·综 述 General review·

定向斑块旋切联合药物涂层球囊治疗股腘动脉病变进展

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【摘要】 股腘动脉硬化闭塞症是影响人类健康的常见疾病。目前腔内治疗已成为主流术式，但术后再狭窄率仍很高。定向斑块旋切术(DA)通过斑块切除改善血管顺应性，但降低再狭窄率效果不明显。药物涂层球囊(DCB)出现为解决这一问题带来曙光，其通过承载的药物进入血管壁防止内皮细胞和平滑肌细胞增殖，从而发挥远期抗内膜增生作用。多项研究表明 DCB 可降低晚期管腔丢失(LLL)和再狭窄率，减少再次手术率。DA 与 DCB 联合应用可提高药物摄取，取得较好疗效。然而目前的研究证据还不充分，仍需更多大样本多中心随机对照研究加以验证。

【关键词】 股腘动脉硬化闭塞症；定向斑块旋切术；药物涂层球囊

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Directional atherectomy combined with drug-coated balloon dilatation for femoropopliteal artery diseases: recent advances in research *CAI Zhiwen, GU Yongquan. Department of Vascular Surgery, Xuanwu Hospital, Capital Medical University; Institute of Vascular Surgery; Academic Department of Vascular Surgery, Capital Medical University, Beijing 100053, China*

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【**Abstract**】 Femoropopliteal arteriosclerosis obliteration has been a common disease affecting human health. Currently, endovascular treatment has become the mainstream of operation, but the postoprative restenosis rate is still very high. Directional atherectomy (DA) can improve blood vessel compliance by removing plaque, but it has no obvious effect in reducing the restenosis rate. The emergence of drug-coated balloon (DCB) has brought the dawn to solve this problem. Through the entry of its loaded drug into the vascular wall to prevent the proliferation of endothelial cells and smooth muscle cells, DCB exerts its long-term anti-intimal hyperplasia effect. A number of studies have shown that DCB can reduce the late lumen loss and the restenosis rate, thus decrease the re-operation rate. Combination use of DA and DCB can improve the uptake of drugs, then, better results can be expected. However, the present research results are not sufficient to support the above theoretical speculation, and large sample and more multicenter randomized controlled studies need to be done before it can be validated.(J Intervent Radiol, 2019, 28: 301-304)

【**Key words**】 femoropopliteal arteriosclerosis obliterans; directional atherectomy; drug-coated balloon

周围动脉硬化闭塞症是世界范围内常见慢性病变，涉及 5%～18%成年人[1]，是继冠状动脉疾病和脑卒中后第三大动脉粥样硬化引起的高发病率、致死性疾病[2]，往往导致患者活动能力减弱、生活质量下降和重大经济负担。股腘动脉病变是最常引起下肢动脉缺血的因素[3]，起初表现为间歇性跛行，逐渐发展为静息痛，最后导致肢端溃疡和坏疽。

1 股腘动脉硬化闭塞症治疗挑战

股腘动脉硬化闭塞症传统治疗方式是开放性旁路转流，但创伤大，且患者往往伴发基础疾病较多，手术耐受性差，因此围手术期并发症发生率高，术后恢复时间长。腔内治疗手术创伤小，术后患者恢复快，逐渐成为首选术式[4-5]。股腘动脉经受扭曲、压缩、弯曲、延展等机械应力，经皮腔内血管成形术

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(PTA)颇具挑战性,术后 6～12 个月再狭窄率高达 58%[6]。对于大部分股腘动脉病变,金属支架提高了近期和中期通畅率,然而支架也存在许多不足,如支架内再狭窄(ISR)、支架断裂和血管内异物遗留。ISR 导致患者 PTA 术后靶血管血运重建(target vessel revascularization,TVR)比例仍高达 7.4%～27.4%[7]。

目前认为 PTA 术后再狭窄机制包括术时机械、生物因素及以后相互作用等多方面,具体环节有:①球囊扩张所致病变血管内膜和壁损伤;②血管被动扩张后回弹及血栓形成;③血管重构不良;④内膜增生[8],由动脉中膜平滑肌细胞刺激细胞外基质引起[9]。

2 定向斑块旋切术

斑块切除术通过物理方法安全有效地切除动脉硬化斑块,恢复血流通畅,减少了支架使用,同时也可保护侧支[10]。其缺点为远端栓塞风险,因此推荐应用保护伞。目前临床上应用的斑块切除术有 4 种类型:定向斑块旋切术(directional atherectomy,DA)、斑块旋磨术、轨道斑块切除术及准分子激光斑块切除术。SilverHawk™、TurboHawk™ 是目前应用的两种 DA 手术器械。文献报道单纯 DA 术治疗股腘动脉原发病变后 12 个月一期通畅率为 54%～84%[11]。一些研究显示 DA 术与普通球囊、支架植入相比无明显围术期或临床疗效优势[12]。DA 术有助于获取影像学上良好结果,但对降低再狭窄率无显著作用[13]。DA 术对血管中膜及更深层次的损伤引发了明显的再狭窄进程,抵消了其改善血管顺应性的优势[14]。

3 药物涂层球囊

药物涂层球囊(DCB)表面承载抗组织增生药物(如紫杉醇),PTA 术时对病变血管内膜进行扩张、加压,单剂量药物在球囊表面短时释放、转移至血管壁中,发挥抑制内膜增生的作用,从而抑制再狭窄[15]。目前已知紫杉醇抗内膜增生机制是能封闭微管分解,因此抑制术后细胞分裂、细胞增殖及细胞生成[16]。紫杉醇与微管结合后抑制纺锤体形成,终止细胞分裂,从而抑制细胞增殖。球囊扩张时 DCB 释放紫杉醇进入血管壁,随着膨胀时间达 30～60 s,其浓度可达动脉外膜且能维持数周[17]。单次 DCB 应用后 28 d,股浅动脉组织中依然可测出紫杉醇浓度,为 3～5 ng/mg[18]。

THUNDER 临床试验研究是最早开展的一项 DCB 多中心随机对照研究,48 例下肢动脉病变患者接受 DCB 治疗,54 例接受普通球囊治疗,病变平均长度为 74 mm,术后 6 个月 DCB 组、普通球囊组患者晚期管腔丢失(LLL)分别为(0.4±1.2) mm、(1.7±1.8) mm(P<0.001),靶病变血运重建(TLR)分别为 4%、37%(P<0.001),术后 24 个月 TLR 分别为15%、52%(P<0.001)[19]。PACIFIER 临床试验研究中 DCB 组 41 例,PTA 组 44 例,病变长度分别为(7.0±5.3) cm、(6.6±5.5) cm,术后 6 个月 LLL 分别为 0.01 mm、0.65 mm(P=0.001),TLR 分别为 7.1%、27.9%(P=0.02),再狭窄率分别为 8.6%、32.4%(P=0.01)[20]。IN.PACT SFA 临床试验研究是一项大规模多中心随机对照研究,DCB 组 220 例,PTA 组 110 例,随访 12 个月结果显示 DCB 组 TLR 明显低于 PTA 组(2.4% 对 20.6%),一期通畅率分别为 82.2%、52.4%,临床效果及踝-肱指数(ABI)升高明显优于 PTA 组[21]。LEVANT Ⅰ临床试验研究纳入 101 例股腘动脉病变患者,DCB 组 49 例,PTA 组 52 例,术后 6 个月LLL 分别为 1.07 mm、1.13 mm(P=0.016)[22]。LEVANT Ⅱ临床试验研究纳入 476 例股腘动脉病变患者,DCB 组 316 例,PTA 组 160 例,平均病变长度为 10.79 cm,术后 12 个月一期通畅率分别为 65.2%、52.6%(P=0.02)[23]。其它一些临床试验研究如 DEBELLUM[24]、DEBATE-SFA[25]、RANGER SFA[26]等均表明,DCB 治疗效果令人满意。

DCB 于 2016 年 6 月在我国上市,一项多中心前瞻性随机对照研究随之开展[27],共入组 200 例股腘动脉病变患者,平均病变长度为 150 mm,术后 6个月 DCB 组、普通球囊组 LLL 分别为(0.05±0.73) mm、(1.15±0.89) mm,再狭窄发生率分别为 22.5%、70.8%(P<0.001),术后 1 年 TLR 分别为 7.2%、39.6%(P<0.001);研究结果依然证明 DCB 治疗具有优势。

综上所述,DCB 术后 12 个月一期通畅率为 65.2%～82.2%,与 PTA 术相比能减少术后 6 个月,甚至 24 个月内 LLL 和再狭窄率,降低二次干预率。但这主要针对泛大西洋学会联盟(TASC)Ⅱ分级 A/B 级病变,目前尚缺乏 DCB 治疗 TASCⅡC/D 级病变的研究结果。目前对 DCB 治疗股腘动脉病变仍存在两个问题有待解决,一是血管壁夹层风险高,增加了补救性支架应用,二是对钙化病变的疗效不理想。THUNDER 临床试验研究亚组分析提示,DCB 术后非限流性夹层即使不植入支架也不会影响治疗效果[28]。Tepe 等[29]研究发现钙化病变经 DCB 治疗后 LLL 发生率高,这与钙化病变抑制药物进入血

管壁有关;推荐在 DCB 术前联用斑块切除,疗效更佳。

4　DA 联合 DCB

早期动物实验数据显示斑块切除后释放药物是安全的[18]。斑块切除目的是改变血管顺应性,提高近期手术效果。DCB 通过释放安全有效的药物剂量进入血管壁,减少斑块切除后再狭窄进程。斑块切除联合 DCB 将获得更好的近期疗效,降低周围动脉病变术后再狭窄。有研究表明 DA 联合DCB 不仅促进抗增殖药物进入血管壁,提高药物摄取并抑制内膜增生,也抑制斑块机械切除后血小板活化引起的炎性反应[30]。目前研究表明 DA 联合 DCB 治疗股腘动脉硬化闭塞症有一定优势。

Cioppa 等[31]采用 DA 联合 DCB 治疗 30 例严重钙化的股腘动脉病变患者,斑块切除后平均内径狭窄度由(93±7)%改善至(23±6)%,DCB 治疗后进一步改善至(9.8±5.8)%,补救支架植入率为 6.5%,术后 12 个月一期通畅率为 90%;结果提示 DA 切除钙化病变扩大了管腔,减少了限流性夹层发生率,DCB 减少了支架植入需要。Sixt 等[32]回顾性分析 89 例股腘动脉再狭窄患者,其中 DA 联合 DCB 治疗 29 例,DA 联合 PTA 治疗 60 例,Kaplan-Meier 生存曲线显示术后 1 年再狭窄率分别为 15.3%、56.2%,再狭窄多因素 Cox 回归分析显示两组术后风险比为 0.28(0.12～0.66,P=0.003 6),DA 联合 DCB 组疗效较优。DEFINITIVE AR 多中心随机对照试验研究纳入 102 例股腘动脉病变致跛行或静息痛患者,分为 DA+DCB 组(48 例)、单纯 DCB 组(54 例),平均病变长度分别为(11.2±4.0) cm、(9.7±4.1) cm(P=0.05),术后 12 个月随访显示一期通畅率分别为 84.6%、81.3%(P=0.78),TLR 分别为 7.3%、8.0%(P=0.90),因此需要更强有力随机对照研究验证 DA 联合 DCB 治疗优势[33]。Stavroulakis 等[34]报道单中心治疗 72 例孤立性腘动脉病变患者中 41 例接受 DA 联合 DCB,31 例接受单纯 DCB 治疗,影响生活质量的跛行患者分别占 86%、74%,平均病变长度分别为42 mm、47 mm,手术成功率分别为 93%、84%(P=0.24),术后 12 个月一期通畅率分别为 82%、65%(P=0.021),免于再次手术率分别为 94%、82%(P=0.072);结果显示 DA 联合 DCB 术后一期通畅率优于单纯 DCB,但 TLR、LLL 等仍需进一步验证。

以上研究表明,DA 联合 DCB 与单纯 DCB 相比降低了限流性夹层发生率及再狭窄风险,提高了术后 12 个月一期通畅率(82%～84.6%),但降低再次手术率效果不明显;纳入研究样本量小,随访时间短,因此需更多大样本、多中心随机对照研究验证 DA 联合 DCB 优于单纯 DCB。

5　结语

目前国内外研究表明 DA 联合 DCB 治疗股腘动脉硬化闭塞症有一定优势,是一值得期待的新疗法。由于其优势尚不够明显,仍需更多大样本、多中心随机对照研究加以证明。此外,球囊涂层技术优化、抗增殖药物选择、药物最佳剂量、治疗费用等诸多问题仍需进一步研究,才能促进临床广泛应用。

[参 考 文 献]

[1] Savji N, Rockman CB, Skolnick AH, et al. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects[J]. J Am Coll Cardiol, 2013, 61: 1736-1743.

[2] Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis[J]. Lancet, 2013, 382: 1329-1340.

[3] Kasapis C, Gurm HS. Current approach to the diagnosis and treatment of femoral-popliteal arterial disease. A systematic review[J]. Curr Cardiol Rev, 2009, 5: 296-311.

[4] Garcia L, Jaff MR, Metzger C, et al. Wire-interwoven nitinol stent outcome in the superficial femoral and proximal popliteal arteries: twelve-month results of the SUPERB trial[J]. Circ Cardiovasc Interv, 2015, 8,pii: e000937.

[5] Leon LR, Dieter RS, Gadd CL, et al. Preliminary results of the initial United States experience with the supera woven nitinol stent in the popliteal artery[J]. J Vasc Surg, 2013, 57: 1014-1022.

[6] Conrad MF, Kang J, Cambria RP, et al. Infrapopliteal balloon angioplasty for the treatment of chronic occlusive disease[J]. J Vasc Surg, 2009, 50: 799-805.

[7] Vardi M, Novack V, Pencina MJ, et al. Safety and efficacy metrics for primary nitinol stenting in femoropopliteal occlusive disease: a meta-analysis and critical examination of current methodologies[J]. Catheter Cardiovasc Interv, 2014, 83: 975-983.

[8] 刘　勇, 刘怡辰. 药物涂层球囊新技术的临床应用进展及述评[J]. 生物医学工程与临床, 2012, 16: 301-303.

[9] Chaabane C, Otsuka F, Virmani R, et al. Biological responses in stented arteries[J]. Cardiovasc Res, 2013, 99: 353-363.

[10] Yongquan G, Lianrui G, Lixing Q, et al. Plaque excision in the management of lower-limb ischemia of atherosclerosis and in-stent restenosis with the SilverHawk atherectomy catheter[J]. Int Angiol, 2013, 32: 362-367.

[11] Quevedo HC, Arain SA, Ali G, et al. A critical view of the peripheral atherectomy data in the treatment of infrainguinal arterial disease[J]. J Invasive Cardiol, 2014, 26: 22-29.

[12] Diamantopoulos A, Katsanos K. Atherectomy of the femoropopliteal artery: a systematic review and meta-analysis of randomized controlled trials[J]. J Cardiovasc Surg(Torino), 2014, 55: 655-665.

[13] Zeller T, Krankenberg H, Steinkamp H, et al. One-year outcome of percutaneous rotational atherectomy with aspiration in infrainguinal peripheral arterial occlusive disease: the multicenter pathway PVD trial[J]. J Endovasc Ther, 2009, 16: 653-662.

[14] Shammas NW. Commentary: the adluminal origin of restenosis in peripheral artery interventions and its implications for the development of future treatment strategies: searching deep into the arterial wall[J]. J Endovasc Ther, 2015, 22: 716-718.

[15] 项以力, 张温凯, 杨 镛. 药物涂层球囊和无涂层球囊治疗股腘动脉缺血性疾病疗效及安全性 meta 分析[J]. 介入放射学杂志, 2017, 26: 500-507.

[16] Axel DI, Kunert W, Goggelmann C, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery[J]. Circulation, 1997, 96: 636-645.

[17] Schmidt A, Piorkowski M, Werner M, et al. First experience with drug-eluting balloons in infrapopliteal arteries: restenosis rate and clinical outcome[J]. J Am Coll Cardiol, 2011, 58: 1105-1109.

[18] Tellez A, Dattilo R, Mustapha JA, et al. Biological effect of orbital atherectomy and adjunctive paclitaxel-coated balloon therapy on vascular healing and drug retention: early experimental insights into the familial hypercholesterolaemic swine model of femoral artery stenosis[J]. EuroIntervention, 2014, 10: 1002-1008.

[19] Tepe G, Zeller T, Albrecht T, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg[J]. N Engl J Med, 2008, 358: 689-699.

[20] Werk M, Albrecht T, Meyer DR, et al. Paclitaxel-coated balloons reduce restenosis after femoro-popliteal angioplasty: evidence from the randomized PACIFIER trial[J]. Circ Cardiovasc Interv, 2012, 5: 831-840.

[21] Tepe G, Laird J, Schneider P, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial [J]. Circulation, 2015, 131: 495-502.

[22] Scheinert D, Duda S, Zeller T, et al. The LEVANT I (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) trial for femoropopliteal revascularization: first-in-human randomized trial of low-dose drug-coated balloon versus uncoated balloon angioplasty[J]. JACC Cardiovasc Interv, 2014, 7: 10-19.

[23] Rosenfield K, Jaff MR, White CJ, et al. Trial of a paclitaxel-coated balloon for femoropopliteal artery disease[J]. N Engl J Med, 2015, 373: 145-153.

[24] Fanelli F, Cannavale A, Boatta E, et al. Lower limb multilevel treatment with drug-eluting balloons: 6-month results from the DEBELLUM randomized trial[J]. J Endovasc Ther, 2012, 19: 571-580.

[25] Liistro F, Grotti S, Porto I, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery)[J]. JACC Cardiovasc Interv, 2013, 6: 1295-1302.

[26] Bausback Y, Willfort-Ehringer A, Sievert H, et al. Six-month results from the initial randomized study of the ranger paclitaxel-coated balloon in the femoropopliteal segment[J]. J Endovasc Ther, 2017, 24: 459-467.

[27] Jia X, Zhang J, Zhuang B, et al. Acotec drug-coated balloon catheter: randomized, multicenter, controlled clinical study in femoropopliteal arteries: evidence from the acoArt I trial[J]. JACC Cardiovasc Interv, 2016, 9: 1941-1949.

[28] Tepe G, Zeller T, Schnorr B, et al. High-grade, non-flow-limiting dissections do not negatively impact long-term outcome after paclitaxel-coated balloon angioplasty: an additional analysis from the THUNDER study[J]. J Endovasc Ther, 2013, 20: 792-800.

[29] Tepe G, Beschorner U, Ruether C, et al. Drug-eluting balloon therapy for femoropopliteal occlusive disease: predictors of outcome with a special emphasis on calcium[J]. J Endovasc Ther, 2015, 22: 727-733.

[30] Beschorner U, Zeller T. Combination of mechanical atherectomy and drug-eluting balloons for femoropopliteal in-stent restenosis [J]. J Cardiovasc Surg(Torino), 2014, 55: 347-349.

[31] Cioppa A, Stabile E, Popusoi G, et al. Combined treatment of heavy calcified femoro-popliteal lesions using directional atherectomy and a paclitaxel coated balloon: one-year single centre clinical results[J]. Cardiovasc Revasc Med, 1900, 13: 219-223.

[32] Sixt S, Carpio Cancino OG, Treszl A, et al. Drug-coated balloon angioplasty after directional atherectomy improves outcome in restenotic femoropopliteal arteries[J]. J Vasc Surg, 2013, 58: 682-686.

[33] Zeller T, Langhoff R, Rocha-Singh KJ, et al. Directional atherectomy followed by a paclitaxel-coated balloon to inhibit restenosis and maintain vessel patency: twelve-month results of the DEFINITIVE AR study[J]. Circ Cardiovasc Interv, 2017, 10, pii: e004848.

[34] Stavroulakis K, Schwindt A, Torsello G, et al. Directional atherectomy with antirestenotic therapy vs drug-coated balloon angioplasty alone for isolated popliteal artery lesions[J]. J Endovasc Ther, 2017, 24: 181-188.

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