

# 体外冲击波疗法治疗骨不连研究进展

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**摘要** 体外冲击波疗法(ESWT)应用于骨不连的治疗已有几十年历史,但 ESWT 促进骨不连愈合的生物学机制仍不明确。ESWT 治疗骨不连的生物学机制可概括为 2 方面:①通过机械传导使陈旧骨痂微骨折,形成骨膜下血肿,促进生物活性因子释放以重新激活骨折愈合机制;②重新平衡成骨细胞和破骨细胞活性并促进骨折部位血管新生以加速骨不连愈合。ESWT 治疗骨不连在临床上已获得广泛认可,但 ESWT 治疗骨不连适用范围较窄,治疗方案和原则尚未统一,各临床研究中心治疗效果也差异较大。现在研究认为,ESWT 治疗骨不连应遵循尽早治疗、多点治疗及分次多疗程治疗,治疗能量应以患者能承受的最大限度为宜。

**关键词** 骨不连;体外冲击波疗法;骨折愈合

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40 年前,体外冲击波疗法(ESWT)是尿路结石的标准疗法之一,凭借其临床效果确切、治疗过程无创及并发症轻微等优势迅速风靡全球,成为该项疗法渗入骨科领域的发展契机。Haupt 在 1990 年通过跟踪随访完成 ESWT 的尿路结石患者,发现部分患者髂骨厚度明显改变,提出 ESWT 对生物组织存在一定干预作用。1991 年 Valchanov 首次将 ESWT 运用于骨不连的治疗,由此开启了 ESWT 治疗骨科疾病的研究热潮。

## 1 生物学机制

体外冲击波作为一种机械波具有以下 4 种特性:①压力峰值较高( $>100\text{ mPa}$ );②间期 $<10\text{ }\mu\text{s}$ ;③升压迅速,达峰时间 $<10\text{ ns}$ ;④压力达到峰值后迅速下降并可低于压力基线。ESWT 通过机械传导产生的剪切力和压力作用于细胞及细胞外基质是其发挥生物学效应的基本机制<sup>[1-3]</sup>,可引起细胞骨架及细胞外基质一过性结构改变,并在 3 h 内恢复,进而改变基因表达,引发特定生物学效应。临床和基础研究都显示,ESWT 的最终效应是通过作用于干细胞、内皮细胞、成骨细胞及炎细胞等黏附、增殖及分化阶段而发挥作用<sup>[4]</sup>。

### 1.1 微损伤促进骨组织修复

ESWT 是一种物理治疗手段,可通过机械传导将脉冲能量直接作用于骨组织和骨周围软组织,造

成点状骨膜下出血及陈旧骨痂微骨折,再通过反复刺激以引发骨折炎性反应,从而释放各类炎性因子及生长因子<sup>[5]</sup>。此外,ESWT 还能募集骨祖细胞并激活处于静息状态的成骨细胞及成纤维细胞以启动骨折愈合<sup>[6]</sup>。另有研究表明,ESWT 可诱导骨缺损区域硫酸糖胺聚糖(GAG)和透明质酸(HA)高表达,从而促进骨组织修复与新生<sup>[7]</sup>。

### 1.2 促进血管新生

ESWT 通过促进血管新生为骨不连部位提供更多血供以改善微循环,进而有利于骨组织修复<sup>[8-11]</sup>。低能量 ESWT 通过机械传导对血管内皮细胞产生剪切力,促进血管内皮生长因子(VEGF)表达<sup>[8, 12-13]</sup>,并刺激血小板内皮细胞黏附因子(PECAM)-1、血管内皮细胞钙黏连蛋白(VE-Cadherin)及血管内皮细胞生长因子受体(VEGFR)2 等冲击波诱导机械感受复合体形成,从而激活下游磷脂酰肌醇 3-激酶(PI3K)/蛋白激酶 B(Akt)/内皮型一氧化氮合酶(eNOS)、VEGFR2/Akt/eNOS 及细胞外调节蛋白激酶(ERK1/2)通路,使内皮细胞发生迁移和分化,促进毛细血管生成<sup>[14-17]</sup>。有学者<sup>[18-19]</sup>发现,ESWT 可通过表达 Toll 样受体(TLR3)促进血管新生。巨噬细胞在血管化过程中同样至关重要,ESWT 通过增强巨噬细胞募集和激活,间接促进血管新生<sup>[20]</sup>。多项研究发现,ESWT 产生的剪切力可诱导平滑肌细胞<sup>[21]</sup>和成纤维细胞增殖分化<sup>[22-23]</sup>,加速血管化进程。

### 1.3 促进骨重塑

ESWT 治疗骨不连时骨缺损组织中重组人骨形

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态发生蛋白(BMP)-2、BMP-3、BMP-4及骨桥蛋白(OPN)有强阳性表达<sup>[24-26]</sup>。ESWT能增强骨髓间充质干细胞(BMSC)分泌及增殖活性<sup>[27]</sup>,有利于血管新生及成骨方向分化<sup>[28-29]</sup>,并抑制其脂肪方向分化<sup>[30]</sup>。ESWT还能增强成骨细胞表面跨膜蛋白 $\alpha 5\beta 1$ 等表达,并可通过三磷酸腺苷(ATP)将胞外信号传导入胞内<sup>[31]</sup>,激活下游p38有丝分裂原活化蛋白激酶(MAPK)、ERK1/2及Akt等通路,从而促进成骨细胞活化和黏附<sup>[32]</sup>。低能量ESWT不仅能募集和激活巨噬细胞<sup>[20]</sup>,而且能增强已活化巨噬细胞的功能。总而言之,ESWT通过增强成骨细胞骨形成作用和巨噬细胞破骨作用,吸收陈旧骨痂的同时促进新骨生成以重新启动骨重塑,最终实现骨不连愈合的目的<sup>[33]</sup>。

## 2 临床研究

### 2.1 适应证、禁忌证及并发症

ESWT治疗骨不连的适应证包括骨折>6个月不愈合、间隙<5 mm及局部软组织条件适合ESWT治疗。禁忌证包括锁骨骨不连、局部软组织条件差、活动性感染、出血性疾病或严重凝血功能障碍、骨折间隙>5 mm、严重心脏疾病及起搏器术后。ESWT治疗骨不连术后并发症较少,主要为局部皮下出血,高能量作用时可能出现轻微的血管和神经损伤。

### 2.2 疗效研究及治疗方案

#### 2.2.1 疗效研究

多项研究表明,ESWT治疗骨不连效果不亚于传统手术治疗<sup>[34]</sup>。Furia等<sup>[35]</sup>将43例第五跖骨基底骨不连患者分为ESWT组( $n=23$ )和手术组( $n=20$ ),愈合率均达到90%以上,两组在愈合率及愈合时间上并无显著差异。Alvarez等<sup>[36]</sup>也得出相同结论。Notarnicola等<sup>[37]</sup>研究118例舟状骨骨不连患者,58例采用ESWT( $0.09\text{ mJ/mm}^2$ ,4 000次脉冲,共3次,间隔72 h),50例采用手术治疗,经12个月随访发现,ESWT组与手术组愈合率无明显差异。分别为79.3%和78.3%,腕关节功能也无统计学差异。Cacchio等<sup>[38]</sup>对比研究ESWT和标准手术治疗长管状骨骨不连的疗效差异,将126例患者分成低能量ESWT组、高能量ESWT组和手术组,经24个月随访,结果显示3组愈合率无明显差异,分别为94%、92%和95%,且ESWT组术后并发症明显少于手术组。另外,ESWT联合BMSC移植等新治疗方式术后疗效更显著<sup>[39]</sup>。

ESWT治疗骨不连的疗效受骨不连类型、骨不

连间隙大小、骨不连部位、ESWT干预时间、治疗能量、次数、频率及疗程等多项因素干扰。骨不连间隙>5 mm是公认的ESWT治疗骨不连预后不良的绝对指征<sup>[40]</sup>。多数学者认为萎缩性骨不连患者行ESWT预后不如肥大性骨不连患者。Kuo等<sup>[41]</sup>对接受ESWT的萎缩性骨不连患者和肥大性骨不连患者进行回顾性研究,发现萎缩性股骨骨不连患者ESWT术后疗效略差于肥大性骨不连患者,但也有学者表示两者并无明显差异<sup>[42]</sup>。骨不连部位不同导致的疗效差异主要取决于局部血供情况。股骨颈、舟状骨、胫骨中下1/3及多段骨折等血供较差部位愈合率均较差,而肱骨干、股骨及肘关节周围等血供较丰富部位ESWT治疗效果较好。因此,在术前须对患者进行筛选,对于明显不适合行ESWT的骨不连患者,应推荐尽早行手术治疗。

#### 2.2.2 治疗方案

骨不连患者在发现骨折愈合延迟时,应尽早进行ESWT干预<sup>[43]</sup>。Kuo等<sup>[41]</sup>研究发现,萎缩性股骨骨不连患者12个月内行ESWT愈合率接近100%,而12个月后再进行干预,愈合率仅有43.6%,说明尽早治疗对预后具有显著影响。ESWT治疗不同部位的骨不连,采用的能量和脉冲次数也会有所不同。Wang等<sup>[44]</sup>报道了ESWT治疗72例长骨骨不连患者的治疗方案:股骨、胫骨 $0.4\text{ mJ/mm}^2$ ,6 000次脉冲;肱骨干 $0.4\text{ mJ/mm}^2$ ,3 000次脉冲;尺桡骨 $0.35\text{ mJ/mm}^2$ ,2 000次脉冲;掌骨 $0.25\text{ mJ/mm}^2$ ,1 000次脉冲。早期ESWT多为单次治疗,而近年有研究发现多次间隔治疗术后疗效更好,但具体次数及间隔时间未有定论,次数从3次到7次、间隔从24小时到1周<sup>[45-49]</sup>均有报道。在治疗部位上,现提倡多点治疗,即通过X线或超声检查选取2~3个治疗部位进行治疗<sup>[50-51]</sup>。对比单点治疗,多点治疗能从多角度刺激骨不连区域以获得更好的效果。至于脉冲能量,Schmitz等<sup>[52]</sup>建议采用患者能够承受的最高能量。

## 3 结语

ESWT作为一种非侵入、不良反应小且经济有效的治疗方式,已广泛应用于跟腱炎、足底筋膜炎、网球肘、腰部疼痛及股骨头坏死等多种骨科疾病的治疗,疗效深受认可。ESWT治疗骨不连是通过体外冲击波机械传导作用,对骨不连部位造成反复微损伤,重新激活骨折愈合机制,并促使内皮细胞、成纤维细胞、平滑肌细胞及巨噬细胞等发挥促进血管新生、激活骨重塑及扭转成骨细胞与破骨细胞失平

衡现象的作用。虽然 ESWT 治疗方案尚未统一,但总体治疗方针应遵循尽早治疗、分次多疗程治疗、骨折部位多点治疗及治疗能量以患者所能承受的最大限度为宜。

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