·综 述·

壁面剪切力在动脉夹层形成中的作用与机制研究进展

张嘉伟,梅峻豪,刘婷婷,贾中芝*

南京医科大学附属常州第二人民医院介入血管科,江苏 常州 213003

[摘 要] 动脉夹层(arterial dissection,AD)的发生是多因素共同作用的结果,壁面剪切力(wall shear force,WSS)是血流与血管壁的摩擦力,是AD发生的重要始动因素。异常WSS通过多种机制引起动脉壁各层结构(内膜、中膜、外膜)的病理性改变,如内皮细胞结构和功能障碍、内弹力板损伤、平滑肌细胞数量减少和表型转化、细胞外基质降解等,最终导致AD的发生。为了更好地了解AD的发病机制,本文对异常WSS引起动脉壁各层结构病理性改变的调控机制进行综述。

[关键词] 壁面剪切力;动脉;夹层

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The role and mechanism of wall shear stress in the occurrence of arterial dissection

ZHANG Jiawei, MEI Junhao, LIU Tingting, JIA Zhongzhi*

Department of Interventional and Vascular Surgery, the Affiliated Changzhou Second People's Hospital of Nanjing Medical University, Changzhou 213003, China

[**Abstract**] The occurrence of arterial dissection (AD) is the result of multiple factors. Wall shear force (WSS), an important initiating factor for AD, is the friction between blood flow and vessel wall. Abnormal WSS can cause pathological changes of arterial wall (intima, media, adventitia) through various mechanisms, such as endothelial cell structure and dysfunction, internal elastic lamina injury, reduction and phenotypic transformation of smooth muscle cells, extracellular matrix degradation, and eventually lead to the occurrence of AD. In order to better understand the pathogenesis of AD, this article reviews the regulatory mechanisms of pathological changes in each layer of arterial wall caused by abnormal WSS.

[**Key words**] wall shear stress; artery; dissection

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动脉夹层(arterial dissection,AD)是指动脉内膜出现破裂口,血液经破裂口进入动脉内膜下及中膜,致使动脉内膜与中膜分离。壁面剪切力(wall shear stress,WSS)是指血流与血管内皮间的摩擦所作用于血管壁单位面积的力,也称切应力。近年来随着计算机流体模拟技术的发展,WSS在AD形成中的作用与机制逐渐被明确[1-2]。为了更好地了解AD的发病机制,本文对WSS在AD发病中的作用与机制进行汇总分析。

1 WSS与AD

WSS的实质是血液流动过程中与血管内皮之间的摩擦力,其大小与血液的黏度、流速和血管内径直接相关,其计算公式为$\tau_w=4\ \mu Q/\pi a^3$,其中μ为血液黏度,Q为平均血流量,a为血管内径。人体大血管的WSS在10~70 dyn/cm^{2}之间。WSS直接作用于动脉内皮,之后内皮细胞(endothelial cell,EC)通过多种信号通路对动脉壁的组成成分产生影响。此外,当血液流经不同形状的动脉而加速或减速时,

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*通信作者(Corresponding author),E-mail:jiazhongzhi.1998@163.com

WSS会因此发生改变，产生壁面剪切力梯度（wall shear stress gradient，WSSG），加速血流产生的WSS逐渐增大，即正WSSG，反之则产生负WSSG，不同的WSSG对动脉壁组成成分的影响不同。

EC通过感知WSS和WSSG的变化，动态调节动脉管壁的组成成分。当WSS和WSSG异常时，可导致动脉壁发生病理性改变，如EC功能障碍、内弹力板断裂、平滑肌细胞（smooth muscle cell，SMC）数量减少和表型转化、细胞外基质（extracellular matrix，ECM）降解等，导致动脉的顺应性、弹性下降和动脉硬化，最终导致AD的发生。

2　WSS引起AD的机制

异常WSS引起动脉壁病理性改变，进而促进AD的发生，以下对相关机制进行详细阐述。

2.1　WSS与动脉内膜

动脉内膜的组成包括EC、SMC、ECM和成纤维细胞（fibroblast，FB），以EC为主。异常WSS引起的内膜撕裂是AD形成的关键[3]。以下将详细介绍WSS引起内膜病理改变的机制（图1）。

2.1.1　WSS与EC

EC可以通过其力学感受器将WSS转导为可以影响基因表达和细胞功能（如形态异常、排列紊乱、增殖、凋亡及通透性升高）的细胞内信号[4]。

WSS影响EC的形态及排列。生理状态下，WSS通过激活血管内皮生长因子（vascular endothelial growth factor，VEGF）受体等多种信号通路重组EC内的肌动蛋白骨架，使其沿血流方向呈梭形排列，这种特殊的形态和排列提高了内膜应对血流“冲击”的能力[5-6]。而当WSS降低或消失后，EC形态呈现椭圆形或多边形，且细胞排列紊乱，使内膜变得“脆弱”[6]。

WSS影响EC的增殖与凋亡。生理状态下，WSS不但可以激活G1/S特异性细胞周期蛋白C和E，从而使EC停滞在G0期；还可以下调相关的EC生长因子，如骨形态发生蛋白4（bone morphogenetic protein 4，BMP4）、转化生长因子（transforming growth factor，TGF）-β2、肝癌衍生生长因子（hepatoma-derived growth factor，HDGF）和成纤维细胞生长因子6（fibroblast growth factor 6，FGF6），从而抑制EC增殖[7]。高/低和扰动WSS均会促进EC细胞周期加速，从而促进EC增殖[8]。另外，正常WSS还可以抑制EC凋亡，而异常WSS则促进EC凋亡[9]。

WSS还会影响EC的通透性。生理状态下，WSS可以通过上调一氧化氮合酶3（nitric oxide synthase 3，NOS3）和酪氨酸激酶（tyrosine kinase，TEK）的表达来降低EC的通透性，维持血管内稳态[10]。而WSS高/低和扰动均可使EC的通透性增加[11]。

总之，异常WSS会导致EC结构和功能障碍，这与AD的发生密切相关[12]。

2.1.2　WSS与内弹力板

内弹力板介于内膜和中膜之间，主要由网状弹力纤维构成，是动脉壁的重要支撑结构，一旦损伤断裂便不能再修复，其不可逆性损伤是AD形成的病理学基础[13]。

异常WSS是内弹力板损伤的重要原因。高WSS促进EC产生尿激酶，而尿激酶可产生纤溶蛋白进而激活基质金属蛋白酶（matrix metalloproteinases，MMP）家族成员，MMP可降解弹力纤维和胶原纤维，继而导致内弹力板损伤、断裂[10]。异常WSS可以刺激EC和SMC分泌MMP-2、MMP-9、血小板反应蛋白解整合素金属肽酶1（a disintegrin and metalloproteinase with thrombospondin motif 1，ADAMTS1）和ADAMTS6，进而导致内弹力板损伤[14]。

2.1.3　WSSG与EC

WSSG和WSS类似，也可以调控EC的功能。正WSSG增强WSS对EC基因表达的调控作用，而负WSSG则削弱WSS的影响[15]。WSSG与WSS协同调节EC的结构和功能。

正WSSG促进EC的增殖、凋亡、ECM的降解及内弹力板损伤。正WSSG不但下调阻滞EC的细胞周期蛋白，还可以上调与增殖相关的基因，如细胞骨架关联蛋白2（cytoskeleton associated protein 2，CKAP2）、染色体结构维持蛋白2（structural maintenance of chromosomes 2，SMC2）、DNA拓扑异构酶Ⅱα（topoisomerase Ⅱ A，TOP2A）和着丝粒蛋白F（centromere protein F，CENPF），进而促进EC增殖[16-17]。正WSSG下调抑制细胞凋亡的基因，如单核细胞趋化蛋白1（monocyte chemotactic protein 1，MCP1）、集落刺激因子2（colony stimulating factor 2，CSF2）、BMP4和凝血酶敏感蛋白1（thrombospondins 1，THBS1），进而促进EC凋亡[18]。正WSSG还可以下调MMP-9的抑制因子转运蛋白（transgelin，TAGLN）来促进ECM的降解[19]。此外，正WSSG可以引起内弹力板损伤，导致动脉管壁的破坏性重塑，继而引起AD的发生[20]。

负WSSG可以激活转录因子细胞核因子κB（nuclear factor kappa B，NF-κB）和早期生长反应因

子-1(early growth responsive gene-1，Egr-1)，以及转录基因 c-Jun 和 c-Fos，进而引起 EC 的增殖、迁移和通透性升高[17]。

总之，异常的 WSSG 和 WSS 共同导致内膜功能障碍，引起动脉内膜病理性改变，进而导致动脉壁强度减弱，最终促进 AD 的发生。

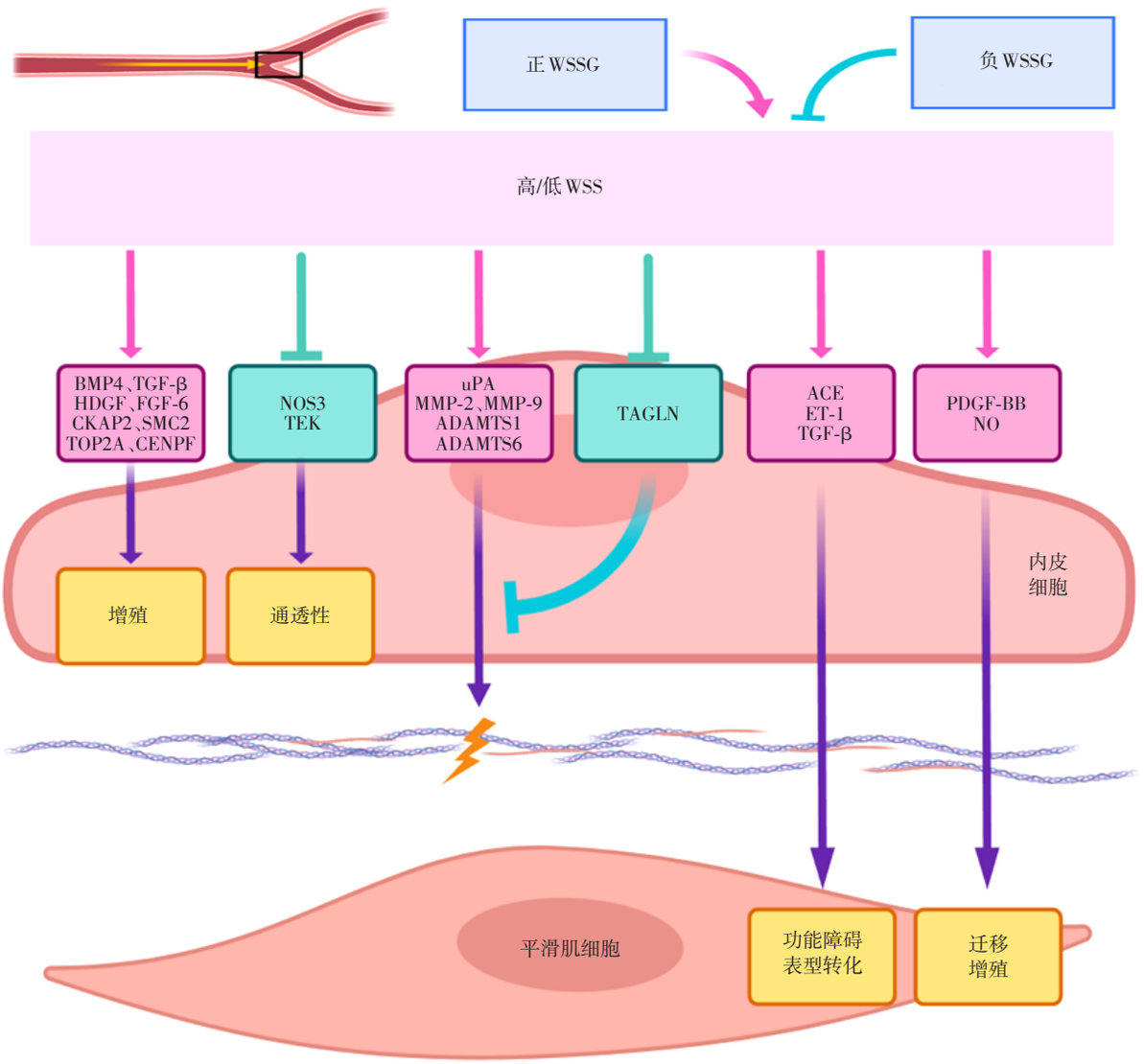
2.2 WSS 与动脉中膜

中膜的组成成分包括 SMC、ECM(胶原纤维、弹性纤维、糖蛋白和糖胺聚糖等)，以 SMC 和弹性纤维为主。SMC 的主要功能是维持和调节血管张力。SMC 具有较低的增殖能力，并表达细胞收缩所需的收缩蛋白。SMC 还具有较高的可塑性，可以在收缩型和合成型之间相互转化，从而在血管的修复和重塑中发挥关键作用[21]。中膜的病理性改变在 AD 的发生中起到关键作用，以下将详细介绍 WSS 引起中膜病理性改变的机制。

2.2.1 EC 与 SMC

WSS 通过 EC 与 SMC/ FB 间的信号通路间接调控中膜 SMC 的结构和功能[22]。SMC 通过与 EC 间的细胞因子、一氧化氮(nitric oxide，NO)和 miRNA 等信号转导途径感受 WSS 的变化并做出反应[23]。

EC 可以通过细胞因子途径影响 SMC 的增殖、迁移和表型转化。高 WSS 促进 EC 分泌血管紧张素转化酶、内皮素-1(endothelin-1，ET-1)和 TGFβ1，它



高/低 WSS 通过上调 EC 中多种信号分子如 BMP4、TGF-β等，促进 EC 增殖，通过下调 NOS3、TEK 增加 EC 细胞通透性；通过上调 MMP-9 和下调 TAGLN 来促进 ECM 的降解；以及通过上调 TGF-β、PDGF-BB 等使 SMC 发生功能障碍、表型转化、迁移和增殖等改变。正 WSSG 可以增强高/低 WSS 对 EC 中信号分子的调控作用，而负 WSSG 则削弱这种作用。

图1 剪切力通过调节 EC 中信号分子引起多种病理性改变

Figure 1 Shear stress regulates the signaling molecules in EC，leading to various pathological changes

们会引起SMC的功能障碍与表型转化[24]。低WSS促进EC通过旁分泌途径分泌血小板衍生因子(platelet derived growth factor,PDGF)-BB,其可以调节EC本身和SMC的增殖与迁移[25-26]。

EC能够通过NO调节SMC的增殖与迁移。异常WSS能够激活EC的内皮型一氧化氮合酶并上调其基因表达,使EC产生大量NO[27]。NO能够激活鸟苷酸环化酶及其下游的一系列通路抑制SMC增殖与迁移[28]。

EC还能够通过其表达的miRNA来调控SMC的形态和功能。体外实验证实:对EC施加WSS后,会抑制其分泌的miRNA-126对SMC的调控作用[29]。此外,异常WSS还可以上调miR-132-3p、miR-370-3p、miR-650,进而引起SMC增殖和表型转化[30-31]。

总之,异常的WSS可以通过EC与SMC之间的信号通路引起SMC功能障碍,使动脉中膜发生退化,应力及抗撕裂强度减弱,最终导致AD的发生。

2.2.2　WSS与SMC

异常WSS会引起SMC的病理性改变,包括增殖、迁移、细胞坏死/凋亡和收缩能力下降[1]。

异常WSS可以引起SMC的增殖和收缩能力下降。当WSS降低为3~25 dyn/cm^{2}时,SMC释放PDGF和FGF增加,进而升高血管紧张素转换酶的活性,促进自身增殖[32-33]。当WSS进一步降低到1 dyn/cm^{2}时,会诱导前列腺素的显著升高,继而引起SMC的舒张,导致动脉管腔扩张[32,34]。

异常WSS会引起SMC从中膜迁移到内膜。正常层流WSS可以通过下调SMC表达的MMP和PDGF受体-β来抑制SMC的迁移[35-36];反之,血流湍流产生的扰动WSS可以通过激活细胞外调节蛋白激酶(extracellular regulated protein kinases,ERK)-1/2与肌球蛋白轻链激酶途径促进SMC的迁移[37]。

异常WSS还可以引起SMC的数量减少。高WSS可以引起SMC凋亡,导致其数量减少,继而引起中膜变薄,降低血管中膜的结构强度,促进AD的发生[39]。

总之,异常WSS也可以直接导致SMC数量减少和功能障碍,进而导致AD发生。

2.2.3　跨壁间隙WSS

在内膜完整的情况下,中膜SMC和外膜FB也会暴露在非常微弱的生理性跨壁间隙血流下,即透过正常内膜和内弹力板窗孔流入中膜和外膜间隙的微弱血流,这些微弱血流也会产生WSS,靠近内膜侧的间隙WSS较靠近外膜侧的大。过去由于这些WSS较小而常被忽略,然而随着计算机流体模拟技术的发展,间隙WSS对血管中膜和外膜的影响逐渐被重视[39]。不仅如此,当内皮因各种因素导致通透性升高后,间隙WSS会进一步升高[40]。

间隙WSS可以调控SMC的表型转化、迁移和收缩。间隙WSS可以通过硫酸乙酰肝素蛋白多糖介导的ERK1/2通路调控SMC的表型转化[41]。间隙WSS可以活化SMC,在EC剥脱早期,中膜的SMC便受到间隙WSS的影响迅速活化并去分化,活化的SMC会加速增殖并最终向内膜迁移导致内膜增厚[42]。间隙WSS可以通过Rho相关的卷曲蛋白激酶-肌球蛋白轻链磷酸酶(Rho kinase-myosin light chain phosphatase,ROCK-MLCP)途径和Ca^{2+}途径来诱导SMC的收缩,以此来维持正常的血管张力[43-44]。间隙WSS可以通上调MMP-3促进SMC和肌成纤维细胞的迁移[45]。总之,不应忽视间隙WSS对AD发生的重要作用。

2.2.4　WSS与ECM

ECM是一大类不断动态变化的基质成分,包括结构蛋白(弹性纤维、胶原纤维)和非结构蛋白(各种糖蛋白、糖胺聚糖、各种生长因子和滞留在基质中的蛋白酶)。其中沿血管壁走行呈网状结构分布的弹力纤维网是动脉中膜ECM的主要组成成分,其强大的结构及功能属性赋予了动脉管壁良好的弹性。异常WSS可以导致中膜弹力纤维降解、断裂,弹力纤维一旦损伤便不可修复,并最终引起动脉管壁的弹性减弱,脆性增加,促进动脉壁结构的破坏,从而导致AD的发生[46]。

2.3　WSS与动脉外膜

外膜的组成包括FB、胶原纤维、弹性纤维,较大的动脉外膜还有滋养血管,以FB和胶原纤维为主。外膜的病理性改变同样在AD的发展中起到了重要作用。

首先,外膜中也存在跨壁间隙WSS,但由于相对"疏松"的外膜通透性高于"致密"的中膜,外膜FB受到的间隙WSS会相对更低[39]。此外,大动脉外膜有自己的滋养血管,由于动脉管腔内的血压远高于外膜滋养血管,产生了从动脉管腔向外膜滋养血管流动的间隙血流[47-48]。这种间隙血流流动模式非常复杂,外膜FB主要通过这种间隙血流感受WSS的变化。

WSS会影响FB的活化、增殖和迁移[49]。生理状态下,外膜的FB及由其活化形成的肌成纤维细胞都能促进血管损伤后的新生内膜形成,继而抑制AD

的发生[50]。异常WSS能够抑制FB的迁移,促进肌成纤维细胞的迁移,尤其是当内皮破损致FB暴露在较强的间隙WSS环境下时,可进一步促进其迁移,加速AD的发生[7]。

3 小 结

异常WSS是AD发生的重要始动因素,其通过多种信号通路引起动脉内膜、中膜和外膜病理性改变,进而诱导AD的发生。了解异常WSS诱导AD发生的机制有利于深入认识AD,从而更好地预防和治疗AD。

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