

卵圆孔未闭相关神经系统疾病的预防与介入治疗

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【摘要】 卵圆孔未闭与脑卒中、偏头痛、阻塞性睡眠呼吸暂停综合征、减压病等神经系统疾病密切相关,卵圆孔未闭封堵术可有效预防与治疗上述神经系统疾病。本文探讨卵圆孔未闭相关神经系统疾病的发病机制、流行病学和临床特点,以及卵圆孔未闭封堵术治疗上述疾病的潜在问题和未来发展方向,以为卵圆孔未闭相关神经系统疾病的诊断与治疗提供指导。

【关键词】 卵圆孔,未闭; 神经系统疾病; 心间隔封堵装置; 综述

Prevention and interventional treatment of neurological diseases related to patent foramen ovale

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【Abstract】 Patent foramen ovale (PFO) is closely related to neurological diseases such as stroke, migraine, obstructive sleep apnea syndrome (OSAS) and decompression sickness (DCS). It has been suggested that PFO closure could be effectively prevent and treat these neurological diseases. This article focus on exploration of the pathogenesis, epidemiology and clinical characteristics of neurological diseases related to PFO, and to discuss the potential complexity and future development of PFO closure for the treatment of these diseases. The aim is to provide guidance for the diagnosis and treatment of neurological diseases related to PFO.

【Key words】 Foramen ovale, patent; Nervous system diseases; Septal occluder device; Review

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卵圆孔未闭(PFO)是一种临床常见的先天性心脏异常,系成年后房间隔通道未正常融合所致。成人卵圆孔未闭发病率约为25%^[1-2],其中8%~10%可以检测到分流^[3]。卵圆孔未闭与脑卒中^[4]、偏头痛^[5]、短暂性脑缺血发作^[6]、阻塞性睡眠呼吸暂停综合征(OSAS)、减压病(DCS)和抑郁症^[7]等多种神经系统疾病密切相关,提示封堵未闭合的卵圆孔可能有助于上述神经系统疾病的预防与治疗,但目前相关研究较少。本文拟通过回顾文献,探讨卵圆孔未

闭相关神经系统疾病的发病机制、流行病学、临床特点,以及卵圆孔未闭封堵术对神经系统疾病的预防与治疗效果,旨在为卵圆孔未闭相关神经系统疾病的预防与介入治疗提供决策依据。

一、卵圆孔未闭的诊断

卵圆孔是心脏房间隔胚胎期的生理性通道。婴儿出生后,随着肺循环的建立,左心房压力增加,推动原发隔与继发隔融合,使卵圆孔闭合,通常2岁前闭合,有15%~35%至成年仍未闭合,称为卵圆孔未闭^[8]。卵圆孔未闭最早于1877年由德国病理学家Cohnheim在尸检中发现^[9]。20世纪80年代,随着超声心动图和生理盐水对比剂的发展,临床逐渐普及卵圆孔未闭的筛查。常见诊断技术包括经食管超声心动图声学造影(cTEE)、经胸超声心动图声学造影(cTTE)和对比增强经颅多普勒超声(cTCD)。

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经食管超声心动图(TEE)是诊断卵圆孔未闭的“金标准”,可提供对治疗决策有重要指导意义的细节特征,如未闭合的卵圆孔宽度和长度、是否存在房间隔瘤等,但其为半创伤检查,操作过程患者比较痛苦,且检查前需禁食禁水,不适用于初筛;cTTE和cTCD是常用的初筛工具,Meta分析显示,与cTEE相比,cTTE诊断卵圆孔未闭的灵敏度和特异度为45.1%和99.6%,cTCD为96.1%和92.4%^[10],提示cTTE的诊断敏感性较低,cTCD仅可检出右向左分流而无法明确诊断卵圆孔未闭^[11]。因此现有的临床指南建议结合多种诊断技术筛查和诊断卵圆孔未闭;于静息态和Valsalva动作时行cTTE或cTCD,若二者检查结果均为阴性仍疑似卵圆孔未闭时,建议行TEE和cTEE^[12-14]。研究发现,卵圆孔未闭的诊断准确性易受操作细节的影响,例如,cTEE亦存在7.9%的假阴性率,这是由于cTEE需将TEE探头插入食管,患者需镇静,此时行Valsalva动作难以产生高胸内压,右心房压力升高不足^[14]。相关诊断指导方针或共识仍在细节上存有争议,例如,cTCD或cTTE过程中Valsalva动作的实施时间,多数学者建议注射对比剂后行Valsalva动作^[15-17],亦有部分学者主张注射对比剂前或期间行Valsalva动作^[18-19],不同实施时间可导致完全不同的检查结果^[20-21]。此外,右心房对比剂显影后3个心动周期内的左心微泡显影考虑来源于右向左分流(卵圆孔未闭),超过6个心动周期的左心微泡显影则考虑为肺内水平分流,但从何时开始计算心动周期尚无明确规定。上述问题均需更详细和标准化的临床实践进一步指导指南或共识的制订或修订,以指导临床实践。值得一提的是,随着诊断技术的革新,心内超声心动图(ICE)逐渐应用于卵圆孔未闭的诊断与治疗。Moon等^[22]首次对比TEE与ICE引导卵圆孔未闭封堵术的有效性和安全性,发现ICE组X线透视时间 $[(22 \pm 18) \text{ min} \text{ 对} (16 \pm 7) \text{ min}, P = 0.030]$ 、照射剂量 $[(498 \pm 880) \text{ mGy} \text{ 对} (196 \pm 111) \text{ mGy}, P = 0.022]$ 和总手术时间 $[(99 \pm 30) \text{ min} \text{ 对} (67 \pm 12) \text{ min}, P < 0.001]$ 均低于TEE组,而两组手术成功率和住院时间无明显差异。此外,与TEE和超声心动图相比,ICE具有更高的图像分辨率,可以从不同角度准确评估未闭合的卵圆孔大小、部位和边缘,更易于明确解剖信息如房间隔瘤、Chiari网和微小血栓等。该项技术的发展有望为卵圆孔未闭的诊断与介入治疗带来新的前景。

二、卵圆孔未闭相关神经系统疾病及卵圆孔未闭封堵术

卵圆孔未闭与多种神经系统疾病密切相关^[23],尤以卵圆孔未闭相关性卒中(PFO-AS)和偏头痛最为常见,其次还包括阻塞性睡眠呼吸暂停综合征、减压病等。

1. 卵圆孔未闭相关性卒中 生理条件下,未闭合的卵圆孔允许少量分流,但不会引起明显的血流动力学改变,而行Valsalva动作、咳嗽、运动、举重时右心房压力明显升高,达分流峰值^[19],此时静脉来源栓子可通过右向左分流进入动脉循环,这种现象称为反常栓塞^[24],是将卵圆孔未闭与缺血性卒中相联系的主要机制^[25]。反常栓塞血栓移位的最常见部位为颅内动脉循环,临床主要表现为急性缺血性卒中或短暂性脑缺血发作^[26]。研究显示,未闭合的卵圆孔直径是发生缺血性卒中的危险因素^[27],卵圆孔直径为1~19 mm(平均4.9 mm)时,允许较大的栓子自静脉系统进入脑循环,堵塞大脑中动脉和大部分皮质支^[28]。不同国家基于社区和多中心的流行病学调查显示,脑卒中患者卵圆孔未闭或右向左分流患病率为23.5%~61.1%^[29-32]。研究显示,卵圆孔未闭可能是隐源性卒中特别是青年患者的新的危险因素^[33-34]。根据隐源性卒中在缺血性卒中的占比以及2019年全球缺血性卒中发病率估算,卵圆孔未闭相关性卒中患病率为(19~28)/10万,尤以55岁以下人群更常见^[35-37]。老年隐源性卒中患者较已知原因脑卒中患者患卵圆孔未闭的概率更高,可能是由于老年人静脉血栓患病率较高,或者未闭合的卵圆孔直径随年龄增长而增加^[38]。2020年,美国医学会(AMA)将此类卒中中明确定义为卵圆孔未闭相关性卒中,即中高风险卵圆孔未闭患者发生浅表、大面积、深部或视网膜梗死,且无其他已证实的致病因素,则命名为“卵圆孔未闭相关性卒中”^[4]。目前,二级预防仍是脑卒中管理的核心。卵圆孔未闭相关性卒中的具体预防措施包括阿司匹林和氯吡格雷双联抗血小板治疗、抗凝治疗(主要是华法林)和卵圆孔未闭封堵术。3项发表于*N Engl J Med*的随机对照试验——CLOSE(Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence)^[39]、REDUCE(Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke)^[40]和RESPECT(Randomized Evaluation of Recurrent Stroke Comparing PFO

Closure to Established Current Standard of Care Treatment)^[41]均显示,卵圆孔未闭封堵术可预防卒中复发。2022年,美国心血管造影和介入学会(SCAI)发布的《卵圆孔未闭管理指南》^[42]推荐,18~60岁的既往有卵圆孔未闭相关性卒中患者应行卵圆孔未闭封堵术,以预防卒中复发;对于卵圆孔未闭与卒中相关性较低或不确定的患者,以及存在卵圆孔未闭封堵术禁忌证(如房颤)的患者,建议行抗血小板治疗或抗凝治疗。应注意的是,卵圆孔未闭封堵术对长隧道未闭合的卵圆孔疗效较差^[43],最佳受益人群尚未明确,仍有诸多争议和问题亟待解决:(1)最佳受益人群。现有的随机对照试验对于卵圆孔未闭高危人群的定义不尽一致^[44],尤其是60岁以上患者是否受益尚存争议。《卵圆孔未闭管理指南》^[42]指出,卵圆孔未闭封堵术的临床获益应重视矛盾栓塞风险评分(RoPE),RoPE评分 ≥ 7 分的患者卵圆孔未闭封堵术获益较大。未来应通过cTCD、cTTE、TEE、ICE等诊断技术,结合未闭合的卵圆孔形态学特征、房间隔解剖学特征和病史,明确受益人群。(2)术后抗血小板治疗时间。卵圆孔未闭封堵术后1~6个月应行双联抗血小板治疗,以防止装置内血栓形成,但目前尚无统一的抗血小板治疗时间。(3)术后房颤。新发房颤是卵圆孔未闭封堵术后较为常见的并发症,多发生于术后45天内。卵圆孔未闭封堵术后房颤以及包括房颤在内的室上性心律失常发生率为37%和20.9%^[45-46]。研究显示,卵圆孔未闭封堵术后新发房颤与男性、年龄和封堵器品牌有关,可能是由于封堵器机械刺激和内皮化所引起^[47-48]。与STARFlex和GORE封堵器相比,应用AMPLATZER封堵器的患者发生术后房颤的风险较低^[48-49],提示封堵器品牌的选择十分重要。此外,隐性卒中RoPE评分较低(0~6分)的患者卵圆孔封堵术后发生房颤的概率较高^[50],提示术后房颤不仅与封堵器品牌和类型有关,还可能是由于术前即存在隐匿性房颤。为降低术后房颤风险,美国神经病学学会(AAN)建议,行卵圆孔未闭封堵术前应先行心电图监测和房颤评估^[51]。

2. 卵圆孔未闭相关偏头痛 偏头痛位居全球非致命负担的第2位^[52],表现为自主神经症状相关自限性、复发性中至重度头痛,美国人群发病率约12%^[53]。卵圆孔未闭与偏头痛相关,特别是有先兆偏头痛(MA)。Meta分析显示,与健康人群相比,偏头痛患者卵圆孔未闭患病率更高($OR = 2.540$,

$95\%CI: 2.010 \sim 3.080$)^[54],有先兆偏头痛患者卵圆孔未闭患病率为19%~77.9%^[55-56],而无先兆偏头痛患者相对较低(16.2%~34.9%)^[57]。我国一项横断面研究显示,无先兆偏头痛在卵圆孔未闭患者中的发生率高于健康人群($OR = 1.710$, $95\%CI: 1.190 \sim 2.470$; $P < 0.001$)^[58]。虽然上述研究结果存在差异,但均提示卵圆孔未闭与偏头痛存在相关性,且中至重度右向左分流的偏头痛患者头痛频率、强度和持续时间均高于轻度右向左分流和非右向左分流患者^[59]。卵圆孔未闭相关偏头痛的治疗主要为药物治疗和卵圆孔未闭封堵术,治疗药物包括噻吩并吡啶类抗血小板药物(如氯吡格雷和普拉格雷)和非噻吩并吡啶类P2Y₁₂抑制药(如替卡格雷)^[60-61];一项针对卵圆孔未闭封堵术的Meta分析纳入3项随机对照试验——MIST (Migraine Intervention with STARflex Technology)^[62]、PRIMA (Percutaneous Closure of Patent Foramen Ovale in Migraine with Aura)^[63]和PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management)^[64],结果显示,封堵组患者偏头痛平均发作次数和每月发作时间少于未封堵组(均 $P < 0.01$),而两组在完全终止偏头痛方面无显著差异($P = 0.140$)^[65],但PRIMA和PREMIUM试验在有先兆偏头痛亚组分析中发现,卵圆孔未闭封堵术可使有先兆偏头痛患者获益^[63-64]。基于此,欧洲经皮心血管介入协会(EAPCI)、欧洲卒中组织(ESO)和欧洲心血管影像协会(EACVI)联合发布的《卵圆孔未闭患者管理欧洲意见书》^[66]建议,卵圆孔未闭封堵术仅可用于临床研究或作为有先兆偏头痛的补充治疗。卵圆孔未闭封堵术治疗偏头痛仍有问题需进一步澄清:(1)获益人群。上述3项随机对照试验所纳入病例均为卵圆孔未闭相关难治性偏头痛合并中至重度右向左分流患者,特别是MIST试验入组患者均为重度偏头痛,临床症状严重且难以改善,主要临床终点(头痛完全缓解)和次要临床终点(偏头痛发作频率等)均未达到,在排除封堵组中2例偏头痛发作时间较长患者后,封堵组偏头痛发作天数显著少于对照组($P = 0.027$);且封堵组术后残留分流较多,手术结果不甚理想;该项研究并未纳入无先兆偏头痛患者,故卵圆孔未闭封堵术对无先兆偏头痛的治疗效果尚不清楚。上述研究结果表明采

取卵圆孔未闭封堵术治疗卵圆孔未闭相关偏头痛,应对偏头痛类型、严重程度等进行分层分析,以明确真正的获益人群。(2)结局指标。上述3项随机对照试验的主要结果存在异质性,且缺乏明确或客观的结局指标,如偏头痛严重程度的评估主要基于头痛影响测验-6(HIT-6)等量表,很大程度受不同个体疼痛耐受性的影响^[60],因此研究结果的主观性较大,未来应选择更敏感、更有说服力的结局指标。

3.其他 阻塞性睡眠呼吸暂停综合征与神经系统疾病显著相关,易导致夜间缺血性卒中、痴呆、认知功能障碍、癫痫等。多项研究显示,阻塞性睡眠呼吸暂停综合征患者卵圆孔未闭的患病率高于健康人群,有27%~69%的阻塞性睡眠呼吸暂停综合征患者并发卵圆孔未闭^[27,67-69],卵圆孔未闭封堵术可改善此类患者的睡眠呼吸紊乱,升高夜间氧饱和度,然而由于样本量较小、非随机对照设计和证据水平较低,其有效性尚存争议^[69-70]。减压病是一种罕见的潜水相关神经系统疾病,由于身体上升和浮出水面时周围环境压力迅速下降,导致氮气气栓滞留于血管和组织中所引发^[66]。减压病可出现多种急性临床表现,从轻度到重度包括持续性瘫痪甚至死亡^[71]。卵圆孔未闭可增加静脉中气泡转移至体循环的风险,导致动脉空气栓塞,进而增加神经系统减压病的风险^[72]。目前关于卵圆孔未闭与减压病之间关系的研究较少,多为个案报道^[73]。一项Meta分析显示,对存在卵圆孔未闭的潜水员行卵圆孔未闭封堵术可以减少减压病的发生($RR = 0.290$, $95\%CI:0.100 \sim 0.890$)^[74]。现有的国际共识建议,主要通过改变潜水行为和潜水技术以防止减压病,如果二者不可变更或变更无效,则可行卵圆孔未闭封堵术^[66]。

综上所述,卵圆孔未闭患病率较高,其解剖学特征是多种疾病的危险因素,亦是影响卵圆孔未闭封堵术疗效的关键因素。制定更精细化、标准化的操作标准和规范以指导手术,以及开发体外无创性检测技术以提高患者依从性,仍是未来研究重点。卵圆孔未闭封堵术作为卵圆孔未闭相关神经系统疾病的非药物治疗方法,对减少脑卒中复发风险具有优势,但其治疗效果仍存争议,因此有必要在基础和临床研究的基础上进一步探究二者之间的潜在联系,以科学指导卵圆孔未闭相关神经系统疾病的诊断与治疗。未来应重视心血管外科联合神经科、超声科等多学科诊疗模式(MDT)的构建,共同

参与讨论适应证的选择、手术时机及术后药物治疗时机、术后并发症预防,以制定个体化治疗策略,造福更多患者。

利益冲突 无

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