·基础研究·

# 不同强度跑台运动对大鼠膝关节软骨Ⅱ型胶原纤维的影响

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【摘要】 **目的** 探讨不同强度跑台训练对大鼠膝关节软骨胶原纤维形态学及基因表达的影响。**方法** 采用随机数字表法将 48 只雄性 SD 成年大鼠分为对照组、低强度运动组、中强度运动组及高强度运动组。3 个运动组大鼠分别进行低、中、高强度跑台运动。于实验进行 8 周后处死所有实验动物,取膝关节软骨标本行天狼星红-饱和苦味酸染色观察胶原纤维排列情况,采用免疫组化技术检测Ⅱ型胶原(Col2)含量;另外本研究同时采用实时荧光定量逆转录聚合酶链反应检测软骨 biglycan(BGN)、fibromodulin(FMOD)及Ⅱ型胶原(Col2)mRNA 表达。**结果** 对照组膝关节软骨胶原纤维排列规则;低、中强度运动组与对照组间无明显差异;而高强度运动组胶原排列不规则、细纤维数量增多;高强度运动组Ⅱ型胶原含量显著低于对照组。与对照组比较,低强度运动组软骨细胞 Col2 mRNA 表达明显增高,高强度运动组 BGN mRNA 表达明显增高。**结论** 低、中强度运动有助于维持关节软骨正常结构及功能;高强度运动能促使关节软骨Ⅱ型胶原纤维减少、排列紊乱,但软骨自我修复可能同时存在。

【关键词】 关节软骨; Ⅱ型胶原纤维; 跑台训练; 富含亮氨酸重复序列的小分子蛋白多糖

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**Intensity-dependent effect of treadmill running on type Ⅱ Collagen of knee articular cartilage in rats**

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【**Abstract**】 **Objective** To investigate the effect of treadmill running with different intensities on type Ⅱ collagen (Col2) of knee joint articular cartilages in rats. **Methods** A total of 48 adult Sprague-Dawley rats were randomly divided into a control (C) group, a low-intensity exercise (L) group, a moderate- intensity exercise (M) group and a high-intensity exercise (H) group, each of 12. Rats in three exercises groups were regularly trained on treadmill at low, moderate, and high intensities respectively. Eight weeks later, all the animals were sacrificed. The right tibial plateau samples were collected to observe collagen fibers under polarizing light microscopy, and the collagen Ⅱ content were examined using immunohistochemistry. The mRNA expression of biglycan (BGN), fibromodulin (FMOD) and Col2 was tested using the quantitative real-time reverse transcription-polymerase chain reaction. **Results** Compared with group C, collagen fibers in group L and M exhibited almost the same organization, whereas, alteration in organization and shape of collagen fibers was found in group H. Significantly lower content of type Ⅱ collagen was found in group H than that in group C. In comparison with group C, group L had significantly higher gene expression of Col2, whereas group H had significantly higher BGN mRNA expression. **Conclusion** Low- or moderate-intensity treadmill running appears to have beneficial effect on articular cartilages to maintain its integrity. High-intensity exercises induce lower content and disorder of type Ⅱ collagen in articular cartilages, but the self-healing of cartilage may still exist.

【**Key words**】 Cartilage; Type Ⅱ collagen; Treadmill running; SLRPs

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细胞外基质(extracellular matrix,ECM)作为关节软骨生物力学特性和生理功能的物质基础,赋予其抵抗形变、吸收冲力、消除剪切力和关节内压力等功能[1-2]。作为 ECM 的重要成分,Ⅱ型胶原纤维高度有序排列,并与其他类型的胶原纤维形成胶原网络支架

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结构,长期反复外界应力刺激下,维持关节正常功能有赖于该网络结构的完整性[3-5]。Ⅱ型胶原纤维减少可破坏该网络结构稳定性,进而导致软骨生物力学特性发生改变,软骨细胞将暴露于高应力环境下,最后导致软骨细胞发生异常生物学反应[6],甚至引发骨性关节炎(osteoarthritis,OA)。

大量研究表明 OA 的发生与软骨 ECM 中富含亮氨酸重复序列的小分子蛋白多糖家族(small leucine-rich proteoglycans,SLRPs)密切相关[7-14]。作为 SLRPs 家族的一类和二类成员,biglycan(BGN)和 fibromodulin(FMOD)在软骨组织中丰富表达[15],且二者与胶原纤维代谢密切相关[9]。跑步是一种常见的负重运动方式,本研究拟探讨不同强度跑台训练对大鼠膝关节软骨中Ⅱ型胶原纤维的影响及其可能相关机制。

## 实验方法

一、实验动物

共选取清洁级雄性 Sprague-Dawley(SD)大鼠 48 只,体重 180~220 g,购自南方医科大学南方医院实验动物中心,给予国家标准啮齿类动物饲料饲养,自由摄食饮水,动物房温度 21~23 ℃,相对湿度 40%~60%,饲养室每天明暗时间为 12 h∶12 h。所有大鼠经平衡膳食 1 周后,采用随机数字表法将其分为对照组、低强度运动组、中强度运动组及高强度运动组,每组 12 只大鼠。

二、实验干预

对照组大鼠不给予跑台运动,笼内自由活动。各运动组大鼠在正式实验前先在电动动物跑步机上适应性训练 3 d,跑台速度和跑台坡度分别为 10 m/min、0°,持续训练 30 min。随后休息 2 d 再开始正式实验,各运动组大鼠根据以往研究采用的跑步方案[16]进行跑台训练,具体训练参数如下:低强度运动组跑台速度及跑台坡度分别为 15 m/min、0°;中强度运动组跑台速度及跑台坡度分别为 20 m/min、5°;高强度运动组跑台速度及跑台坡度分别为 25 m/min、10°。3 组大鼠均每天运动 1 h,每周训练 5 d,共持续训练 8 周。

三、标本取材及检查

于实验进行 8 周后处死所有实验动物,取大鼠右侧胫骨组织,从每组随机挑取 6 个标本固定、脱钙、包埋后制作石蜡切片,行天狼星红-饱和苦味酸及免疫组化染色。在冰面上用消毒过的手术刀片刮取右侧胫骨平台上的剩余软骨组织,于-80 ℃环境下保存备用。采用 RT-PCR 法检测各组大鼠软骨中 BGN、FMOD 及 Col2 mRNA 表达情况。各目标基因 PCR 引物应用 ABI Premier 5.0 软件自行设计,引物序列情况详见表 1。

**表 1** 目标基因引物序列及合成厂家信息

| 目标基因 | 基因序列 | 合成厂家 |
|---|---|---|
| BGN(103 bp) | F:5′-AGCCTGACATCCTAGTCCAC-CAAC-3′ | 宝生物工程(大连)有限公司 |
| | R:5′-AGCAGCAAGGTGAGTAGCC-ACA-3′ | |
| FMOD(165 bp) | F:5′-ACTAACAATGGCCTTGCTAC-CAACA-3 | |
| | R:5′-CGTGCAGAAACTGCTGATG-GA-3′ | |
| Col2(126 bp) | QT02423407 | QIAGEN 公司 |

四、统计学分析

本研究所得计量资料以($\bar{x}\pm s$)表示,采用 SPSS 18.0版统计学软件包进行数据分析,多组间比较采用单因素方差分析,若方差齐性,进一步两两比较则采用最小显著差异法(least-significant difference,LSD);若方差不齐,则采用 Kruska-Wallis H 检验进行比较,$P<0.05$表示差异具有统计学意义。

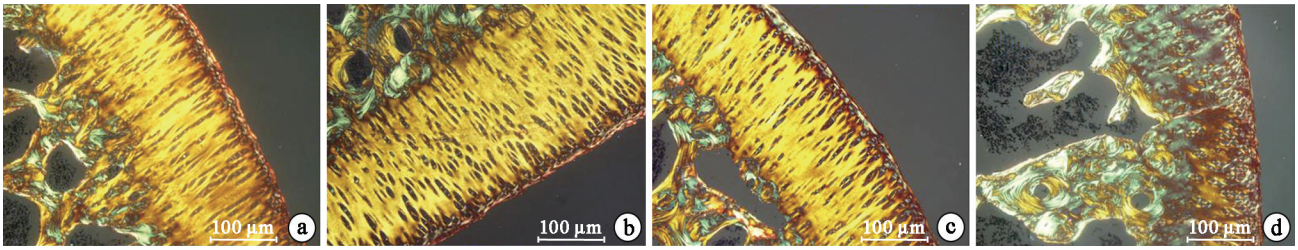
## 结 果

一、各组大鼠膝关节软骨天狼猩红-苦味酸染色分析

经天狼星红-苦味酸染色的胶原纤维在偏振光显微镜下其颜色随纤维粗细发生变化,即纤维由细到粗变化时,其相应的颜色将从绿到黄、橙色,最后呈现红色[18-19]。本实验对照组膝关节软骨胶原纤维排列规则,软骨细胞均匀规则嵌在纤维支架内,组织切片软骨层染色均一,以黄色为主,在软骨表层可见区别于其它层的颜色,这可能与不同分层胶原纤维排列方向及直径不同有关(图 1a);与对照组比较,低、中强度运动组胶原纤维排列及染色无明显差异(图 1b、1c);高强度运动组膝关节软骨胶原排列不规则,软骨细胞无序嵌于纤维支架内,组织切片出现黄、橙、绿等多种颜色,即粗、细纤维相互混杂呈蜂窝状,绿色细纤维明显增多(图 1d)。

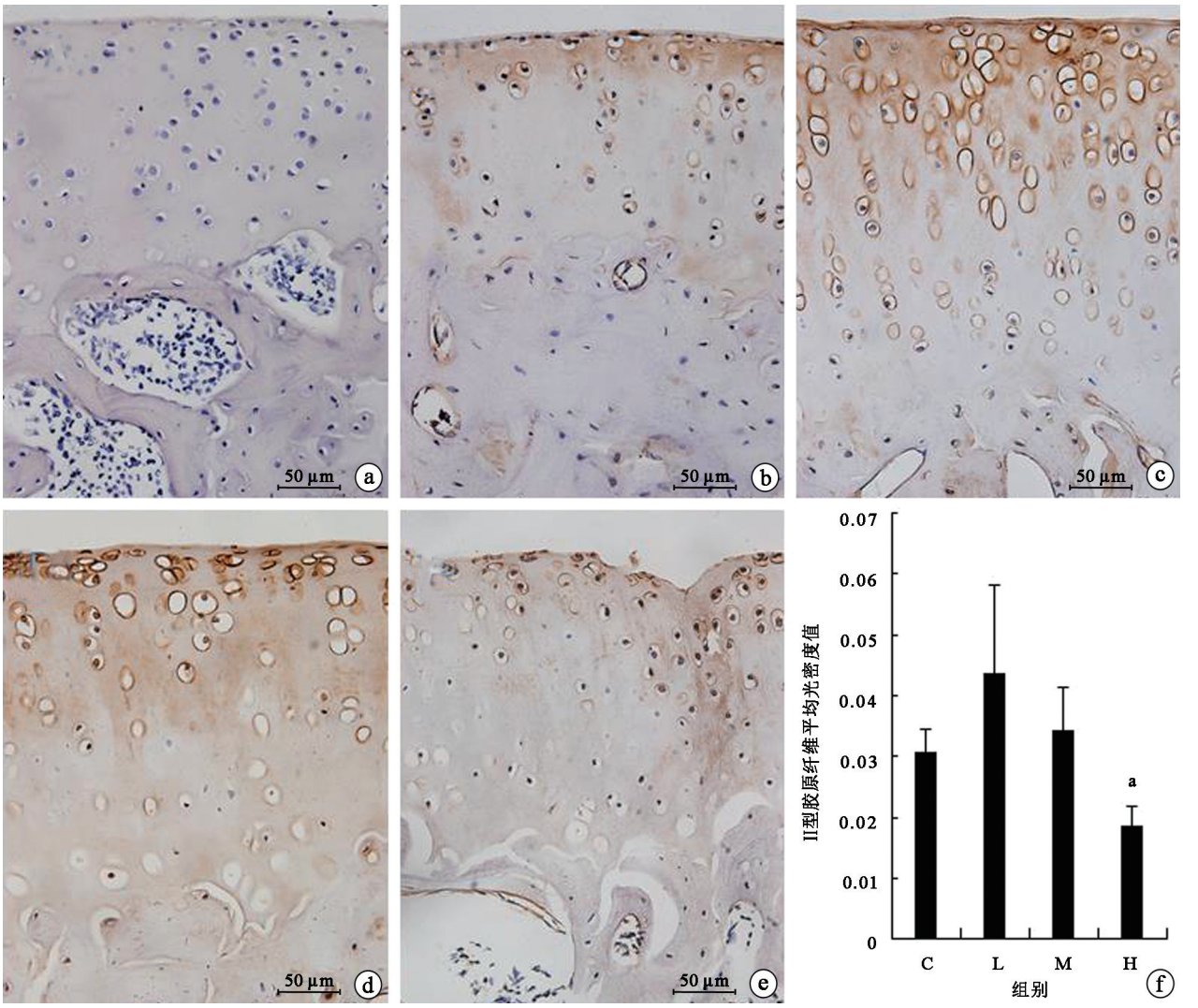
二、各组大鼠膝关节软骨Ⅱ型胶原免疫组化结果比较

免疫组化阴性对照显示软骨表面光滑,基质呈淡紫色(图 2a);对照组膝关节软骨基质Ⅱ型胶原纤维染色呈棕黄色,主要分布于软骨表层及放射层(图 2b),平均光密度值为(0.0309±0.0036);低、中强度运动组Ⅱ型胶原纤维染色较对照组深,分布较对照组广(图 2c、2d),平均光密度值分别为(0.0437±0.0144)和(0.0344±0.0071),但与对照组间差异无统计学意义($P>0.05$);高强度运动组膝关节软骨基质中Ⅱ型胶原染色较对照组浅(图 2e),其平均光密度值(0.0188±0.003)较对照组显著减少,组间差异具有统计学意义($P<0.05$)。各组大鼠Ⅱ型胶原平均光密度值详见图 2f。




注：图 1a 可见膝关节软骨胶原纤维排列规则，软骨细胞均匀规则嵌在纤维支架内，组织切片软骨层染色均一，以黄色为主，在软骨表层可见区别于其它层的颜色；图 1b 可见膝关节软骨胶原纤维排列规则，软骨细胞均匀规则嵌在纤维支架内；图 1c 可见胶原纤维排列规则，软骨细胞位于纤维支架内且排列规则；图 1d 显示关节软骨胶原排列不规则，组织切片出现黄、橙、绿等多种颜色相互混杂呈蜂窝状，绿色明显增多

**图 1**　各组大鼠软骨天狼星红-饱和苦味酸染色（×200）（图中微标尺 = 100 μm）




注：图 2a 可见软骨表面光滑，基质呈淡紫色；图 2b 可见软骨基质Ⅱ型胶原染色呈棕色，主要分布于浅层和放射层；图 2c 可见Ⅱ型胶原染色呈棕褐色，分布较广；图 2d 可见基质呈棕色，主要分布于浅层和放射层；图 2e 可见软骨细胞周围出现浅褐色，分布不均；图 2f 可见高强度运动组Ⅱ型胶原平均光密度值较对照组显著降低（$^{a}P<0.05$）

**图 2**　各组大鼠膝关节软骨基质中Ⅱ型胶原纤维免疫组化染色图（×400）及平均光密度值分析（图中微标尺 = 50 μm）

三、各组大鼠膝关节软骨 Col2、BGN 及 FMOD 基因表达比较

与对照组（0.5929±0.1501）比较，低强度运动组 Col2 mRNA 表达（1.18±0.2649）明显增高（$P<0.05$），中、高强度运动组 Col2 mRNA 表达［分别为（0.9252±0.1784），（0.6387±0.0574）］也有一定幅度增高，但与对照组间差异均无统计学意义（均$P>0.05$）。与对照组（1.1864±0.2662）比较，低、中、高强度运动组软骨细

胞 BGN mRNA 表达水平[分别为(1.3453±0.1671),(1.3840±0.2681)和(1.4832±0.4700)]均有一定程度增高,其中以高强度运动组的增高幅度较显著,与对照组间差异具有统计学意义($P<0.05$)。与对照组(0.7562±0.2881)比较,低、中、高强度运动组软骨细胞 FMOD mRNA 基因表达水平[分别为(0.8449±0.1871),(0.8828±0.1983)和(0.8868±0.2498)]逐渐增高,但与对照组间差异均无统计学意义($P>0.05$)。

## 讨 论

本研究前期实验从软骨组织形态学观察到低、中强度跑台训练能保持关节软骨表面光滑,高强度运动可导致软骨早期 OA 样改变[16]。一定范围内的负荷可维持关节软骨完整性,防止其早期退变;而低于或高于该范围的负荷均会导致该组织破坏[19-20]。本实验证实低、中强度跑台训练能维持关节软骨Ⅱ型胶原纤维有序排列,Ⅱ型胶原纤维含量增多;而高强度运动组Ⅱ型胶原纤维含量较对照组明显减少。既往研究也表明高强度运动可引起关节软骨早期退行性改变,包括胶原含量减少等[21]。Ⅱ型胶原纤维是 ECM 中主要的大分子物质,与其他类型胶原纤维组成的网络支架结构是关节软骨生物力学特性的主要承担者;因其代谢转换率非常低,一旦被降解,以它为主的纤维网络结构将会受到不可逆破坏[3,22-23]。本实验通过免疫组化及天狼星红-饱和苦味酸染色,进一步证实高强度运动组 ECM 中胶原含量明显减少,各层胶原纤维排列紊乱,细纤维增多,而细纤维增多可能为软骨细胞自我修复重塑[18]。一定范围内的应力刺激是维持关节软骨内环境稳定的必要因素[24]。长期高强度运动使关节力学传导紊乱,软骨表面应力负荷在极短时间内达到应力峰值,当应力超出胶原网络结构的承受范围时,网络结构被破坏,关节软骨发生退变[25]。本研究推测低、中强度跑台训练可使 ECM 内胶原网络支架结构更加结实,关节软骨的生物力学特性也得到进一步改善,进而能承受更大的应力刺激。

高强度运动在诱发运动损伤同时,可能还伴随着软骨自我修复过程[26]。本实验各运动组大鼠膝关节软骨细胞 Col2 mRNA 表达水平均较对照组有所增强,并以低强度运动组增强幅度显著,免疫组化检查同样显示低、中强度运动组Ⅱ型胶原含量增多,这提示低、中强度运动对软骨组织具有一定塑性作用,活跃的软骨细胞不断提高基因表达水平并合成基质中主要成分(如Ⅱ型胶原蛋白)以进一步适应外界负荷改变。与基因表达相反,高强度运动组Ⅱ型胶原纤维含量较对照组明显减少,可能是因为高载荷引起的软骨早期退变刺激了残存软骨细胞,为了试图进行自我修复,残存的软骨细胞 Col2 基因表达水平增高;但退变的软骨细胞也不断合成新的胶原酶,亦或是退变的软骨组织 Col2 基因在转录翻译成蛋白过程中受到其他因素影响而致使纤维含量减少。这与 Young 等[27]在切除山羊半月板 OA 模型中观察到的结果一致。

基质金属蛋白酶家族(matrix metalloproteinases,MMPs)通过识别并裂解胶原纤维上特异的位点导致胶原网络结构破坏,如对Ⅱ型胶原有高度降解活性的 MMP-8、MMP-13 通过三螺旋位点、而 MMP-3 在非螺旋位点对Ⅱ型胶原进行降解[28-29]。胶原纤维通常不单独存在,而是与其他各种蛋白(如纤维相关蛋白和 SLRPs 等)相互结合,这些蛋白分子实质上是胶原纤维表面的一种保护衣[30]。在Ⅰ、Ⅱ型胶原纤维上也有特殊的 SLRPs 结合位点,MMPs 在胶原纤维上的酶切位点位于 gap 和 overlap 之间,而 SLRPs 与纤维的结合位点也在该区域上[31-32],故 SLRPs 与胶原纤维结合后形成于胶原纤维表面的保护衣可作为一种空间位阻以限制胶原酶进入纤维的酶切位点,从而使胶原纤维网络结构免受破坏。同时有研究发现 SLRPs 对胶原的形成、组装及稳定性具有关键作用,对胶原纤维的直径及排列走向也有影响作用[33-34]。

与对照组比较,低、中强度运动组 BGN 和 FMOD 基因表达轻度增高可能是由于在接受适度负荷后其软骨力学性能得到进一步改善,为了能承受更大的负荷,软骨细胞 SLRPs 基因表达水平增多以进一步合成相应蛋白,从而使胶原纤维网络支架结构更为稳固。有研究证实 SLRPs 中的 FMOD 可将细小胶原纤维连接在一起形成更大、更粗、力学性能更强的胶原纤维。剔除小鼠 BGN/FMOD 基因后可影响胶原原纤维形成,合成的胶原纤维纤细、不规则,力学性能变差[9,15,34]。本研究高强度运动组 BGN 和 FMOD 基因表达较其他组均有一定程度升高,并以 BGN 的升高幅度尤为显著,与先前研究结果基本一致[27,35]。关节软骨在高负荷下发生早期 OA 样改变,但残存的软骨细胞仍能启动自我修复程序。从天狼星红-饱和苦味酸染色可以观察到高强度运动组 ECM 中细纤维增多,考虑为此时软骨细胞合成的 MMPs 增多,结合在胶原表面的 SLRPs 首先被蛋白酶降解,为了保护Ⅱ型胶原结构的完整性,软骨细胞的合成代谢反应性增强,SLRPs 基因表达水平增高,但 SLRPs 蛋白合成的速度不及被降解得快,最终导致胶原纤维被降解;同时 SLRPs 减少能影响胶原纤维直径及走向,粗纤维减少、细纤维增多,新形成的纤维网络结构力学特性变差[8]。以上结果证实高强度运动引起软骨Ⅱ型胶原纤维减少及纤维结构改变,但软骨细胞自我修复同时存在。由于胶原纤维的代谢转换率极为低下,如这种高强度的运动持续存在,

软骨的损害超过了自我修复,则关节软骨内纤维网络支架将面临更为严重的损害甚至不可逆转,最后导致软骨生物力学性能丧失。

综上所述,本实验通过观察不同载荷下软骨基质中胶原纤维结构及含量变化,证实低、中强度跑台运动有益于维持关节软骨Ⅱ型胶原纤维结构与功能;而高强度跑台运动能导致Ⅱ型胶原纤维含量减少、直径变细及排列紊乱,这些改变与 SLRPs 密切相关,另外高强度运动在损伤软骨同时,机体亦存在自我修复过程。

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·外刊撷英·

## Bone marrow aspirate for knee osteoarthritis

**BACKGROUND AND OBJECTIVE** Osteoarthritis (OA) of the knee is a painful, degenerative condition that affects millions of patients. The American Academy of Orthopedic Surgeons recently published a position paper which recommended against most conservative theraples. This study reviewed the effects of bone marrow asplrate concentrate (BMAC), without as a treatment for OA of the knee.

**METHODS** Subjects included 25 patients seen for bilateral knee OA between 2013 and 2015. All had been unresponsive to conventional treatments. Each patient received a random ly determined intra-articular injection of BMAC. (harvested from the patient's superior iliac crest) into one knee, and a similar volume of normal saline pl acebo into the contralaleral knee. At baseline and follow-up.the patients were assessed using the Osteoarthritis Research Society International (OARSI) measures, the Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire and visual analog scale (VAS) pain scores.

**RESULTS** Significant improvement was noted in both groups in ICOAP scores and VAS pain scores, with no significant difference found between the treatment groups. In addition, while there was significant improvement in the actlvity levels of both groups compared to baseline, there was no significant difference in the degree of improvement between the two treatment groups at any of the follow-up periods.

**CONCLUSION** This study of patients with chronic osteoarthrltis of the knee found that niections with saline produced similar results in pain reduction and functional abilities as did injections with bone marrow aspirate concentrate.

【摘自:Shapiro SA, Kazmerchak SE, Heckman MG, et al. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. Am J Sports Med. DOI:10. 1177/0363546516662455.】

## Short-term, low intensity blood flow restricted interval training mproves both aerobic fitness and muscle strength

**BACKGROUND AND OBJECTIVE** While research has demonstrated that both strength training and aerobic fitness training contribute significantly to health. there is interest in identifying efficient training methods which can simultaneously improve both cardiovascular and neuromuscular performance. Given the research concerning blood flow restricted (BFR) training, this study was designed to determine the aerobic and strengthening effects of intermittent BFR exercise.

**METHODS** Thirty-seven adults, with an average age of 23.8 years, were randomly assigned to one of four training groups : high intensity (HIT) interval training, low intensity interval training with BFR, low intensity interval training without BFR or HIT interval training with BFR (every session performed 50% as BFR and 50% as HIT). At baseline and affer four weeks of training (three sessions per week), subjects were assessed for maximal oxygen uptake, maximal power output, onset blood lactate accumulation (OBLA) and muscle strength. The training power was 30% of PMax for low and BFR training groups, and began with 110% in the HIT group. The BFR group wore pressure cuff belts inflated to 140 mmHg, progressing by 20 mmHg after three complete sessions up to 200 mmHg in the last session.

**RESULTS** After 12 sessions, low intensity interval BFR training resulted in significant improvements in all selected variables, including VO2Max PMax. OBLA and muscle strength. Those in the HIT and BFR+HIT training groups only produced improvements in aerobic variables. although HIT provided a higher effect size compared with BFR and BFR+HIT training. The low-intensity interval training on its own without occlusion (LOW) was not sufficient to improve VO2max, Pmax or muscular strength,but did improve OBLA.

**CONCLUSION** This study demonstrated the advantage of short-term, low intensify, interval blood flow restricted training as a method to concurrently improve aerobic parameters and muscle strength.

【摘自:Oliveira MF, Caputo F, Corvino RB, et al. Short-erm, low intensity, blood flow restricted interval training improves both aerobic fitness and muscle strength. Scand J Med Sci Sports, 2016, 26(9):1017-1025.】