在于单纯瘤腔

内弹簧圈填塞不能有效完成瘤颈内皮化, 外科手术夹闭则有效地促进了内皮化。GDC 治疗颅内动脉瘤组织病理学研究发现, 瘤腔内血凝块和血栓防止了再出血, 瘤颈口覆盖有一层不同于内皮化的细长细胞固体瘢痕形成, 虽可降低早期再出血率, 但远期随访仍存在较高复发率和再出血率, 尤其是宽颈动脉瘤。这是临幊上一亟待解决的问题。为此, 三维弹簧圈、表面修饰弹簧圈和放射性弹簧圈等一系列新型弹簧圈随之而生, 旨在防止和降低颅内动脉瘤复发率和再出血率, 促进瘤颈内皮化。

三维弹簧圈俗称成篮圈, 目的是为了更致密和方便地填塞宽颈动脉瘤, 防止弹簧圈受血流冲击进一步压缩。Vallee 等^[5]总结 8 个临幊中心 160 例颅内动脉瘤患者, 得出三维弹簧圈可有效提高宽颈动脉瘤填塞率。Wakhloo 等^[6]进一步证实了三维弹簧圈的疗效。

表面修饰弹簧圈有水凝胶弹簧圈、生物活性涂层弹簧圈及带纤毛弹簧圈。水凝胶涂层具有膨胀性, 可增加单位长度弹簧圈体积密度。有研究发现水凝胶弹簧圈具有明显更大的体积栓塞率(84.8%/29.8%), 降低了弹簧圈长度和 X 线辐射时间, 且随访造影发现颅内动脉瘤复发率和再治疗率明显降低(10%/17%)^[7]。Serafin 等^[8]meta 分析研究 1 683 例颅内动脉瘤经水凝胶弹簧圈治疗结果, 其动脉瘤复发率低于裸弹簧圈治疗。动物模型研究显示, 水凝胶弹簧圈比铂金弹簧圈增加了瘤颈新生内皮和渗透弹簧圈团块的血管化纤维结缔组织覆盖。生物活性涂层弹簧圈(如 Matrix、Cerecyte)是在铂金弹簧圈表面覆盖了一层生物可吸收聚合物(90%聚乙醇酸和 10%聚乳酸)。文献中关于 Matrix 弹簧圈研究较 Cerecyte 弹簧圈多。Murayama 等^[9]动物模型研究显示, Matrix 弹簧圈置入后 12 d 观察到新生内皮几乎完全覆盖动脉瘤瘤颈, 术后 14 d 完全由纤维膜覆盖; 证实颅内动脉瘤经 Matrix 弹簧圈治疗后瘤颈新生内皮形成和纤维化得以增强, 可防止瘤体再通。Taschner 等^[10]采用单纯 Matrix 弹簧圈治疗 6 例、Matrix 弹簧圈联合 GDC 治疗 19 例颅内动脉瘤患者, 结果显示 Matrix 弹簧圈联合 GDC 治疗效果更显著。但 Pierot 等^[11]前瞻性多中心研究发现 Matrix 弹簧圈和裸弹簧圈单独栓塞治疗颅内动脉瘤中期闭塞率和复发率差异均无统计学意义。而且 Cerecyte 弹簧圈和 Nexus 纤毛弹簧圈远期随访结果仍不明确^[12]。

放射性弹簧圈是在普通铂金弹簧圈基础上离子注入 0.13~0.26 mCi/cm³²P 制成, 其 β 射线能防

止弹簧圈栓塞后再通。但实验结果并不一致^[13-14],且放射性弹簧圈安全性仍在进一步研究中。

2.2 瘤腔内血流装置

目前应用的瘤腔内血流装置均为弹簧圈延伸产物,如编织型腔内桥梁(woven endobridge, WEB)装置。它是瘤腔内扰流装置,由镍制金属线编制而成,专为宽颈和分叉部动脉瘤治疗设计,理论上可从瘤颈水平中断动脉瘤内血流,促进瘤囊内血栓形成,降低复发率。一项 meta 分析总结 15 篇文献 588 枚颅内动脉瘤,WEB 装置即刻完全闭塞率、次全闭塞率分别为 27%、59%,中期随访完全闭塞率、次全闭塞率分别为 39%、85%;中期随访临床证据表明宽颈动脉瘤和分叉部动脉瘤栓塞率优于支架辅助弹簧圈,尤其是破裂宽颈动脉瘤,但仍需远期临床证据^[15]。近年 Kwon 等^[16]也研究报道一种类似于 WEB 的瘤腔内卵形金属网状自膨胀装置(Luna),动物实验发现术后 3 个月该装置表面被内膜组织完全覆盖,动脉瘤瘤腔内有疏松结缔组织填充,瘤颈有新生内膜组织形成。还有新型瘤腔内血流装置——Medina 栓塞装置^[17],初步研究结果提示该装置可使颅内动脉瘤从循环中快速隔离,但远期效果有待进一步研究观察。

2.3 液体栓塞剂

由于大型/宽颈颅内动脉瘤及其它复杂动脉瘤用弹簧圈或其它辅助栓塞技术不能达到理想的完全栓塞率,有学者尝试应用液体栓塞剂治疗。继 2002 年首次报道液体栓塞剂 Onyx HD-500 胶栓塞巨大颅内动脉瘤后,陆陆续续有这一新技术的研究报道。该技术栓塞率较高,但外渗和穿支血管闭塞是其严重并发症^[18]。目前已很少作为瘤腔内栓塞剂填塞治疗颅内动脉瘤。

2.4 辅助栓塞技术

瘤体破裂、瘤体大、颈宽、位于后循环、弹簧圈栓塞率低,均为弹簧圈栓塞后再通和复发的危险因素。报道显示弹簧圈栓塞后远期再治疗率为手术夹闭术后 6.9 倍^[19],因此各种提高栓塞率和降低复发率的辅助栓塞技术逐渐发展起来。最初辅助技术包括微导管和微导丝辅助弹簧圈栓塞颅内动脉瘤,在此不多赘述。

球囊辅助弹簧圈栓塞技术旨在防止弹簧圈突入载瘤动脉和术中破裂出血,常用于治疗颅内宽颈和小/微小动脉瘤。Moret 等 1997 年最早报道血管内球囊辅助技术治疗 56 例颅内动脉瘤。Pierot 等^[20]2011 年多中心前瞻性研究分析经单纯弹簧圈栓塞

和球囊辅助栓塞治疗颅内动脉瘤破裂患者,结果就围手术期并发症和临床疗效而言,两种技术安全性相似,球囊辅助并不增加围手术期出血和血栓等并发症。目前文献中还有双球囊辅助技术的报道,这项技术可用于累及大脑中动脉主干动脉瘤和前交通动脉巨大动脉瘤等血管内治疗。

支架辅助弹簧圈填塞技术已广泛应用于血管内治疗颅内动脉瘤,其优点:①防止弹簧圈突入载瘤动脉;②更加致密栓塞动脉瘤,提高栓塞率,降低复发率;③重塑载瘤动脉;④重塑瘤颈,方便其内皮化,部分实现重建瘤颈。罕见的尸检病理研究提示 Neuroform 支架植入术后 4 个月支架完全内皮化,颅内动脉瘤颈有明显新生弹性纤维组织^[21]。脑血管支架研究始于 20 世纪 90 年代。Wakhloo 等^[22]早期采用球扩式钽支架和自膨式镍钛支架治疗颈内动脉瘤模型,发现球扩式钽支架治疗后瘤颈残留率较高,植入支架血管段最大狭窄率达 40%,而自膨式镍钛支架治疗后未见不完全栓塞,植入支架血管段狭窄率不超过 15%,但球扩式钽支架治疗后内皮纤维细胞组织增长明显好于自膨式镍钛支架治疗。2002 年首枚专为颅内动脉设计的自膨式开环支架 Neuroform 问世,拉开了动脉瘤治疗史再次飞跃的序幕。此前很多学者尝试外周支架治疗颅内动脉瘤,后来陆续出现有 Leo 支架、Enterprise 支架和 Solitaire 支架等。中远期随访研究显示支架辅助弹簧圈比单纯弹簧圈栓塞的颅内动脉瘤闭塞率更高,再通率更低。近年陆续又出现低剖面可视化腔内支架(LVIS)、Barrel 支架、Acandis Acclino 支架、pCONus 支架和 PulseRider 支架装置等^[23-27]。尽管这些新型支架装置中期研究均取得了一定成果,但尚需远期随访进一步证明有效性和安全性。目前支架辅助弹簧圈技术包括单支架辅助和多支架辅助,前者又分为支架外微导管弹簧圈栓塞技术和经支架网眼微导管弹簧圈栓塞技术,后者包括平行技术(重叠和并排)、X 型、Y 型和 T 型支架技术等,常用于治疗复杂宽颈和分叉部颅内动脉瘤。有研究报道采用 Y 型和 X 型支架技术治疗 193 例分叉部动脉瘤,技术成功率达 98.5%,随访 186 例动脉瘤再通率仅 2.2%,表明多支架技术安全有效,为宽颈动脉瘤提供了远期有效的治疗方法^[28]。支架辅助弹簧圈栓塞技术易引起血栓栓塞事件,且需长期抗血小板聚集治疗。虽然支架植入术后抗血小板聚集治疗至今无统一标准,但越来越多急性破裂颅内动脉瘤应用支架辅助治疗,其风险和获益需进一步研究。

3 截瘤动脉重建

随着技术发展和临床医师认识提高,颅内动脉瘤已被认为是截瘤动脉母体血管病理改变所致,因此重建截瘤动脉可从根本上治愈该疾病。目前覆膜支架和血流导向装置临床应用为颅内动脉瘤治疗提供了新方法,成为颅内动脉瘤治疗史上又一革新。母体血管腔内隔绝技术能克服现有血管内介入治疗技术及材料不足,达到直接隔绝动脉瘤,重建母体动脉目的,从而恢复病变区域正常血流动力学,使病变自行愈合。

3.1 覆膜支架

Saatci 等^[29]2004 年率先报道采用 Jostent 外周覆膜支架成功治愈 25 例颅内动脉瘤,且超过 6 个月随访无动脉瘤再通,表明覆膜支架治疗颈内动脉瘤切实有效。Li 等^[30-31]在我国率先设计颅内血管专用球膨式覆膜支架——Willis 支架,其优点是覆盖动脉瘤瘤口,即刻隔绝动脉瘤并重建截瘤动脉,术后 12 个月完成内皮化,达到永久闭塞动脉瘤目的;经动物实验和临床试验后已成功进入大规模临床应用,目前可治疗颅内段颈内动脉假性动脉瘤、复发或原发囊性动脉瘤、外伤性假性动脉瘤和外伤性颈动脉海绵窦瘘等病变,技术成功率达 97.6%,远期随访表明该支架可重建截瘤动脉。但 Willis 覆膜支架仍存在支架贴壁不良和迟发性支架内狭窄等缺陷和内皮化延迟问题,有望在新一代支架研究中得到改进。临幊上目前仍采用各种外周覆膜支架治疗颅内动脉瘤,而颅内专用覆膜支架经历实验终止后,近年又有学者开始新的实验研究^[32]。

3.2 血流导向装置

血流导向装置是在自膨式支架基础上发展而来,由数十根金属丝编织成致密金属管状结构(不同于前述普通支架,其金属覆盖率常低于 15%,而普通支架高于 30%,甚至达 50%),具有良好的径向支撑力,能改变动脉瘤瘤颈和瘤腔血流动力学,促进血栓形成和重建截瘤动脉腔,为血管内膜重建提供载体。临幊前动物实验表明血流导向装置能有效闭塞动脉瘤模型,不影响分支血管,术后 1 个月即有瘤颈胶原内膜增生,3~6 个月瘤颈处新生内膜增厚,表明装置合适设计及良好贴壁能促进动脉瘤早期愈合^[33-34]。人体病理研究显示单纯血流导向装置治疗巨大或梭形血栓动脉瘤存在不能完成内皮化风险,可能需要联合弹簧圈治疗^[35]。

临幊应用最广泛的是 Pipeline 支架装置,已发展至第 3 代,不仅改进了输送和释放技术,而且涂

有合成磷酸胆碱聚合物,可减少血栓形成。5 年随访研究显示,Pipeline 支架完全闭塞率由术后 6 个月 73.6% 提高至术后 5 年 95.2%,进一步证实其远期有效性和安全性;其适应证由最初治疗成人岩段至垂体上段颈内动脉大型/巨大型宽颈动脉瘤扩大至小动脉瘤、夹层动脉瘤及远端小血管动脉瘤等^[36-37]。目前临幊应用的还有 Silk、Surpass、FRED、P64 和国产 Tubridge 支架装置,它们的远期疗效将拭目以待。Lubicz 等^[38]报道新一代 Silk 支架治疗颅内动脉瘤,47 例患者术后 22 个月中期随访表明治疗安全有效。Wakhloo 等^[39]报道多中心采用 Surpass 支架治疗颅内动脉瘤,结果显示其安全性好,闭塞率高。Luecking 等^[40]、Briganti 等^[41]分别报道表明 FRED 支架、P64 装置治疗颅内动脉瘤安全有效。Zhou 等^[42]报道初步提示国产 Tubridge 支架治疗颅内巨大动脉瘤有效。但血流导向装置仍然存在至今无法解决的困惑,如穿支血管闭塞、累及分支血管的瘤体不能完全闭塞、延迟性动脉瘤破裂出血及脑内出血等。

4 技术发展

为治疗特殊颅内动脉瘤研制的微小弹簧圈(1 mm)、超大 P400 弹簧圈及改进后具血流导向作用的新型混合 eCLIPs 装置目前已开始临幊应用。实验研究仍在探索和开创颅内动脉瘤治疗新技术——生物可降解覆膜支架/吸收支架、载药弹簧圈、多孔覆膜支架或覆膜血流导向支架,以及射频治疗等^[43-45]。此外,术中 CT 能及时发现术中并发症并确认支架准确定位,为血管内治疗颅内动脉瘤保驾护航,在此不赘述。

近年有学者应用生物可吸收支架治疗颅内动脉瘤,可能代表了新技术发展方向^[46]。改良支架及其衍生物表面附着物(如附着超薄镍钛诺涂层或不对称补片、可降解生物膜、特殊药物支架已在研发中),将避免和减少围手术期血栓事件、术后抗血小板聚集药物需求,并关键地促进内皮化进程^[47-49]。本综述所涉及技术与方法均毫无例外地在于确保血管内治疗颅内动脉瘤安全性和远期有效性,颅内血管覆膜支架和血流导向装置研究将殊途同归,生物降解支架是目前发展的重要方向。

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