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植入冠脉支架患者择期非心脏手术的围术期抗血小板治疗方案探究

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【摘要】 植入冠脉支架患者正在逐渐成为接受择期非心脏手术（non-cardiac surgery, NCS）的患者中不可忽视的一个群体。既往心脏疾病、冠脉支架以及抗血小板药物使这类患者在围术期面临着血栓形成和出血的双重风险。制定适宜的围术期抗血小板治疗方案将有助于降低风险，保障患者安全。本文将围绕目前支架患者择期NCS围术期抗血小板治疗的各个环节总结分析现有治疗方案，并探讨该领域未来的研究方向。

【关键词】 冠脉支架　非心脏手术　抗血小板治疗

Perioperative Antiplatelet Therapy in Patients with Coronary Stents Undergoing Elective Non-Cardiac Surgery

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【**Abstract**】 Among patients undergoing elective non-cardiac surgery (NCS), those with coronary stent implants are gradually becoming a patient group that cannot be easily overlooked. Previous history of heart disease, coronary stents and antiplatelet agents expose these patients to dual perioperative risks of thrombosis and bleeding. Formulating appropriate plans for perioperative antiplatelet therapy will help reduce the risks and ensure the safety of patients. We herein reviewed and analyzed various aspects of perioperative antiplatelet therapy for patients with coronary stent implants undergoing elective NCS, and discussed prospective research directions in the field.

【**Key words**】 Coronary stents　Non-cardiac surgery　Antiplatelet therapy

随着冠心病发病率的增高，接受经皮冠状动脉介入治疗（percutaneous coronary intervention, PCI）的患者也在逐渐增多。植入冠脉支架患者（以下简称“支架患者”）在PCI术后必须接受抗血小板治疗（antiplatelet therapy, APT），以预防支架内血栓形成（stent thrombosis, ST）。此类患者在接受择期非心脏手术（non-cardiac surgery, NCS）时面临的出血风险与血栓风险一直是麻醉科医师关注的焦点。本文旨在讨论目前支架患者在择期NCS围术期APT的临床管理方案（涉及风险评估、药物选择、持续时间、术前停用、桥接治疗和术后重启多个环节，见图1），并探讨该领域未来的研究方向。

1　支架患者择期NCS的围术期抗血小板治疗

据统计，支架患者一年内接受各种手术的概率约为4%~20%，其中约86%为NCS[1-3]。APT是影响此类患者围术期缺血和出血平衡的重要因素。2016年美国心脏病学学会/美国心脏协会（ACC/AHA）指南建议：所有患者应在第二代药物洗脱支架（drug-eluting stent, DES）植入后至少6个月后再接受择期NCS，如果推迟手术的风险更高，可以考虑在第二代DES植入后3~6个月进行手术；手术推迟期间需要不间断的双重抗血小板治疗（dual antiplatelet therapy, DAPT）[4]。

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然而，上述指南缺少对不同特点患者的讨论，“一刀切”的方案显然并不适用于所有患者。其次，指南的建议大都来源于专家共识和回顾性研究，证据等级不高。所以针对支架患者在择期NCS围术期APT的研究层出不穷，且争论持续存在。

1.1　缺血与出血风险的个体化评估

缺血与出血风险的个体化评估是整个围术期APT的第一步。由于NCS中支架患者的心肌供血和术野出血主要是麻醉科医师同时管理，所以麻醉科医师迫切需要可靠的评估工具来预测患者的缺血和出血风险。

患者的缺血风险评估主要考虑4个方面：患者的临床特征、PCI到NCS的间隔时间、支架类型、抗血小板药物的暂停时间[5]。现有研究发现多发性心梗、慢性肾病、糖尿病以及一些血管造影特征，比如长支架、重叠支架、冠脉分叉病变等，均会造成缺血风险增加[6-8]。目前公认的支架患者缺血风险分层由ROSSINI等[5]提出，该分层结合支架类型、间隔时间等因素对缺血风险进行了划分。

出血风险要考虑患者因素，比如服用抗凝药、肝功能不全、既往出血病史等[9]，YEH等[10]提出了DAPT评分用于评估患者在持续APT后的出血或缺血风险。此外，出血风险还要考虑手术本身，包括手术类型、时长、以及出血可能导致的后果等。已有研究对不同手术进行了出血风

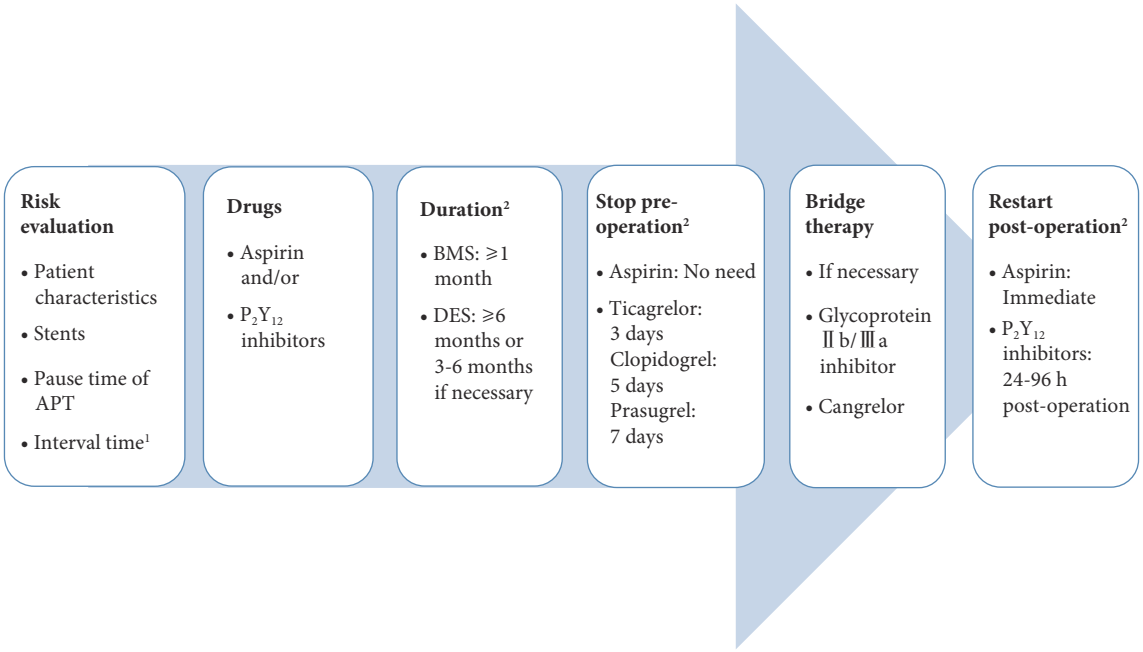

图 1 支架患者择期非心脏手术围术期抗血小板治疗方案

Fig 1 Perioperative antiplatelet therapy for patients with coronary stents undergoing elective NCS

1: Interval time indicates the interval from PCI to surgery; 2: The data comes from the latest guide. APT: Antiplatelet therapy; BMS: Bare metal stent; DES: Drug-eluting stent.

险分级[11-12], 这些分级可以为评估围术期APT的安全性提供有效信息。

上述评估工具的不足在于证据等级低、缺少有效性验证、难以实现动态定量评估等。更高质量的评估工具仍有待开发。

1.2 APT的药物选择

抗血小板药物种类众多(表1), CURE试验发现[13]: 与单独服用阿司匹林相比, 阿司匹林联合氯吡格雷可将复合终点(心血管相关死亡、心肌梗死、中风)降低20%, 同时出血风险并没有明显增加(P= 0.64)。但是CURE试验中接受PCI的患者过少, 随后的CREDO试验弥补了这一不足并得到了基本一致的结论[14]。因此, 阿司匹林联合氯吡格雷成为支架患者APT管理的基石。

随后, TRITON-TIMI 38试验[15]和PLATO试验[16]分别证实了普拉格雷和替格瑞洛在减少心源性死亡、心肌梗死等方面优于氯吡格雷。而且这二者具有更高、更稳定的血小板抑制率, 其中替格瑞洛起效最快。ACC/AHA指南建议急性冠脉综合征(acute coronary syndrome, ACS)患者优先使用替格瑞洛来维持P_2Y_{12}受体抑制剂治疗[4]。

目前, DAPT方案正在不断遭受挑战。有两项研究发现西洛他唑、阿司匹林和氯吡格雷组成的三抗方案降低了主要不良心脏事件(major adverse cardiac event, MACE)的发生, 较DAPT有更大的临床获益[17-18]。但是这两项研究仅随访了6个月, 且仅针对有特殊情况的患者, 比如糖尿病、冠脉病变或支架长度较长。除了多药联合, 还有研究发现PCI术后阿司匹林或P_2Y_{12}抑制剂单药治疗与DAPT相比具有非劣效性[19-20], 可能的解释是: 围术期导致MACE的主要原因是心肌氧供需失衡, 而不是血栓形成[21]。上述研究提示我们可能需要重新考虑对支架患者围术期使用DAPT的必要性, 但部分研究的对象为非手术患者, 所

表 1 常见抗血小板药物的药理特点

Table 1 Pharmacological characteristics of common antiplatelet agents

Drug	Target	Administration route	Onset	Elimination half-life	Percentage of platelet function inhibition	Recovery time of platelet function
Aspirin	Irreversible cyclooxgenase-1 inhibitor	Oral	60 min	3-6 h	60%-70%	5-7 d
Clopidogrel	Irreversible P_2Y_{12} inhibitor	Oral	2-8 h	6 h	70%-90%	7 d
Prasugrel	Irreversible P_2Y_{12} inhibitor	Oral	1-3 h	7 h	>90%	7-10 d
Ticagrelor	Reversible P_2Y_{12} inhibitor	Oral	30 min-2 h	7 h	>90%	3-5 d
Eptifibatide	Reversible glycoprotein Ⅱb/Ⅲa inhibitor	Intravenous	Immediate	2.5 h	>90%	4-6 h
Tirofiban	Reversible glycoprotein Ⅱb/Ⅲa inhibitor	Intravenous	Immediate	1.5 h	>90%	4-8 h

以我们应当谨慎看待这些结论的普适性。

1.3　APT的最佳持续时间

有研究显示，高达75%的ST发生在支架植入1年以后[22]，而且PCI后停用APT是ST的最强预测因子之一[23]，所以过早停止APT会造成危险。DAPT试验发现延长DAPT使ST和心脑血管事件发生率降低，这些结果与P_2Y_{12}受体拮抗剂的种类无关[24]。一项Meta分析发现延长DAPT的收益在第一代DES和依维莫司洗脱支架更加显著；而在其他第二代DES中的收益是下降的[25]。这提示延长APT或许只有在特定人群中才能体现出优势。但是，上述研究均没有得出APT的最佳持续时间。

与上述研究的结论相反，PALMERINI等[26]报道3~6个月DAPT与12个月DAPT相比，全因死亡率降低（P= 0.05），原因是短期DAPT的出血相关死亡显著降低。多项研究也发现3~6个月和12个月的APT具有等效的抗缺血保护作用[27-28]。正是基于目前研究结果，欧洲心脏病学会（ESC）以及ACC/AHA指南建议将稳定型缺血性心脏病患者植入第二代DES后的强制DAPT持续时间缩短至6个月[4, 29]，同时根据患者的出血或缺血风险，考虑更短或更长的策略。

综上所述，在APT最佳持续时间的讨论中，有些研究的结论是矛盾的，这可能是由患者的临床特征、支架类型等因素造成的。所以，最好的方法是对患者进行分层，并根据分层结果对患者实施个体化的APT治疗。

1.4　APT的术前停用

多项研究证实，术前不停用阿司匹林虽然会增加出血的发生率，但不会增加出血的严重程度，同时可以降低MACE的风险[3, 30]。所以ACC/AHA和ESC指南支持将75~100 mg阿司匹林作为大多数支架患者择期NCS围术期的背景治疗[4, 29]。但是对于特殊的手术类型以及有较高出血风险的患者，术前仍需停用阿司匹林。

此外，目前一致认为在术前需要停用P_2Y_{12}受体拮抗剂。有研究发现，在不停用阿司匹林的情况下，术前停用替格瑞洛或氯吡格雷的时间过短可以作为冠状动脉旁路移植术出血相关并发症的预测因子并会导致血小板输注率增加[31-32]。但是目前尚无NCS出血事件与P_2Y_{12}抑制剂停用时间的关系的报道。上述指南建议支架患者择期NCS术前停用普拉格雷7 d，氯吡格雷5 d，替格瑞洛3 d[29]。同样，对于出血风险高的手术或患者，停药时间需要适当延长。

1.5　APT的桥接治疗

APT的桥接治疗是指使用短半衰期的抗血小板药物替代长半衰期药物，适用于缺血和出血风险均较高的患者，比如与PCI间隔时间小于指南推荐的手术。理想的用于桥接治疗的抗血小板药物应该具备以下特征：起效快、半衰期短、作用可逆、血小板抑制率高、不良反应少、有特异性拮抗剂。目前临床上比较符合上述条件的药物主要有替罗非班、依替巴肽和坎格瑞洛。

SAVONITTO等[33]对需要接受紧急大手术或眼科手术，同时具有ST形成高风险的DES患者实施替罗非班桥接治疗，未观察到死亡、心脏缺血事件和需要进行手术治疗的出血并发症。也有学者报道了依替巴肽用于桥接治疗的有效性[34-35]。但是上述研究的病例数较少，而且患者类型、手术方式、治疗方案等均存在较大差异，不能作为推广桥接治疗的有力依据。

坎格瑞洛是一种新型、短效、静脉使用的P_2Y_{12}受体拮抗剂，BRIDGE试验首次将其用于桥接治疗，结果发现治疗组的血小板反应性较安慰剂组显著下降且两组的出血率没有差异[36]。随后有回顾性研究也得出了类似的结论[37]。但是，这些研究纳入的患者较少且手术类型多为心脏手术，缺少在NCS中应用坎格瑞洛的数据。

综上所述，桥接治疗在支架患者围术期APT管理中具有广阔的应用前景，但仍需要更多的前瞻性研究来提供指导意见，以确定最佳获益人群、使用剂量、疗效监测方法以及不良反应的处理。

1.6　APT的术后重启

如上所述，阿司匹林可作为大多数支架患者NCS围术期的背景治疗，仅在手术或患者具有较高的出血风险时停用，而P_2Y_{12}受体拮抗剂均需要在术前停用。对于APT的术后重启，我们不仅要考虑支架患者脱离APT后的缺血风险，也要考虑术后发生出血并发症的风险。目前尚无针对NCS的相关研究，但指南和专家共识基本达成一致：如果阿司匹林术前被停用，术后应立即开始重启使用；氯吡格雷、普拉格雷或替格瑞洛应在术后24~96 h后重启使用，对于最近（< 6周）接受PCI或出现ACS的患者，最好是在术后48 h内启用[29, 38]。对于出血风险较大或者出现出血并发症的患者，APT的术后重启需要延迟，具体的延迟时间有待进一步研究。

2　未来的探索

2.1　血小板功能检测提供合理指导

血小板功能检测被视为APT治疗效果的一种靶向检测手段，可以为围术期APT管理提供客观参考。有研究指出：在血小板计数正常的情况下，停止服用阿司匹林3~4 d后健康的血小板会大于30%，足以正常止血[39]。这一结论提示我们，有效的血小板功能检测有助于准确判断术前APT的暂停时间，同时降低患者的缺血和出血风险[40]。

这项技术的另一个用途是指导支架患者缺血和出血风险的动态评估,因为已有多项试验证实其作为一种客观指标来预测缺血和出血风险的有效性[41-42]。这一点弥补了前述风险评估工具的不足。同时,床旁检验的发展极大地拓展了该技术的应用场景,使动态评估得以实现。

2.2 新的药物改变APT管理方案

有研究发现了一种命名为PB2452的单克隆抗体片段,是替格瑞洛的特异性拮抗剂。Ⅰ期临床试验发现PB2452可以在5 min内逆转替格瑞洛的作用,且持续时间超过20 h,停药后没有血小板活性反弹[43]。作为抗血小板药物的首个拮抗剂,PB2452为围术期APT管理提供了一个新的思路:在替格瑞洛被指南推荐为ACS患者一线治疗方案的背景下,PB2452可以使替格瑞洛的使用更加安全,减少出血并发症的发生。同时,作为一种快速逆转药物,可以满足支架患者接受急诊手术时快速恢复血小板功能的要求。更多的证据有待进一步实验的结果。

3 总结

按照目前的趋势推算,支架患者将成为所有接受择期NCS的患者中一个不可忽视的群体。围术期APT中任何一个环节的疏忽都可能给患者带来灾难性的后果。鉴于患者之间的个体差异和来自于医师决策、手术等多方面因素的干扰,不同研究的结论很难达成一致。同时随着新的检测技术和药物的开发,我们需要更加广泛和深入的研究为临床工作提供指导。

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