

Progress of lower limb arterial calcification and the impact on endovascular therapy of arteriosclerosis obliteration in lower extremity

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[Abstract] With the aging of population, the prevalence of peripheral arterial disease (PAD) shows a trend of rising. Lower limb arteriosclerosis occlusion disorder (ASO) is the most common disease of PAD. Endovascular therapy is the preferred treatment for ASO in lower extremity. As the characteristic of lower limb ASO, vascular calcification has an important impact on the efficacy and prognosis of interventional therapy, which is closely related to the rates of amputation and all-cause mortality. The correct understanding and active intervention of vascular calcification are helpful for the treatment and prognosis. The advancements of lower limb arterial calcification and vascular calcification affecting endovascular therapy of ASO in lower extremity were mainly reviewed in this article.

[Keywords] arteriosclerosis obliterans; lower extremity; calcification; interventional therapy

DOI:10.13929/j.1672-8475.201807008

下肢动脉钙化研究进展及其对下肢动脉硬化闭塞症介入治疗的影响

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[摘要] 随着人口老龄化加快, 外周动脉疾病发病率逐年升高, 其中以下肢动脉硬化闭塞症(ASO)最为常见, 对此血管腔内介入治疗是目前临床首选治疗方法。血管钙化作为 ASO 的特征表现, 其严重程度对介入治疗的疗效及预后均具有重要影响, 与截肢及全因死亡率密切相关。正确认识并积极干预血管钙化有利于提高疗效, 改善患者预后。本文主要对下肢动脉钙化的研究进展及其对下肢 ASO 介入治疗的影响做一综述。

[关键词] 动脉硬化, 闭塞性; 下肢; 钙化; 介入治疗

[中图分类号] R543; R815 **[文献标识码]** A **[文章编号]** 1672-8475(2019)03-0182-04

随着我国社会人口老龄化进程加快, 外周动脉疾病(peripheral arterial disease, PAD)的发病率呈逐年上升趋势^[1], 且 PAD 与心血管疾病发病率和死亡率增高有关^[2]。PAD 中, 下肢动脉硬化闭塞症(arteriosclerosis occlusion disorder, ASO)最为常见,

在 70 岁以上人群中发病率达 15%~20%, 且男性患者多于女性^[3]。血运重建是治疗下肢 ASO 的主要思路。相对于传统外科手术治疗, 血管腔内介入治疗具有创伤小、并发症少、死亡率低等优点, 目前已成为临床治疗下肢 ASO 的首选方法, 且对介入治疗失败者

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[收稿日期] 2018-07-06 **[修回日期]** 2019-01-29

仍可改用开放手术进行治疗^[3-4]。血管钙化是 ASO 的特征性表现^[5],影响下肢 ASO 患者血管腔内介入治疗的预后,血管钙化越严重,截肢及全因死亡率越高^[6]。正确认识并积极干预血管钙化对 ASO 的治疗具有重要意义。本文对下肢动脉钙化的分类、危险因素、发生机制等方面的研究进展及血管钙化对下肢 ASO 介入治疗的影响进行综述。

1 下肢动脉钙化的分类

血管钙化按其发生部位主要分为内膜钙化和中膜钙化,形成机制不尽相同,但可在机体中同时存在,甚至在同一动脉位置上同时存在^[7]。血管内膜钙化相对更为常见,与脂质沉积和炎性因子刺激等有关,常见于大动脉,如主动脉、颈动脉,多局限于动脉粥样硬化斑块中^[7-9]。血管中膜钙化也称 Mönckeberg 钙化,沿内弹性膜发生于平滑肌细胞周围,为血管壁中膜内的血管平滑肌细胞(vascular smooth muscle cells, VSMCs)向成骨样细胞分化的结果^[10],常见于四肢中小动脉(如股动脉、腓动脉)^[11],是下肢 ASO 中血管钙化的主要原因^[12]。

依据钙化灶直径,血管钙化可分为微钙化(或称为点状钙化,直径 ≤ 2 mm)与大钙化(直径 > 2 mm)。微钙化一般发生于内膜动脉粥样硬化斑块中,可增加斑块破裂的风险;大钙化则更常见于动脉中膜,常导致血管腔狭窄^[13-14]。

2 下肢动脉钙化的相关危险因素

下肢 ASO 的主要病因为动脉粥样硬化,年龄增长是血管发生结构和功能改变的独立危险因素。随着年龄增长,血管舒缩次数不断增加,血管壁中的钙、脂质及胶原成分增多,平滑肌及弹力蛋白减少,最终导致血管壁出现钙化^[15]。血管钙化的危险因素还包括高血压、高脂血症、糖尿病、慢性肾功能不全等^[3,16]。此外,氧化应激等在内的炎症刺激及包括高钙血症、高磷血症在内的矿物质代谢异常也为血管钙化的危险因素^[16]。Huang 等^[6]回顾性分析 82 例有症状的 PAD 患者的下肢动脉钙化情况,结果显示年龄、糖尿病和高脂血症为下肢血管钙化的独立危险因素。Ohtake 等^[17]报道,炎症与冠状动脉钙化的发生及进展有关,以 C 反应蛋白为代表的炎症因子为下肢动脉钙化的独立危险因素^[18]。

3 下肢动脉钙化的发生机制

血管钙化是一个活跃且复杂的过程,既往认为引发血管钙化可能的病理生理学机制主要为血清钙和磷水平升高,加之机体对钙化过程抑制不足,从而发生钙

盐沉积,最终导致钙化形成^[19];而目前普遍认为血管钙化的形成类似于骨形成中所发生的主动调控过程,是巨噬细胞和 VSMCs 向成骨细胞分化的细胞内分子进程^[20]。VSMCs 通过向成骨细胞分化并产生基质囊泡,致使血管壁中磷酸钙沉积,在介导血管钙化中具有不可或缺的作用^[21]。血清中钙和磷水平改变或局部产生的炎症刺激、内源性 VSMCs 钙化抑制剂(如基质 Gla 蛋白,焦磷酸盐和诱导型骨桥蛋白抑制剂)和循环抑制剂(如胎球蛋白 A)丢失均可促进血管壁中 VSMCs 向成骨细胞分化^[22]。

4 检测及定量评价

常规 X 线、CT 检查均可用于下肢血管钙化的检测,但对微钙化的检测较为困难。动脉粥样硬化斑块内存在微钙化可增加斑块不稳定性,使其更易破裂^[8,23],故早期检测血管壁微钙化对及早诊断下肢 ASO 并合理进行临床干预具有重要意义。利用血管内超声(intravascular ultrasound, IVUS)及光学相干 CT(optical coherence tomography, OCT)可较好地检测出微钙化,但 IVUS 属有创性检查,OCT 检查受限于其可穿透深度,临床应用均受到一定影响^[23]。采用¹⁸F-NaF 作为示踪剂的 PET/CT 检查是检测血管微钙化较为理想的手段^[24-25]。较大且稳定的钙化在 PET/CT 图像中不显示¹⁸F-NaF 吸收,而生物矿化活跃的微钙化则显示¹⁸F-NaF 吸收,有利于对微钙化的检测^[13,25]。相对于完善的冠状动脉血管钙化评分体系,目前尚无规范、统一的外周动脉钙化评分系统。Agatston 等^[26]1990 年提出的方法被广泛应用并进一步改良,Mary 等^[27]基于此将 3 mm 层厚各层图像中 CT 值 > 130 HU 的钙化灶面积与其密度分数的加权重作为钙化评分。此外,临床对 ASO 常采用血管腔内治疗,可在介入治疗的同时评估血管钙化情况,Rocha-Singh 等^[20]提出基于 DSA 的外周动脉钙化评分系统,用以分析钙化类型、评估血管钙化程度。

5 血管钙化对介入治疗的影响

下肢 ASO 患者存在血管钙化、尤其是股动脉以下水平血管钙化,可对血管腔内介入治疗的疗效产生重大影响^[20]。严重血管钙化可能导致血管介入治疗装置损坏,且明显增加治疗中发生不良事件(如夹层、血管穿孔、动脉栓塞等)的风险,甚至导致治疗失败。

在对有症状的下肢 ASO 患者进行血管腔内介入治疗过程中,约 50% 涉及对最常见于股浅动脉的慢性完全闭塞(chronic total occlusion, CTO)血管的处理^[28]。处理 CTO 血管是腔内介入治疗严重下肢

ASO 的关键^[29]。对完全闭塞段血管进行再通时,血管钙化可能阻碍导丝通过真腔,使其进入内膜下,且无法越过钙化的内膜或中膜返回血管真腔,导丝不得不在更远端返回真腔,从而延长介入治疗时间、增大并发症风险^[20]。

血管腔内成形术通过扩张血管壁达到血运重建的目的,但血管钙化可改变动脉壁形态,降低其顺应性,导致血管扩张不充分或产生回缩,增加成功开通闭塞血管的难度。应用支架治疗时,血管壁钙化可造成动脉壁顺应性下降,导致支架膨胀不完全及贴壁不良。此外,释放支架时对血管壁产生较大压力,钙化的存在使血管壁受力不均,也可导致支架膨胀不良、错位并增大支架断裂的风险^[30]。血管钙化还可使血流与血管壁之间的应力发生改变,增大限流性夹层的发生风险。Bausback 等^[31]研究显示,与完全膨胀相比,支架膨胀不良时管腔残余狭窄常 $>30\%$ 。在药物洗脱球囊治疗方面,血管壁钙化形成的机械屏障阻挡药物向血管壁中渗透,且贴壁不良或局部屏障可同时影响药物的渗透和分布。Tzafiriri 等^[32]应用离体动脉制作可控的药物输注模型,分析钙化所产生的屏障对药物渗透和分布的影响,并与采用斑块旋切术处理的动脉进行对比,证实紫杉醇血管内渗透和分布受内膜钙化斑块的屏障限制,而以斑块旋切术切除斑块可解除此限制。

此外,在 ASO 患者血管腔内介入治疗预后中,血管钙化的发生与截肢及死亡有关。Huang 等^[6]发现有严重下肢动脉钙化的 ASO 患者血管腔内介入治疗预后差,截肢率及死亡率均高,并提出应增加血管钙化作为 PAD 患者新的危险因素。

6 治疗及预防措施

斑块旋切术是切除钙化斑块组织的常用方法,在支架扩张血管前采用斑块旋切术切除钙化斑块,可提高支架通畅率,并减低支架膨胀不良或断裂的风险。在药物洗脱球囊治疗前切除钙化斑块,可增加血管壁的顺应性,减少血管回缩,避免钙化对药物渗透的影响,从而减低发生再狭窄的风险。Cioppa 等^[33]报道,采用药物洗脱球囊治疗前切除严重钙化斑块,术后 1 年血管通畅率可达 90%。

目前尚无有效的能够预防下肢动脉钙化的直接手段,减缓其进展的方法多数基于对相关疾病进行治疗,包括动脉粥样硬化、高血压、骨质疏松症及慢性肾病等^[21]。

血清钙、磷水平升高可促进血管钙化的发生,日常饮食中控制钙、磷摄入或使用磷酸盐黏合剂可减少血

管钙化^[34]。Lau 等^[35]对小鼠进行实验,发现维生素 D 受体激动剂钙三醇或帕立骨化醇均有助于减少主动脉钙化。应用拟钙剂可通过抑制甲状旁腺激素的分泌并降低血清钙水平,从而减少血管钙化^[36]。双膦酸盐可以抑制破骨细胞功能,减少骨吸收并降低骨质疏松的水平,但其对血管钙化的抑制作用尚无统一意见,且其肾毒性较大,对肾功能不全者应慎用^[21]。Mary 等^[27]发现 2 型糖尿病患者中,二甲双胍的应用与较低的膝下动脉钙化评分独立相关,推测二甲双胍对血管钙化具有抑制作用;尽管尚无多中心前瞻性研究证实,但这也为治疗血管钙化合并其他疾病提供了参考。

7 小结

血管钙化是导致下肢 ASO 中不良事件发生及预后不良的高危因素,明确其形成机制并制定相应的治疗和预防措施对治疗下肢 ASO 至关重要。目前尚缺乏完善的下肢动脉的相关影像学定量评价系统。制定统一的下肢动脉钙化评分标准,并在不同介入治疗或相关预防方案中对其疗效及预后进行评价,是亟待解决的关键问题。

[参考文献]

- [1] 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. *Lancet*, 2013, 382(9901):1329-1340.
- [2] Olin JW, White CJ, Armstrong EJ, et al. Peripheral artery disease: Evolving role of exercise, medical therapy, and endovascular options. *J Am Coll Cardiol*, 2016, 67(11):1338-1357.
- [3] 中华医学会外科学分会血管外科学组. 下肢动脉硬化闭塞症诊治指南. *中华医学杂志*, 2015, 95(24):145-151.
- [4] May KK, Robless PA, Sidhu HR, et al. Limb salvage in patients with peripheral arterial disease managed by endovascular first approach. *Vasc Endovascular Surg*, 2014, 48(2):129-133.
- [5] Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*, 2006, 47(8 Suppl):C7-C12.
- [6] Huang CL, Wu IH, Wu YW, et al. Association of lower extremity arterial calcification with amputation and mortality in patients with symptomatic peripheral artery disease. *PLoS One*, 2014, 9(2):e90201.
- [7] Demer LL, Tintut Y. Inflammatory, metabolic, and genetic mechanisms of vascular calcification. *Arterioscler Thromb Vasc Biol*, 2014, 34(4):715-723.
- [8] Otsuka F, Sakakura K, Yahagi K, et al. Has our understanding of calcification in human coronary atherosclerosis progressed? *Arterioscler Thromb Vasc Biol*, 2014, 34(4):724-736.

- [9] Budoff MJ, Achenbach S, Blumenthal RS, et al. Assessment of coronary artery disease by cardiac computed tomography: A scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*, 2006, 114(16):1761-1791.
- [10] Byon CH, Chen Y. Molecular mechanisms of vascular calcification in chronic kidney disease: The link between bone and the vasculature. *Curr Osteoporos Rep*, 2015, 13 (4): 206-215.
- [11] Lanzer P, Boehm M, Sorribas V, et al. Medial vascular calcification revisited: Review and perspectives. *Eur Heart J*, 2014, 35(23):1515-1525.
- [12] David Smith C, Gavin Bilmen J, Iqbal S, et al. Medial artery calcification as an indicator of diabetic peripheral vascular disease. *Foot Ankle Int*, 2008, 29(2):185-190.
- [13] 叶斐, 严金川, 徐绥宁, 等. 血管钙化研究的新进展. *中华心血管病杂志*, 2017, 45(2):170-173.
- [14] Vengrenyuk Y, Carlier S, Xanthos S, et al. A hypothesis for vulnerable plaque rupture due to stress-induced debonding around cellular microcalcifications in thin fibrous caps. *Proc Natl Acad Sci U S A*, 2006, 103(40):14678-14683.
- [15] Takeuchi K, Zhang B, Ideishi M. Influence of age and hypertension on the association between small artery compliance and coronary disease. *Am J Hypertens*, 2004, 17 (12): 1188-1191.
- [16] Chen NX, Moe SM. Vascular calcification: Pathophysiology and risk factors. *Curr Hypertens Rep*, 2012, 14(3):228-237.
- [17] Ohtake T, Ishioka K, Honda K, et al. Impact of coronary artery calcification in hemodialysis patients: Risk factors and associations with prognosis. *Hemodialysis Intl*, 2010, 14 (2): 218-225.
- [18] Ohtake T, Oka M, Ikee R, et al. Impact of lower limbs' arterial calcification on the prevalence and severity of PAD in patients on hemodialysis. *Vasc Surg*, 2011, 53(3):676-683.
- [19] Karwowski W, Naumnik B, Szczepański M, et al. The mechanism of vascular calcification—a systematic review. *Med Sci Monit*, 2012, 18(1):RA1-RA11.
- [20] Rocha-Singh KJ, Zeller T, Jaff MR. Peripheral arterial calcification: Prevalence, mechanism, detection, and clinical implications. *Catheter Cardiovasc Interv*, 2014, 83 (6): E212-E220.
- [21] Leopold JA. Vascular calcification: Mechanisms of vascular smooth muscle cell calcification. *Trends Cardiovasc Med*, 2015, 25(4):267-274.
- [22] Bessueille L, Magne D. Inflammation: A culprit for vascular calcification in atherosclerosis and diabetes. *Cell Mol Life Sci*, 2015, 72(13):2475-2489.
- [23] Hutcheson JD, Maldonado N, Aikawa E. Small entities with large impact: Microcalcifications and atherosclerotic plaque vulnerability. *Curr Opin Lipidol*, 2014, 25(5):327-332.
- [24] Chen W, Dilsizian V. Targeted PET/CT imaging of vulnerable atherosclerotic plaques: Microcalcification with sodium fluoride and inflammation with fluorodeoxyglucose. *Curr Cardiol Rep*, 2013, 15(6):364.
- [25] Dweck MR, Chow MW, Joshi NV, et al. Coronary arterial ¹⁸F-sodium fluoride uptake: A novel marker of plaque biology. *Am Coll Cardiol*, 2012, 59(17):1539-1548.
- [26] Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *Am Coll Cardiol*, 1990, 15(4):827-832.
- [27] Mary A, Hartemann A, Liabeuf S, et al. Association between metformin use and below-the-knee arterial calcification score in type 2 diabetic patients. *Cardiovasc Diabetol*, 2017, 16(1):24.
- [28] Banerjee S, Sarode K, Patel A, et al. Comparative assessment of guidewire and microcatheter vs a crossing device-based strategy to traverse infrainguinal peripheral artery chronic total occlusions. *J Endovasc Ther*, 2015, 22(4):525-534.
- [29] Banerjee S, Jeon-Slaughter H, Tsai S, et al. Comparative assessment of procedure cost and outcomes between guidewire and crossing device strategies to cross peripheral artery chronic total occlusions. *JACC Cardiovasc Interv*, 2016, 9 (21): 2243-2252.
- [30] Adlakha S, Sheikh M, Wu J, et al. Stent fracture in the coronary and peripheral arteries. *J Interv Cardiol*, 2010, 23(4): 411-419.
- [31] Bausback Y, Botsios S, Flux J, et al. Outback catheter for femoropopliteal occlusions: Immediate and long-term results. *J Endovasc Ther*, 2011, 18(1):13-21.
- [32] Tzafriri AR, Garcia-Polite F, Zani B, et al. Calcified plaque modification alters local drug delivery in the treatment of peripheral atherosclerosis. *J Control Release*, 2017, 264: 203-210.
- [33] Cioppa A, Stabile E, Popuso 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. *Cardiovasc Revasc Med*, 2012, 13 (4): 219-223.
- [34] Finch JL, Lee DH, Liapis H, et al. Phosphate restriction significantly reduces mortality in uremic rats with established vascular calcification. *Kidney Int*, 2013, 84(6):1145-1153.
- [35] Lau WL, Leaf EM, Hu MC, et al. Vitamin D receptor agonists increase klotho and osteopontin while decreasing aortic calcification in mice with chronic kidney disease fed a high phosphate diet. *Kidney Int*, 2012, 82(12):1261-1270.
- [36] Meiting W, Cameron R, Cecilia M. Vascular calcification: An update on mechanisms and challenges in treatment. *Calcif Tissue Int*, 2013, 93(4):365-373.