

卵圆孔未闭封堵术后偏头痛缓解指标研究进展

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摘 要

在成年偏头痛患者中, 约有四分之一存在卵圆孔未闭的情况, 研究表明, 因右向左的房间血液分流, PFO与偏头痛之间可能存在相关性。尽管PFO封堵术已取得广泛应用, 但不同研究对于PFO伴偏头痛患者在封堵术后缓解有效率仍存在争议。为筛选出可能获益的患者群体, 以提高PFO封堵术后偏头痛缓解有效率及评估术后疗效, 偏头痛相关缓解指标的研究则显得尤为重要。本文旨在对卵圆孔未闭封堵术后偏头痛缓解指标的研究进展进行综述。

关键词

卵圆孔未闭, 卵圆孔封堵术, 偏头痛, 综述

Research Progress on the Indicators of Migraine Relief after Closure of Patent Foramen Ovale

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Abstract

In adult patients with migraines, approximately one-quarter are found to have a patent foramen ovale (PFO). Emerging studies suggest a potential association between PFO and migraines, which may be attributable to right-to-left shunting of blood between the atria. Although PFO closure procedures are routinely performed, the efficacy of these interventions in mitigating migraine symptoms remains a subject of ongoing debate. It is imperative to identify patient populations that may derive benefit from PFO closure and to evaluate the outcomes following such procedures. Consequently,

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research focused on migraine relief indicators is of paramount importance. This review aims to synthesize the current advancements in the investigation of indicators of migraine relief after closure of patent foramen ovale.

Keywords

Patent Foramen Ovale, Patent Foramen Ovale Closure, Migraine, Review

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1. 引言

卵圆孔未闭(Patent foramen ovale, PFO)是迄今为止最常见的先天性心脏缺陷病,是一种因原发隔与继发隔融合不完全引起的先天性心脏解剖结构异常,当右心房压力长期或短暂升高超过左心房压力时,薄弱的原发隔被推开,导致 PFO 开放并出现右向左(RLS)的房间血液分流[1]。偏头痛(Migraine headache, MHA)是一种常见的神经系统疾病,已成为全球第二大致残性疾病,我国年患病率约 9.3%。约 20%至 25%的成年偏头痛患者中存在 PFO [1] [2],特别是先兆偏头痛[3]。

目前针对 PFO 的封堵术已出现 30 余年,在预防隐性卒中、治疗斜卧呼吸-直立性低氧血症综合征等方面得到了广泛应用[4] [5],但因 PFO 与偏头痛之间的病理生理学及潜在受益患者群体未明确,该术式对于治疗偏头痛的应用仍有争议[6]。PFO 导致偏头痛的机制目前有两种认可度较高的学说:一种认为血管活性物质未通过肺循环直接进入左心系统,触发了偏头痛;另一种则认为微血栓导致短暂性脑供血区低灌注,进而引发偏头痛[7]-[9]。目前,针对 PFO 封堵术治疗偏头痛的三项随机对照研究(MIST、PRIMA 和 PREMIUM)均没有达到预期效果[10]-[12],但在有先兆症状和脑血管病患者的亚组分析中显示,相比药物,PFO 封堵对偏头痛改善效果更好,因此推测未达到预期效果可能是纳入了一些非致病性 PFO 的患者。基于这个理由,研究该群体术后偏头痛缓解的相关指标可能对于未来的研究及临床实践具有重要意义。

2. PFO 封堵术治疗偏头痛的研究现状

PFO 患者发生偏头痛的机制目前认为与右向左的分流相关[7]-[9],PFO 患者中合并偏头痛人群有较高的自发右向左分流率和较大的分流量也间接佐证了这一观点[13] [14]。目前研究表明先兆偏头痛(migraine with aura, MA)与 PFO 有更强的关联性[3],且 PFO 封堵治疗对于有先兆偏头痛疗效最好,其次是无先兆偏头痛,最后是慢性偏头痛[15],但以上三种类型的偏头痛在不同研究中,均未达到的某一亚型人群完全缓解。故对于 PFO 相关偏头痛的封堵术治疗效果仍存在争议。一些研究表明,PFO 封堵术是安全并对偏头痛缓解有效[5] [16] [17]。但另一些研究表示,PFO 封堵术并不能减少总的偏头痛天数或达到主要疗效终点[10]-[12] [18] [19]。一项 meta 分析指出,尽管 PFO 与偏头痛之间存在总体关联,但是 PFO 封堵治疗偏头痛疗效的证据级别较低[13]。

PFO 患者目前多因药物治疗偏头痛效果不佳或潜在栓塞风险选择 PFO 封堵术[6]。因此为筛选出可能获益的患者,一项回顾性研究针对患者偏头痛特征进行分析,指出量化偏头痛发作对患者工作、家庭和社交活动的干扰程度的偏头痛残疾程度评估问卷(MIDAS)评分较高及每月发作次数较多是 PFO 闭合后偏头痛缓解的重要预测因子[20],但仍需进一步研究来确定这些指标的具体阈值,有望为精准筛选手术患者

以及术后随访评估提供科学依据。以下,将对过往研究中潜在缓解预测性指标进行详细阐述。

3. PFO 相关偏头痛临床指标

3.1. 生化指标

PFO 相关的偏头痛机制与多种生化因素有关。这一机制可能涉及血小板活化及引起三叉神经血管系统激活的相关递质。如血小板相关活化指标在 PFO 相关偏头痛的患者中显示异常,包括可能增加血栓形成风险的 TFpos 血小板以及血小板活性氧、血小板压积(PCT)及血小板衍生生长因子-BB (PDGF-BB),值得注意的是,术前异常升高的 PDGF-BB 水平在术后降低[21]-[23]。其次,血清降钙素原基因相关肽(calcitonin gene-related peptide, CGRP)是一种新发现可用作偏头痛非侵入性的标志物,一项观察性研究发现血清 CGRP 浓度与 RLS 分级及头痛评分(HIT-6)呈正相关。提示了较高的血清 CGRP 水平对偏头痛患者可能患有 PFO 有一定的预测价值[22]。此外,在 PFO 伴卒中的患者中,同型半胱氨酸水平的升高与 PFO 分流程度相关,并在 PFO 封堵术后稳定下降至健康对照组水平[24],又因偏头痛的程度、是否伴有先兆与 PFO 分流量之间存在一定的关联[25],基于这些发现,同型半胱氨酸水平有望作为评估 PFO 封堵术疗效的潜在随访指标。在偏头痛缓解方面,还原型谷胱甘肽增加和凝血酶生成减少被认为是相关生物标志物[23]。综上,在 PFO 相关偏头痛的患者中,血小板活化相关指标、CGRP、还原型谷胱甘肽、凝血酶以及同型半胱氨酸均显示出作为随访指标的潜力,未来研究有望进一步验证其临床应用价值。

3.2. 超声检查

PFO 的诊断中,常用检查方法包括对比增强经颅多普勒超声(cTCD)、经胸超声心动图(TTE)、经食管超声心动图(TEE)和右心声学造影[6],一般认为微气泡数大于 10 微泡/帧对诊断 PFO 有参考价值[26]。近期研究表明,10~20 微泡/帧的分流与 PFO 相关偏头痛关联较密切,伴静息分流、较大的左心房直径和容量的 PFO 患者在封堵术后实现完全缓解概率更高[27]-[29]。术前有原位血栓或心内膜不规则、术后没有残余右向左分为偏头痛长期缓解的重要预测因子[7][16]。这些发现对于术前筛选 PFO 潜在治疗收益的患者具有临床指导意义。

3.3. 核磁共振检查

影像技术为深入探究 PFO 与偏头痛之间的联系提供了重要手段。贾志坚等研究者[30]通过功能性磁共振成像(fMRI)技术,观察到 PFO 患者颞叶、双侧小脑半球和丘脑等脑区显示出异常的成像特征,这些区域与偏头痛的发生联系紧密。进一步使用 fMRI 的研究表明,PFO 患者的静息态功能连接(rsFC)在多个脑网络之间存在变化,枕极网络(OPN)与内侧视觉网络(MVN)之间的 rsFC 与头痛影响测试-6 (HIT-6)评分呈负相关,证实了 PFO 与偏头痛间的相互作用能够调节视觉网络间的 rsFC,进而可能导致偏头痛痛感的加剧[31]。偏头痛患者发作时伴随疼痛侧血管的扩张现象,药物诱导单侧偏头痛的研究中,通过磁共振血管造影观察到脑膜中动脉的扩张与偏头痛密切相关[32]。此外,脑血管功能不全可能降低动态脑血流自动调节功能(dynamic cerebral autoregulation, dCA) [33]。PFO 伴偏头痛患者显示出显著的 dCA 降低,而封堵术后,这种功能有所恢复[21]。因此,以上影像学指标有望成为监测 PFO 相关偏头痛疗效的工具。

3.4. 电生理检测与成像技术

针对 PFO 相关偏头痛患者的研究还发现,部分患者的脑电图显示异常慢波,其动脉氧分压(PaO₂)普遍低于健康对照组。在常压吸氧后,74.4%的患者头痛显著减轻,PaO₂水平显著提升,脑电图异常慢波也得到改善[34],进一步支持了 PFO 相关偏头痛可能与脑血管及脑血流调节相关的假设。另一研究提示该

类患者脑电图在较高频率范围(β 和较低 γ)的功率增加[35]。此外, PFO 可能会改变偏头痛患者枕叶皮层的兴奋性, 因此, 光刺激时枕叶上的 β 带功率谱密度可能是衡量 PFO 患者偏头痛严重程度的一个客观指标[36]。一项研究中利用光学相干层析成像(OCT)评价 PFO 的微观结构, 特别关注了偏头痛患者中常见的原位血栓形成和心内膜异常。结果表明, PFO 封堵术对于伴有原位血栓的偏头痛患者具有更高疗效[7]。上述研究表明, 脑电图及 OCT 成像技术有望成为封堵术患者筛选及术后评价的潜在指标。

4. 治疗

即使有研究表明术后中长期缓解率较高, 如张玉顺团队在平均随访 2 年的队列中得出, 193 例患者中偏头痛完全消失约 62.7%, 明显缓解 92.2% [28], 但并非所有患有 PFO 的偏头痛患者在接受封堵手术后都能获得满意的效果。并且有报道描述右向左分流封堵术后发生房颤、新发偏头痛的风险增加[37][38], 对于术前评估及患者筛选仍需进一步探讨。

因 PFO 是一种先天性心脏病, 一些患者的偏头痛病情可能长期持续。规范药物及生活方式的改善是预防偏头痛的主要策略[6], 但偏头痛治疗中部分患者仍存在治疗耐受性不佳[39]。随着偏头痛新型药物研发的进展, 已有 4 种小分子 CGRP 拮抗剂和 4 种 CGRP 单克隆抗体获得批准上市[40], 5-HT_{1F} 受体激动剂药物也在研发中[41], 这些新药也许为 PFO 相关偏头痛患者提供了新的治疗选择。且值得关注的是, 长期的偏头痛症状使得患者不得不频繁服用各种止痛药物, 这不仅可能导致药物依赖性偏头痛, 还常伴随着焦虑等情绪问题[42], 使部分患者在就诊时往往处于偏头痛、药物依赖和焦虑共存的复杂状态。

因此, 对于 PFO 封堵术后偏头痛未达到缓解终点的患者, 相关因素亟需探究, 以寻求更有效的治疗策略。在这方面, 抗血小板药物的使用提供了一种思路[43]。TRACTOR 研究显示, PFO 合并偏头痛患者中, 替格瑞洛能有效减轻难治性偏头痛症状[18]。目前封堵术后常规使用抗血小板药物[6], 研究表明, 氯吡格雷对 PFO 伴偏头痛患者达到每月偏头痛天数减少 $\geq 50\%$ 的终点有较高反应性[44]。可能由于与健康个体相比, PFO 伴偏头痛患者表现出更强的促血栓表型和氧化应激变化[23], 氯吡格雷特异性阻断二磷酸腺苷受体, 对血小板血栓前表型的影响较阿司匹林更强, 且导致血小板聚集减少后转化为与偏头痛发作相关的血清素或促炎细胞因子等物质的释放减少, 在单药治疗下, 氯吡格雷较阿司匹林对偏头痛缓解反应性更佳[23][45]。另一些研究指出, 阿司匹林的效果与安慰剂相似, 而 PFO 封堵术后单独使用氯吡格雷或与阿司匹林联合使用, 可以降低先兆症状及新发偏头痛的发生频率[37][46]。目前, 关于抗血栓药物与标准偏头痛治疗在 PFO 患者中的疗效比较研究正在进行中(临床试验编号 NCT05546320), 这项研究有望为临床实践提供更多证据[47]。

5. 结语及展望

偏头痛是人群中常见的疾病, 其病理生理机制目前尚未完全阐明。PFO 为其临床常见合并症之一, 部分患者在接受 PFO 封堵术后获得了偏头痛症状的显著缓解。对于未达到缓解标准的相关偏头痛患者, 应积极寻找潜在病因, 并考虑多种治疗手段的联合应用。

现有研究已经揭示了先兆偏头痛、偏头痛程度较重、PFO 分流量较大、术前有原位血栓或心内膜不规则及术后没有残余右向左分流等特征可能是术后受益的患者特征, 并提出了若干潜在的随访指标, 我们期待在未来的临床实践中验证这些指标的实际有效性, 以助于对 PFO 术后可能获益患者精准筛选, 提高偏头痛患者治疗的总体预后。

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