

经皮经肝肝内门体分流术后肝性脑病发病机制及其预防

刘 锋, 张春清

■背景资料

食管胃底静脉曲张出血和顽固性腹水是肝硬化失代偿期严重并发症, 传统的内科保守治疗远期效果差, 外科切脾+断流或者外科分流, 创伤性大, 而且对患者肝功储备等一般情况要求较高, 且外科分流分流口径难于控制往往会造成反复肝性脑病。TIPS应用后, 由于操作简便、安全、创伤小, 曾备受临床重视, 但TIPS后支架狭窄和术后肝性脑病的问题始终困扰着TIPS的发展。

刘锋, 张春清, 山东大学附属省立医院消化科 山东省济南市 250021

作者贡献分布: 刘锋整理文献, 写作论文, 张春清进行审校。
通讯作者: 张春清, 250021, 山东省济南市, 山东大学附属省立医院消化科. zhchqing@medmail.com.cn

电话: 0531-86701339

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Pathogenesis of hepatic encephalopathy and its prevention after transjugular intrahepatic portosystemic shunt

Feng Liu, Chun-Qing Zhang

Feng Liu, Chun-Qing Zhang, Department of Gastroenterology, Provincial Hospital Affiliated to Shandong University, Jinan 250021, Shandong Province, China

Correspondence to: Chun-Qing Zhang, Department of Gastroenterology, Provincial Hospital Affiliated to Shandong University, Jinan 250021, Shandong Province, China. zhchqing@medmail.com.cn

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Abstract

With the increasing use of transjugular intrahepatic portosystemic shunt (TIPS), we have obtained a breakout progress in the therapy of acute esophageal and gastric-fundus variceal bleeding and refractory ascites. whereas the patency of stent and hepatic encephalopathy (or namely portal-systemic encephalopathy, PSE) after TIPS become two great problems for TIPS. The patency of stent has been improved greatly after the use of covered stent such as Viator stents or covered vascular stents. But the problem of hepatic encephalopathy has not been well solved. In this review, we try to explore the pathogenesis of hepatic encephalopathy and its prevention after TIPS.

Key Words: Transjugular intrahepatic portosystemic shunt; Hepatic encephalopathy; Portal systemic encephalopathy

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摘要

随着经皮经肝肝内门体分流技术(transjugular intrahepatic portosystemic shunt, TIPS)的不断应用, 其在食管胃底静脉曲张破裂出血和顽固性腹水的治疗方面, 取得了突破性进展。然而, TIPS术后支架的狭窄闭塞和反复高发的肝性脑病(hepatic encephalopathy, HE)或称为分流性脑病(portal-systemic encephalopathy, PSE)成为困扰TIPS技术发展的两大难题, 前者在近期带膜(血管)支架的大量应用后, 得到极大的改善; 后者始终未得到根本的解决, 我们参阅了国内外的最新资料, 在此进一步阐述TIPS术后另一难题-肝性脑病的发生情况。

关键词: 经皮经肝肝内门体分流; 肝性脑病; 分流性脑病

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0 引言

肝硬化是各种慢性肝病(病毒性肝炎、酒精性肝病、自身免疫性肝病等)的终末阶段, 尤其在肝硬化失代偿期。由于肝脏被持续性破坏, 肝脏假小叶形成, 使门脉回流障碍而引起门脉高压, 侧枝循环的形成, 此时往往并发上消化道出血、腹水等并发症。对于首次发作的上消化道出血、腹水情况保守的内科治疗一般能起到效果。但是伴随着疾病的进展, 肝硬化后上消化道出血、腹水的发生很可能越来越频繁, 达到1年发生3-5次上消化道出血或腹水内科保守治疗后无效、对症放腹水后很快重复出现(2-5 d), 此时如继续内科保守治疗不仅花费大, 而且治疗效果差且患者因并发症而死亡的可能增大。过去TIPS治疗前外科处理不仅患者创伤大、对患者肝功储备要求高, 而且术后肝性脑病发生极高并且门脉血栓高发严重影响患者肝移植的手术,

■同行评议者

张吉翔, 教授, 南昌大学第二附属医院消化内科; 李靖, 副教授, 中国人民解放军第三军医大学新桥医院肝胆外科

从而广受争议. 自TIPS应用后, 由于其创伤小、治疗效果明显, 基本替代外科手术治疗门脉高压及其并发症, 并且为患者活体肝移植提供了等待机会, 曾备受临床重视, 但TIPS后支架狭窄和术后肝性脑病的问题始终困扰着TIPS的发展, 而近年来覆膜支架应用后远期通畅率得到极大的改善, 被誉为“TIPS第二个春天来临”, 随着TIPS应用的不断增加, 使TIPS后肝性脑病的控制摆在了一个更加突出的位置.

1 经皮经肝肝内门体分流

经皮经肝肝内门体分流(transjugular intrahepatic portosystemic shunt, TIPS)由Rosch于1969年首先进行动物实验研究. 1989年Richter首次用于临床, 特别是20世纪90年代初, 自膨式支架问世后, 其临床应用不断增多. TIPS指穿刺颈内静脉成功后, 通过导丝、导管、穿刺针的配合, 在肝内建立肝静脉和门脉的分流通路, 通过降低门脉压力, 而达到治疗效果. 主要用于治疗门脉高压引起的食管胃底静脉曲张破裂出血(acute variceal bleeding), 反复的难于控制的腹水(refractory ascites), 肝移植前的等待准备等, 术后以支架狭窄和肝性脑病为主的并发症的发生率极高, 严重束缚了其应用. 因此目前TIPS主要用于内镜治疗无效的急性上消化道出血或肝移植前的术前准备. 自TIPS应用开始到大约20世纪末主要应用裸支架, 由于TIPS在肝内穿刺后造成的胆道损伤从而引起胆汁漏出, 漏出到血管内造成不同程度的黄疸, 漏出到支架周围造成不断的炎性刺激从而引起支架的狭窄或闭塞(胆汁漏出学说). 据大量的回顾性研究证实, 1年狭窄率约为50%-70%, 2年狭窄率为80%-100%^[1-3,5,6,8,18-19,23,25,27,33,40,42,44,47,66], 因此其应用受到极大的束缚. 20世纪初始, 覆膜血管支架和Viator TIPSS专用支架的应用, 极大地降低了支架的狭窄率. 据目前观察资料研究, 覆膜支架的1年狭窄率约为0%-20%, 2年狭窄率约为20%-40%^[1-3,7,11,23,25,27,33,39-40,42,44,57]. 有人因此将覆膜支架应用后, 支架问题的解决誉为“TIPS治疗的第二个春天的来临”, 然而, TIPS术后肝性脑病的问题始终未得到解决^[7,13-14,27-28,58], 甚至在覆膜支架应用后某种程度的加重肝性脑病的发生. 故肝性脑病的解决或许是覆膜支架应用后, 影响TIPS治疗的“最后一个寒冬”^[2-3,11,23,25,49-51,55,66,71].

2 TIPS后分流性脑病的发生机制

TIPS后分流性脑病发生机制, 目前认为主要是分流引起或加重的体内含氮物质增多(主要以

血 $\text{NH}_3/\text{NH}_4^+$ 为主)引起的中枢神经系统的功能紊乱. 与肝性脑病相同, 主要是血氨浓度的增加引起脑内兴奋性和抑制性神经递质的失调, 表现为精神的兴奋或抑制. 分流性脑病(portal-systemic encephalopathy, PSE)与肝性脑病(hepatic encephalopathy, HE)不同主要表现在分流引起或加重的HE: 主要通过(1)直接分流; (2)分流后引起肝脏血流的变化; (3)分流后引起脑血流的改变而起作用, 分述如下.

2.1 直接分流 TIPS后肝内建立的门体分流通路, 使部分肠道吸收的营养物质及细菌代谢产物未经肝脏解毒而直接进入体循环, 进入体内各个器官, 进入到脑内. 细菌代谢产物导致血脑屏障开放后, 从而使肠道吸收的含氮物质更容易进入脑内引起脑功能的紊乱, 其对PSE的发生主要与分流口径密切相关, 口径的大小某种程度上决定了PSE/HE的发生, 口径过大导致分流量的增多, 含氮物质的增多, 超过中枢神经系统的承受能力, 最终引起PSE/HE的发生^[1,10,13-14,16,18,28-29,34,48,59].

2.2 分流后肝脏血流的变化 肝脏是一个巨大的代谢器官, 对肠道吸收的物质起着解毒作用, 其营养物质70%靠门脉供血来提供. 门脉血流的减少使肝细胞供血减少, 肝细胞受损甚至引起肝脏的缺血坏死, 损伤肝功能. 因此TIPS后肝脏门脉血流的变化影响着肝脏功能的变化, 肝脏功能的改变又某种程度上决定了体内血氨浓度的变化, 从而决定了PSE/HE的发生. 因此, TIPS术中分流的同时肝脏门脉血流的保护对术后肝性脑病的发生起着主要作用^[15-16,26,41,49,56,60,67,69-70,72].

2.3 分流后脑血流的改变 Jalan *et al*^[65]观察到, TIPS后脑内血流增多, 颅内压增加, 从而引起脑水肿, 加重或引起脑功能的紊乱, 而未行TIPS治疗的患者被观察到存在毛细血管阻力的增加, 从另一方面解释了TIPS后脑血流量暂时增加后引起脑水肿的机制, 即灌流量增加. 脑功能的改变还被观察到, 在发生反复出血、低钠血症的患者中更容易发生. 脑水肿是直接因为TIPS分流引起还是继发于TIPS后肝损伤目前未明^[4,21,45-46,54,61-65,75].

总之, TIPS术后发生肝性脑病的机制不明, 具体情况, 尚待进一步观察研究. 目前来看, TIPS后发生的PSE可进一步区别为: PSE I 和 PSE II, PSE I 主要指分流后即发生的PSE, 在没有高蛋白进食、感染、电解质紊乱、消化系出血等诱因的情况下发生的PSE, 多在术后1 mo内发生, 直接与分流口径(或术后肝脏血流动力

■研究前沿

随着腹膜支架应用, TIPS在肝硬化治疗中的作用得到进一步体现, 然而术后高发肝性脑病的情况更加凸显出来, 严重影响着其在治疗中的应用.

■相关报道

TIPS后肝性脑病在TIPS应用之初既被大家观察到,也投入不少研究,其中Chung *et al*、Maleux G *et al*在控制支架口径方面、Jacquier *et al*在根据患者术前肝功能方面、Deng *et al*、张家宝 *et al*在观察术前后肝血流方面、Chu *et al*在左右支选择上分别阐述了控制TIPS后肝性脑病或者探讨TIPS后肝性脑病发病机制,使我们大家得到珍贵的研究资料。

学的改变)和术前肝功能相关,常规的内科治疗效果差;PSE II,分流后未产生PSE,主要指在分流的基础上,与体循环大量有毒物质增多相关,分流后在分流的基础上高蛋白进食、感染、电解质紊乱、消化系出血等诱因的情况下发生的PSE,常规的内科治疗效果好。

3 影响因素与预防

3.1 支架口径与门脉压力 外科全分流之所以渐被外科限制性分流和TIPS分流所替代,一个主要原因就是分流口径未能很好控制,导致术后门脉压力过低,引起难治的分流性脑病的发生。限制性分流和TIPS的应用极大地改善了这一点,为探求门脉压力在不引起致命并发症的情况下,能降低得最大限度,Chung *et al*^[3]研究得出: TIPS后门脉压应 ≥ 5 mmHg(敏感性100%,特异性72%),否则会引起致命的并发症。关于支架的口径目前较为一致观点认为TIPS支架口径应 ≤ 10 mm,最大应不超过12 mm,分流口径过大并引起门脉压力过度降低而造成难治性分流性脑病,主要根据门脉压力情况做调整。Maleux *et al*^[9]通过观察介入前后门脉压力变化来观察TIPS术后肝性脑病的发生情况,并对术后发生肝性脑病的患者重新测压发现其分流后平均门脉压为6.8 mmHg(范围为2-16 mmHg),进一步对患者进一步平行支架植入后患者PSE明显改善,说明在某种特定的因素下PSE的发生与支架口径决定的门脉压力的降低密切相关。Lyon *et al*^[6]报道,在PSE后,进一步平行支架的原TIPS支架拐角处的植入明显的纠正PSE I发生,进一步证实,支架口径以及由此决定的术后门脉压力的变化某种程度上决定了PSE的发生,因此术中需根据情况,严格控制支架的口径。

3.2 术前肝功能 大量的研究证实^[1-2,36,74], Child-Push分级中Child-Push C级患者较Child-Push A、B级患者分流后PSE的发生率更高,Child-Push分级中, A、B、C级组,肝性脑病的发生情况分别为32%、51%、100%,术前的肝功能某种程度上决定了分流的口径。其中Jacquier *et al*^[22]在术前评价肝功能,对Child-push分级3级中根据以往的经验术后倾向于发生PSE的Child-push B、C级患者进行分步分流的方法,首先给予口径为6 mm分流,2-6 mo后继续将口径扩大到10 mm,取得满意的效果,术后PSE发生明显减少,术后2 mo未发生死亡病例。进一步说明术前肝功能对术后PSE的影响,并给

出了针对术前倾向发生PSE的患者合理的分流方法: 口径由小到大的分步分流的方法,渐进性影响肝功能,从而达到预防分流性脑病发生的目的。

3.3 术前后肝脏血流的变化 我国Deng *et al*^[26,72]超声下观察到在肝血流动力学改变对TIPS术后肝性脑病发生的影响,相同分流口径下向肝血流术后PSE的发生明显多于离肝血流,二者术后PSE的发生率分别为32.1%, 15.3%, 分析原因,进一步观察到,肝脏靠门脉系统和肝动脉共同供血,门脉血流的减少一定程度上靠肝动脉代偿,而离肝血流的患者较向肝血流的患者更能适应TIPS术后肝血流改变的影响。张家宝 *et al*^[70]研究进一步根据TIPS术前、后血流的变化,将TIPS术后血流改变分为三级: 将TIPS术后门静脉主干及分支血流均呈向肝型者定为I型(未改变),将TIPS术后仅支架所伸入的门静脉支血流呈离肝型者,其他分支仍为向肝血流者定为II型(部分变化)。将门静脉血流均呈离肝型,血流方向为门静脉左右支 \rightarrow 肝内分流道 \rightarrow 肝静脉定为III型(完全改变),其研究证实肝性脑病的发生III型 $>$ II型 $>$ I型,分别为60%, 14%, 3%, 说明术后肝血流动力学的改变严重影响到PSE的发生。二者均可说明术前术后肝脏血流的变化影响了术后PSE的发生。目前研究更倾向保护向肝血流,因其直接与肝功能相关,而肝功能又影响术后PSE的发生。目前术中向肝血流的保护仍是需要进一步研究的问题。

3.4 左右支的选择 由于右支解剖关系的优越性,大多TIPS治疗倾向于肝右静脉与门脉右支之间建立分流通道。Chu *et al*^[52,73]研究进一步提示采用10 mm分流口径,门脉左支分流后肝性脑病发生率较右支低,术后观察1年,发生率分别为1.47%和6.1%。其分流道再狭窄率亦明显降低,其可能存在的原因是门静脉左支主要供应占肝脏体积20%-25%的左叶的血流,即便是将左支血液完全性分流,也只有约1/4的肝功损害,与门静脉右支分流后造成75%-80%的肝功能损害相比,优势是显而易见。所以行门静脉左支门腔分流患者的肝功能可以受到极大地保护,自然具有较好的远期疗效。另外其进一步的动物实验中证实: 血氨浓度肠系膜上静脉 $>$ 门静脉 $>$ 脾静脉 $>$ 外周静脉,左支分流,主要分流脾静脉学院,进一步减少血氨的向体循环的分流,从而减少PSE的发生; 以上情况说明分流时左右支的选择也对PSE的发生有一定的影响,术中合理的

选择左、右支也能起到一定的预防肝性脑病的作用。

3.5 其他 近期亦对其他因素进行了大量研究,倾向于年龄大者较年龄小者易发;女性较男性易发(国外);非酒精性肝病者较酒精性肝病者易发;既往有肝性脑病史较既往没有肝性脑病患者发生率高,具体机制不详,尚需进一步理论研究证实^[1,37,43,65]。

4 治疗

目前尚没有对PSE发生根治性方法,主要以预防为主。术后1 mo内发生PSE I 首先给以保守的药物治疗,如无效多采用平行支架植入或支架栓塞的方法解决^[12,17,18,20,22,24,30,38],均可对PSE治疗起到满意的效果,但支架栓塞后对术前原发病的治疗起不到治疗,而对术后分流性脑病的控制效果较迅速;相对的平行支架的植入,虽兼顾原发病的治疗,但延长术后分流性脑病的治疗时间;而对倾向于术后发生PSE的患者进行的分步的渐进性的小口径的分流有效的降低了该组患者的PSE的发生, PSE II 的发生主要是在TIPS门体分流的基础上,高蛋白进食、感染、电解质紊乱、消化系出血、大量放腹水、利尿等诱因的情况下,不同程度增加体内血氨的浓度,从而引发PSE。其以分流为基础,在一个或几个不恰当的因素下诱发PSE。在术后限制蛋白,乳果糖、谷氨酰胺、间断抗生素应用后,可以得到较好的预防。治疗主要同非TIPS术HE相同,主要以支链氨基酸、鸟氨酸、谷氨酸钾/钠为主,其中鸟氨酸通过增加肝内氨的转化起作用,降低血氨。支链氨基酸增加肝内蛋白质的合成,减少蛋白质的分解,来降低血氨。谷氨酸钾/钠通过抑制脑内 γ -GABA而起作用^[31-32,35,53,68]。

5 结论

从目前来看,覆膜支架应用后,相同分流口径下确实使PSE发生较前增多, PSE的具体机制仍不十分清楚。倾向于基于分流引起或分流加重的代谢紊乱,与肝性脑病相同主要是含氮物质的增多有关,与分流后引起门脉-肝静脉的短路,引起肝脏血流动力学的变化,以及由此产生的肝功能和脑血流动力学的变化相关;主要和术前肝功能和分流支架的口径及由其决定的术后门脉压力的降低程度密切相关,也与术后向肝血流的保护和左右支的选择相关,以上因素相互关联,都与TIPS术前、后肝脏的血流动力学相

关,对TIPS后肝性脑病的发生起着一定的作用。其他相关因素尚需进一步证实;在治疗方面主要以小口径分步分流方式和术后限制蛋白,乳果糖、间断抗生素应用等预防性治疗措施为主。术后发生PSE I 内科治疗无效后多采用平行支架植入或支架栓塞的方法解决。以上预防措施以及对患者一般状况的对症及时的处理,加上覆膜支架应用后对同一患者实际分流口径减小,我们对TIPS后肝性脑病控制必将得到极大的提高,患者的生活质量将明显改善,必定会是目前带膜支架应用后对TIPS治疗的极大支持。然而,目前亦对TIPS后无明显临床肝性脑病的症状的患者进行研究。证实49%患者中存在轻微肝性脑病或亚临床肝性脑病的情况,其虽不影响患者一般生活,但对患者进行如开车、书写、画画等精细操作受到一定的限制。总体上,覆膜支架应用后确实使TIPS的治疗作用进一步的得到体现,而术后PSE的发生始终没能得到根本解决,仍是TIPS治疗的真正春天来临的又一难题。

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■创新盘点

本文系统、全面、多角度阐述TIPS后肝性脑病的发生、治疗和预防。

■应用要点

本文为TIPS治疗后更好控制肝性脑病提供进一步的理论支持。

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同行评价

本文作者重点综述了近年来有关TIPS后肝性脑病的发生机制、影响因素、预防及治疗方面的进展, 比较全面, 所引用的文献均比较新, 对读者进一步认识TIPS后肝性脑病的发生及其治疗有一定指导作用。

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• 消息 •

2009年广东省中西医结合、中医脾胃消化病学术会议暨 国家级继续教育项目消化病进展研讨班征文通知

本刊讯 由广东省中西医结合学会脾胃消化病专业委员会, 广东省中医药学会消化病专业委员会主办的2009年脾胃消化病学术会议暨国家级继续教育项目消化病进展研讨班将于2009-09-25/27在广东省广州市召开, 现将会议征文有关事项通知如下:

1 征稿内容

中西医结合、中医治疗消化系统疾病的基础理论研究、临床经验总结、诊治的新进展, 名老中医、西医和中西医结合专家个人诊治特色总结.

2 征稿要求

论文资料务必真实可靠, 书写规范, 简明扼要, 每篇以3000字以内为宜, 并附800字左右的摘要1份; 来稿请用电脑打印, 用word软件编入, 并附软盘, 或发送电子邮件, 文稿中请注明作者姓名、单位、通讯地址、邮政编码及联系电话. 截稿日期: 2009-07-30

3 交流方式

专题报告、论文宣读与讨论答疑相结合. 入选论文并参会者给予记I类学分6分, 另外将择优编入《现代消化及介入诊疗》杂志. 参加继续教育研讨班者另给予国家级一类学分12分.

4 投稿地址

(1)E-mail: zhangwdcn@163.com; (2)全文、摘要并附软盘寄至广东省广州市广州大道北1838号南方医院消化编辑部罗永华同志(邮编: 510105); 并注明脾胃消化病学术会议投稿. 无论文者也欢迎参会或报名参加研讨班.

5 联系方式

姚永莉, 510105, 广东省广州市广州大道北1838号, 南方医院消化内科, 电话: 13189096556