

卵圆孔未闭相关疾病及封堵术研究进展

杜康^{1,2} 张育大¹ 陈奎全² 刘盼² 杨颖¹

(1. 川北医学院附属医院心血管内科, 四川 南充 637000; 2. 广元市第一人民医院心血管内科, 四川 广元 628000)

【摘要】 卵圆孔未闭(PFO)是一种常见的结构异常性先天性心脏病,普通人群中约 25% 的人存在 PFO。既往认为 PFO 是一种良性改变而对其缺乏关注,现大量研究已证实 PFO 与隐源性脑卒中、偏头痛、减压病、晕厥等存在关联,最新报告显示也可能与癫痫、心绞痛等有关,其相关疾病谱在不断增加。针对 PFO 相关疾病的治疗,研究显示封堵术效果较好且可降低某些疾病的复发风险,但其安全性与有效性尚不完全清楚。现对 PFO 相关疾病及封堵术效果的最新研究进展做一综述。

【关键词】 卵圆孔未闭;卵圆孔未闭相关疾病;封堵术

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Diseases Related to Patent Foramen Ovale and Its Closure

DU Kang^{1,2}, ZHANG Yuda¹, CHEN Xiquan², LIU Pan², YANG Ying¹

(1. Department of Cardiology, The Affiliated Hospital of North Sichuan Medical College, Nanchong 637000, Sichuan, China; 2. Department of Cardiology, The First People's Hospital of Guangyuan, Guangyuan 628000, Sichuan, China)

【Abstract】 Patent foramen ovale (PFO) is a common congenital heart disease with structural abnormalities, and about twenty-five percent of the general population have PFO. In the past, PFO was considered a benign change and lacked attention. Presently, a large number of studies have confirmed that PFO is associated with cryptogenic stroke, migraine, decompression sickness, syncope, etc. The latest reports show that it may also be related to epilepsy, angina pectoris, etc, and its spectrum of related diseases is increasing. Regarding the treatment of diseases related to PFO, studies have shown that closure has good therapeutic effects and can reduce the recurrence rate of certain diseases, but its safety and effectiveness are not yet fully understood. This article summarizes the latest literature reports on diseases related to PFO and closure effects.

【Keywords】 Patent foramen ovale; Diseases related to patent foramen ovale; Closure

卵圆孔是胚胎时期位于原发隔与继发隔间的一个生理性通道,出生后肺循环启动,原发隔和继发隔互相融合形成房间隔。3 岁之后卵圆孔仍未完全融合即卵圆孔未闭(patent foramen ovale, PFO),一般人群患病率为 15%~35%^[1]。正常情况下,由于左心房压力高于右心房,卵圆孔通道保持闭合状态。当右心房压力升高超过左心房时卵圆孔开放,血液经通道从右向左分流(right to left shunt, RLS),致使静脉内的微栓子、血管活性物质等直接进入动脉系统引起一系列临床症状。研究显示 PFO 与隐源性卒中(cryptogenic stroke, CS)、偏头痛、晕厥、减压病等存在关联,最近报告显示也可能与癫痫、心绞痛和焦虑抑郁等有关,这些疾病对患者身心健康造成不同程度的影响。针对 PFO 相关疾病的治疗,相关性卒年轻患者推荐行封堵术,这在国内外已达成共识,但偏头痛、晕厥等其他

相关疾病是否行封堵术尚未达成一致,封堵术效果及预后也存在不确定性,尤其是年龄>60 岁的老年患者。现对 PFO 相关疾病及其封堵术效果的研究进展做一综述。

1 PFO 的诊断

PFO 的诊断方法主要包括对比增强经颅多普勒超声、经胸超声心动图(transthoracic echocardiography, TTE)、经食管超声心动图(transesophageal echocardiography, TEE)、右心声学造影、选择性心血管造影(右心房造影)、心腔内超声心动图(intracardiac echocardiography, ICE),其中 TEE 是诊断 PFO 的“金标准”。PFO 检测一般先行 TTE 检查,但敏感性较低。有报告^[2]显示心电图下壁导联 Crochetage R 波及右束支传导阻滞联合 TTE 可提高 PFO 诊断的准确性与敏感性。此外,CT 作为常用影像学检查方法,其诊断

PFO 的准确性尚不清楚。一项前瞻性研究^[3]显示,整个心动周期内心脏 CT 诊断 PFO 的敏感性为 89.4%,特异性为 92.3%。而在最近一项研究^[4]中,心电门控心脏 CT 诊断 PFO 的敏感性为 25%,特异性为 96%。急性脑卒中患者常规需行 CT 检查,扫描过程中获取的心脏 CT 能否诊断 PFO 还有待进一步研究。相比 CT,心脏磁共振成像可更清楚地显示心脏结构,电影序列可完整捕捉心脏运动周期,心脏磁共振成像诊断 PFO 的可行性与准确性是未来值得探索的问题。

2 PFO 相关疾病

2.1 PFO 相关卒中

缺血性脑卒中和短暂性脑缺血发作是最常见的脑血管疾病,约 25% 的缺血性脑卒中找不到明确的原因,即 CS。国内外大量研究已证实 PFO 与 CS 存在关联,其可能的病理生理学机制包括反常栓塞、心律失常、原位血栓形成^[5]。之前几项大型随机试验^[6-8]显示 PFO 相关性卒中患者行封堵术比药物治疗效果好且术后复发率显著降低,但对于年龄>60 岁的患者是否行封堵术仍存在争议。在最近一项研究^[9]中作者将 437 例 PFO 老年患者[年龄(68.0±6.4)岁]纳入研究,其中 161 例行封堵术,276 例仅接受药物治疗。药物治疗组脑血管病复发率为 18.1%($n=50$),封堵术组为 8.7%($n=14$),其复发率显著低于药物治疗组,尤其是高风险 PFO 患者(存在房间隔膨出瘤或大的心房分流),但封堵术后发生心房颤动的风险更高。在 2024 年《卵圆孔未闭规范化诊疗中国专家共识》^[10]中,中国专家对 PFO 相关卒中患者的临床策略建议如下:16~60 岁患者建议行 PFO 封堵术;60 岁以上的患者建议行 PFO 封堵术,但需术前评估风险与获益;16 岁以下的患者术前必需行包括神经病学专家在内的多学科讨论,原则上不建议(或不要)对婴幼儿和儿童患者实施封堵术。此外,有研究^[11]显示超声声学造影联合同型半胱氨酸水平及中性粒细胞/淋巴细胞比值有助于评估 PFO 患者脑卒中发生风险,D-二聚体水平与脑卒中复发相关^[12]。生物标志物水平是否可成为 PFO 封堵术的参考指标,这可能是未来的研究方向之一。

2.2 偏头痛

偏头痛是以反复发作和搏动性疼痛为临床表现的慢性神经系统疾病,是人类致残的第二大原因,是 50 岁以下女性致残的首要原因^[13]。一项荟萃分析^[14]提示 PFO 与偏头痛显著相关,尤其是先兆性偏头痛。其发病机制尚不清楚,可能的假说包括 RLS、反常栓塞、血管活性物质及遗传因素。回顾性研究及荟萃分析显示封堵术可有效减轻患者偏头痛症状,且比药物

治疗效果好^[15-16],但目前无随机试验结果,之前 3 项随机试验(MIST、PRIMA 及 PREMIUM)均未达到其设定终点^[17-19]。PFO 合并偏头痛患者是否行封堵术还存在较大争议。中国学者正在进行一项多中心、大型随机临床试验^[20],旨在比较 PFO 封堵术与药物治疗缓解偏头痛的有效性和安全性,结果将于 2025 年公布。另外,有研究^[21]显示合并脑血管病的偏头痛患者行 PFO 封堵术能缓解或终止偏头痛症状,而对于既往无 PFO 相关卒中的偏头痛患者则不建议行封堵术^[22]。这是否提示 PFO、偏头痛和脑卒中之间存在动态联系?研究^[23]发现合并 PFO 的严重偏头痛患者动态脑血流自动调节(dynamic cerebral autoregulation, dCA)功能低于未合并 PFO 的偏头痛患者,并且在行封堵术后 dCA 功能迅速增强,而 dCA 功能会影响脑卒中的发生与发展,推测在偏头痛患者中 dCA 受损可能是 PFO 与脑卒中之间的中间环节。

2.3 减压病

减压病是指人体从高压环境快速进入低压环境时(如潜水员、高空飞行员或航天员等),突然的压力变化导致血液或身体组织内形成氮气泡并积聚在静脉系统,从而影响组织或抑制血液流动,导致一系列病理生理变化的疾病。PFO 相关性减压病可能的病理生理学机制是静脉系统内的氮气泡通过 PFO 通道进入动脉系统。一项单盲随机试验^[24]结果显示存在 RLS 的潜水员减压病的发生率是无 RLS 潜水员的 3.02 倍。Lee 等^[25]将 100 名经验丰富的潜水员(每年潜水>50 次)纳入研究,其中 68 名存在 PFO(37 名高风险,31 名低风险),PFO 组有 12 名潜水员发生 PFO 相关减压病(每 1 万名潜水人员减压病的发生率:无 PFO vs 高风险 PFO vs 低风险 PFO 为 0 vs 8.4 vs 2.0, $P=0.001$),平均随访时间为 28.7 个月。多变量分析显示高风险 PFO 导致减压病发生率增加且为独立危险因素($OR=9.34$, 95% CI 1.95~44.88)。如果潜水员只出现一次轻微的减压病症状,则无必要行 PFO 检测。反之,如多次出现减压病则需行 PFO 筛查。此外,对患有先兆偏头痛、先天性心脏病或 PFO 家族史等高危人群的筛查也是必要的。

一项大型前瞻性研究^[26]对 829 名潜水员进行 PFO 筛查和危险分层,最终 702 名纳入分析。PFO 分级为Ⅲ级(>30 个微泡/帧)的潜水员分别行封堵术(封堵组)和保守治疗(高级别组),PFO 分级为Ⅰ~Ⅱ级的潜水员行保守治疗(低级别组),无 PFO 的为对照组。结果显示封堵组和低级别组减压病发生率与对照组相似,而高级别组发病率仍较高,这似乎提示Ⅲ级 PFO 潜水员行封堵术效果更好,而Ⅰ~Ⅱ级 PFO 潜

水员无需行封堵术。虽然已证实 PFO 封堵术可有效降低潜水员减压病的发生率,但目前缺乏大规模随机对照试验,因此封堵术不推荐作为一线治疗措施,并且封堵术后如果存在残余分流就有复发的可能,即便是完全封堵也有可能因组织内氮气泡过度膨胀或通过肺循环导致动脉气体栓塞而复发^[27]。但对于无减压病病史却计划行深度减压活动的 PFO 患者,可选择性行封堵术预防减压病的发生^[28]。

2.4 晕厥

晕厥是指一过性全脑组织血液灌注减低导致的短暂性意识丧失,普通人群发病率约为 30%。经临床医生全面体格检查、行心电图检查等,病因仍无法明确的晕厥称不明原因晕厥,在晕厥患者中占比约 50%。Zhang 等^[29]分析了 260 例 PFO 患者的临床表现,其中晕厥患者占 21% (54 例)。一项前瞻性研究^[30]纳入 1 000 例研究对象,其中 PFO 患者晕厥发生率为 6.7% (11/163),无 PFO 的晕厥发生率为 1.6% (13/837)。研究提示 PFO 可能与成人不明原因晕厥有关,而一项关于 PFO 与儿童晕厥相关性的研究^[31]结果显示,PFO 与儿童晕厥风险增加无关,这与成人结果相矛盾。分析可能的原因是儿童静脉系统的微栓子和血管活性物质比成人少,通过 PFO 进入体循环的微栓子数量较少。PFO 直径与疾病严重程度呈正相关,当直径<4 mm 时血液分流轻微,发生反常栓塞的概率较低。Wang 等^[32]对 111 例不明原因晕厥合并 PFO 的患者行封堵术,与非封堵组相比,封堵术可减少晕厥发作次数(平均随访时间为 31 个月),但该研究样本量较小。

2.5 斜卧呼吸-直立性低氧血症综合征

斜卧呼吸-直立性低氧血症综合征 (platypnea-orthodeoxia syndrome, POS) 是一种临床表现为呼吸困难(立位或坐位时明显,卧位时缓解)的一种少见疾病,其特点是体位性低氧血症。确切的病理生理学机制尚不清楚,主要由心内分流和心外因素(肺动静脉分流或肺部通气/灌注不匹配)所致,由心内分流所致大约占 80%^[33]。卵圆孔是最常见的心内分流部位,PFO 也是导致 POS 的主要原因,封堵术是治疗 POS 的主要手段^[34]。Gama 等^[35]对 168 例 PFO 患者进行检查,其中 14 例患者存在 POS 且均行封堵术,12 例患者获得完全临床成功(动脉血氧饱和度>94%),氧合指数从 155.9 ± 50.6 增加至 318.3 ± 73.4 ($P=0.002$),在长期[(37±20)个月]随访中血氧饱和度持续维持,并且在 12~14 个月的随访中未出现明显的残余分流。但有报告^[22]对 PFO 合并 POS 患者的观察性研究进行荟萃分析,发现封堵术后 PFO 患者血氧饱和度增加并

有统计学意义,但该研究存在严重异质性。

2.6 其他

头晕是临床常见症状,对 15%~35% 的人群造成影响。Cao 等^[36]对 244 例头晕患者进行前瞻性研究,“有原因”头晕患者 123 例,其中 34 例合并 PFO,“不明原因”头晕患者 121 例,其中 79 例合并 PFO,患病率明显高于“有原因”头晕组。

癫痫是由多种因素引起中枢神经功能损害的一种慢性脑部疾病。徐扬舟等^[37]将研究对象分为癫痫组和非癫痫组,结果显示癫痫组 PFO 阳性率为 40.6%,高于一般人群阳性率。Tang 等^[38]的研究显示,约 39% 的癫痫患者患有 PFO,患病率明显高于无癫痫者(24.25%),且患有 PFO 的癫痫患者患偏头痛和耐药性癫痫的风险更高。

有研究^[39]认为 PFO 可能与变异型心绞痛有关,或许与某些缩血管物质或致栓因子等未能在肺循环清除有关。该作者报告了 9 例 PFO 女性患者,她们有心绞痛性胸痛(均排除其他原因所致心绞痛且存在 PFO),其中 7 例患者行封堵术后症状均有所改善。此外,Zhai 等^[40]报告了 1 例因焦虑抑郁加重伴头晕入院的女性患者,该患者无心脏或肺部疾病,但出现发绀和急性低氧血症,经颅多普勒超声检查发现患者有 PFO 并存在 RLS,经抗焦虑抑郁治疗后好转。该作者认为焦虑抑郁状态下,PFO 导致 RLS 可能引起急性全身性低氧血症,当焦虑症状改善时缺氧也随之改善。

3 PFO 封堵术

PFO 封堵术是通过在未闭的卵圆孔处放置封堵器来阻断心房之间的通道,防止血液经过 PFO 逆流进入左心房。该手术可在 X 射线、TEE、ICE 或 TTE 的引导下完成,美国心血管造影与介入学会^[41]推荐在 X 射线和 TEE(或 ICE)联合引导下进行,通过 TEE 或 ICE,术者在术中可多切面、多角度对房间隔及邻近结构进行清楚全面地观察,从而准确判定封堵器的位置。封堵术是一种安全的治疗手段,但仍存在一定的风险,包括心包积液、心脏穿孔、术后心律失常、装置侵蚀和移位、镍钛合金装置引起的镍超敏反应等。封堵术后发生心律失常逐渐被关注,有报告^[42]显示封堵术后心律失常发生率较低,一般<5%。但一项大型队列研究^[43]显示封堵术后心律失常发生率为 11.9%。此外,封堵装置除了会对组织产生直接影响外,其大小也会影响心房颤动的发生,较大的封堵器术后发生心房颤动的概率更高。目前国内外均在新型封堵器的研究,包括 PFO 隧道内封堵器、新型生物可降解封堵器、PFO 介入缝合装置等。

4 小结

PFO 在一般人群中发病率较高,其相关疾病逐渐

被认识,疾病谱也在不断增加。未来不仅要注意 PFO 相关的常见疾病,也要注意可能相关的少见疾病,且不同疾病之间也可能存在动态关联,如偏头痛与脑卒中。针对 PFO 相关疾病的封堵术效果,虽然大部分回顾性研究显示封堵术比药物治疗效果好,但除 CS 外其他所有相关疾病均缺乏随机对照试验,还需大型随机试验证据支持。此外,封堵术的安全性相对较高,同时也应关注其长期效果以及术后并发症的影响。

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