许博洋,庞小娟,曾禹铭,等. 肩袖肌腱损伤诱导性动物模型构建评价及研究进展[J]. 中国实验动物学报, 2020, 28(4): 545-550.
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Doi:10. 3969/j.issn.1005-4847. 2020. 04. 016

肩袖肌腱损伤诱导性动物模型构建评价及研究进展

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【摘要】 肩袖(rotator cuff,RC)肌腱损伤是肩关节急慢性疼痛、活动度受限的主要原因,急性损伤全层撕裂时通常需要进行外科手术的及时干预。临床上 RC 损伤的修复难点在于骨-肌腱界面的重建,虽然目前已经建立了多种手术创伤诱导性肩袖损伤动物模型,但仍缺乏合适的动物模型以及确切的治疗方法。本文将对国内外 RC 肌腱损伤诱导性动物模型的建立方法及适用范围进行总结归纳,探讨动物模型的选择及功能评估方法,以期为 RC 损伤的基础科研提供相应的理论依据。

【关键词】 肩关节;肩袖肌腱损伤;动物模型;组织构建;软组织生物力学
【中图分类号】Q95-33 **【文献标识码】**A **【文章编号】**1005-4847(2020) 04-0545-06

Evaluation and progress of the construction of a rotator cuff tendon injury-induced animal model

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【Abstract】 Rotator cuff tendon injury is the main cause of acute and chronic shoulder pain and a limited range of motion. Surgical intervention is usually needed in cases of acute injury with full-thickness tears. The difficulty in repairing rotator cuff injuries lies in reconstructing the bone-tendon interface. Although various animal models of rotator cuff injuries induced by surgical trauma have been developed, suitable animal models and exact treatment method are lacking. This paper summarizes the establishment method and applicable scope of rotator cuff tendon injury-induced animal models and explores the selection of animal models and functional evaluation method to provide a corresponding theoretical basis for basic scientific research on rotator cuff injuries.

【Keywords】 shoulder joint; rotator cuff injury; animal model; tissue construction; soft tissue biomechanics
Conflicts of Interest: The authors declare no conflict of interest.

[基金项目]国家自然科学基金重点项目(81330088),国家级大学生创新创业训练项目(201910063002)。
Funded by National Natural Science Foundation of China (81330088), National College Students' Innovative and Entrepreneurial Training Program (201910063002).

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肩关节是人体中最易移动且受约束最少的关节,其功能稳定性和固有关节活动度之间的平衡依赖于整个肩部静态和动态稳定系统的共同复合作用[1]。RC 是由肩胛下肌(Subscapularis, SSc)、冈上肌(Supraspinatus, SS)、冈下肌(Infraspinatus, IS)和小圆肌(Teres minor, TM)所组成的肌群,在肩关节的动态稳定机制中扮演着重要角色。RC 通过肌肉的收缩活动平衡机械载荷所引起的去稳定化和稳定化作用,其中 SS 和 SSc 通过施加于冠状面和水平面上的应力应变作用来帮助肩部运动,同时将肱骨头居中压在肩胛盂上,从而保证在整个运动弧线上的关节稳定[2-3]。因此,当发生肩袖肌腱损伤后,肩关节失去肩袖的主被动约束作用,稳定性急剧下降。传统意义上认为,退行性 RC 撕裂好发于 SS 肌腱的前部,与肱二头肌肌腱相邻。现认为其主要发生于肱二头肌后方约 15 mm 处的 SS 和 IS 的交界处[4]。急性创伤引起的 RC 损伤,通常以 SS 肌腱的受累较为常见,损伤部位多位于距肱骨大结节止点约 1 cm 处。目前在临床上,RC 修复技术通常是使用缝合锚钉将断裂的肌腱锚定在其解剖足迹上,修复的肌腱-骨连接逐渐被纤维瘢痕界面取代,而不是通过纤维软骨区域天然附着部位而重建[5]。因此,由于 RC 肌腱与骨骼之间的愈合能力不好,术后再撕裂率和并发症发生率仍处于较高水平,积极开发有利于肌腱解剖学上的软-硬组织过渡的生物材料或外科技术,对 RC 损伤的修复效果有一定的积极意义。成熟的动物模型能为我们理解 RC 肌腱损伤的发病机制有着很大的推进作用。本文将以肌腱-骨骼的生物力学特性为出发点,介绍国内外各种急慢性 RC 损伤动物模型的制备方法及功能评估,为后期 RC 损伤的基础科研提供一定参考。

1　肩袖肌腱的生物力学环境

RC 又称腱袖、旋转袖,组成 RC 的四块肌肉分别从肩胛骨向前延伸包绕肱骨头,维持肩关节稳定。SS 起源于肩胛骨的冈上窝,其肌腱穿过肩胛下间隙,附着于大结节的上、中面;IS 和 TM 起源于冈下窝和肩胛骨外侧缘背面,其肌腱分别附着于大结节的中部和下侧;SSc 起源于肩胛下窝,其肌腱附着于肱骨小结节。四块肌肉的肌腱在其附着点附近融合成一个连续的结构。肌腱与骨的结合部位便是腱-骨止点,主要包括肌腱致密纤维结缔组织层、纤维软骨层、钙化软骨层和骨组织层,这四个依次连续渐变的组织结构[6]。肌腱组织层主要由 I 型、XII 型胶原纤维以及蛋白聚糖组成,含有纺锤状成纤维细胞[7]。随着肌腱软组织向骨组织的过渡,细胞类型由成纤维细胞向骨细胞或成骨细胞转变,纤维蛋白的种类和走向也由整齐排列的 XII 胶原纤维向随机分布高度矿化的 I 型纤维变化[8-9]。其纳米微观角度的关键机制在于:轴向载荷介导下,盘曲的三螺旋小分子结构逐渐发生轴向拉伸,最终导致纤维结构的解螺旋过程,从而引起胶原纤维分层排列的疏密转变[10]。胶原纤维的变化是维持 RC 肌腱良好粘弹性和异质性的主要原因,循环加载诱导胶原纤维偏向力的方向,并在应变时产生非线性刚度,增加肌腱强度[11-12]。当异常载荷变化作用于 RC,肌腱细胞通过分泌基质金属蛋白酶加速胶原纤维代响应刺激,促进炎性细胞因子的分泌和细胞凋亡基因表达,将造成腱细胞大量凋亡、肾上腺素能受体增加(但并不会发生明显的炎症反应)。在长期损伤的持续累积下组织机械性能会大幅度降低,显著的局部肌腱应变集中,将易于发生肌腱的表面部分性断裂,最终演变为 RC 的全层撕裂[13-14]。

2　肩袖损伤动物模型的建立

动物模型是了解 RC 肌腱损伤的组织生物学及病理学基础、开发新技术以改善现有治疗方法的实用手段。从目前的研究报道来看,针对不同阶段的病理进程,现已建立出较多的 RC 肌腱损伤模型。

2.1　急性肩袖肌腱撕裂模型

目前,国内外主要是通过手术创伤的方式诱导急性 RC 肌腱损伤动物模型建立,通常以 SS 为施术部位,建立 SS 肌腱损伤模型(Carpenter 模型)。主要操作是通过肩胛冈远端前内侧或肩肱关节头侧作 1.0 cm 小切口,沿肩胛冈下缘钝性分离皮下组织和三角肌,向肩峰方向寻找并暴露 SS 肌腱,于肱骨大结节止点处钝性离断,然后以 6-0 可吸收缝线将其原位缝合。术前术后可通过注射青霉素、庆大霉素以及头孢曲松钠预防感染并于术后苏醒允许自由行走,1 ~ 2 周成模。进一步的研究证实,为了防止实验动物自发肌腱愈合或瘢痕形成,通常需要修整肱骨大结节附着点与冈上肌腱,剔除多余软组织,刮净离断处肱骨端残留纤维软骨层直至骨质。如若对 SS 肌腱 2 ~ 3 mm(< 50%止点处肌腱宽度)或 0.5 cm × 0.5 cm 的组织施以切除[15-16],则将建立全层 RC 损伤模型。此外,也有通过离断 SSc 肌

腱建立 RC 损伤动物模型的报道,但研究数量不多。然而,为了使肩关节获得较高的机械稳定性,对于在 RC 损伤修复缝合过程中应用单排还是双排固定技术目前仍存在争议。从长期效益来看,双排修复技术确实可以提高肌腱的愈合速度并降低复发率。而由于成本效益的考虑和目前质量不高的临床证据,不建议使用双排技术修复所有的 RC 损伤过程[17]。

2.2　慢性肩袖肌腱损伤模型

慢性退行性劳损是目前临床上最为常见的 RC 损伤诱因,RC 肌腱与肩峰或盂肱关节下表面的频繁接触被认为是 RC 损伤的发病机制之一,因此实验研究中主要使用肩峰下撞击模型进行模拟[18],通过剪取同侧肩胛骨的 1 ~ 2 块小骨块移植固定到肩峰的下表面,模拟 SSc 的肩峰撞击过程。然而有研究提出,肌腱的撞击过程与 RC 损伤之间并没有直接联系,可能并不是衰老相关退行性 RC 病变的本质[19]。目前有研究通过微创的方式进行慢性 RC 损伤模型的制备,主要通过紧贴肩峰内侧刺入植入物,并于刺入后紧贴肩峰下表面行进, 至三角肌后缘从肩峰外侧刺出[20]。除此之外,也有研究采用 A 型肉毒素注射的方式进行模型制备[21]。

3　肩袖损伤动物模型的选择

从目前的研究来看,肌腱韧带等软组织的损伤在外科临床中一直缺乏有效的治疗,乃至通过药物等其他替代疗法的干预中也显得异常困难和复杂。其中最大的障碍便是缺乏成熟且标准量化的活体 RC 损伤动物模型。虽然曾有研究对多种实验动物在肩袖损伤造模中的应用进行评估[22-23]。但实际上除人类以外,大多数动物都是依靠四肢支撑,即使存在偶尔的双后肢支撑短暂站立行为,双前肢仍需要发挥较多的承重功能。因此,人类的肩部解剖结构是极具特异性的,与大多数动物的软组织结构并不相似。肩峰、喙肩弓以及通过其下方的韧带结构是 RC 损伤模型的必要构造。另外,RC 损伤模型建立的过程中,应满足以下条件[24]:①RC 肌腱损伤后没有自发性肌腱愈合或瘢痕形成的现象;②滑膜内损伤炎症环境存在;③有可用于人类缝合修复技术的肌腱大小;④存在可控的术后康复能力;⑤慢性肌腱损伤后能出现相关肌肉不可逆转的萎缩、僵硬和脂肪浸润。我们通过阅读相关文献,针对 RC 损伤造模应用过程中不同动物种类的优缺点,归纳总结如表 1,以便后期的研究人员基于具体的情况建立出更为合适的模型。

从表中我们不难看出,根据目前的实际情况,使用大鼠和兔来制备 RC 肌腱损伤模型可基本满足 RC 损伤模型的选择原则,是比较符合实际的建模动物。对于兔 RC 肌腱损伤模型来说,兔盂上结节下方中走行的 SSc 肌腱是以类似于人类 SS 的附着方式附着于肱骨小结节,并在 RC 损伤过程中会出现明显的脂肪浸润。尽管目前大部分的实验都集中于以兔 SS 为造模对象,但已逐渐有使用 SSc 造模的趋势,因此我们更推荐将 SSc 作为造模的首选干预肌腱。大鼠模型手术操作成熟,成本低廉易获取,但关节较小,组织处理时应更加精细。同时需要注意的是,由于大鼠与人类 RC 组织高度相似的解剖学特征,大鼠模型对于 SS 肌腱损伤机制介导的 RC 肌腱损伤过程能够很好的进行描述。但在大鼠 SS 肌腱损伤模型中并未有明显的脂肪浸润,有研究[37]提出大鼠 IS 在损伤后经历着与人类相似的脂肪堆积和肌肉萎缩等病理过程,该模型可能是贴合人类 SS 肌腱损伤的更好的动物模型。对于早期退行性 RC 损伤的动物模型选择,犬类动物似乎要比绵羊和山羊更具有优势。关节镜下的肩部损伤犬模型更有利于观察肩内神经肌肉组织病理和肌腱载荷能量的变化。

4　肩袖损伤动物模型的功能评估

在 RC 肌腱损伤模型建立的过程中,组织学和行为学分析是衡量造模成功与否必不可少的条件。疼痛是 RC 损伤后的典型症状,包括机械和触觉异常性疼痛。对于小型动物来说,可表现为步态异常、自发笼内运动和攀爬行为增多、梳理行为以及食物和水的消耗量变化。而对于那些大型动物,大多数的功能性测量比在大鼠等小型动物中更容易观察到。通常在我们的疼痛评估实验室中,纤毛测痛仪机械痛和热辐射痛实验中所反应出的数值主观性较低。另外某些测试中由刺激引起的行为变化也被广泛用作疼痛的量化指标。比如可通过楼梯实验用以评估前肢的精细运动控制[38]。同时在使用这些测试时,有些实验主观性较强,通常凭借斜眼、四肢缩回或发声来识别那些处于疼痛状态的动物[39]。因此需要尽可能引入某些客观参数,来补偿主观性较高情况下所缺乏的可靠性和可重复性,如食物和水的摄入量、体重和体温的变化、肌肉的

表 1 不同种类动物模型优缺点

Table 1 Advantages and disadvantages of different animal models

动物种类 Animal species	优点 Advantages	缺点 Disadvantages
小鼠 Mouse	存在喙肩弓和纤维软骨过渡区的附着点[25]； 具备测试特定信号通路及分子对肌腱变性和修复作用的潜在属性； 主要用于局部解剖-外科模型中，研究与 RC 肌腱撕裂相关的退行性变，也是研究肌腱-骨愈合的合适模型[26] There are attachment points for the transition zone of the beak and shoulder arch and fibrocartilage[25]. It can test the potential properties of specific signal pathways and molecules on tendon degeneration and repair. It is mainly used in the local anatomical-surgical model to study the degeneration related to RC tendon tear, and it is also a suitable model to study tendon-bone healing[26].	体型较小，操作难度较大 The size is smaller and the operation is more difficult.
大鼠 Rat	存在喙肩弓，在肱骨近端较大结节处有明显的 SS 肌腱附着点，与人类解剖学相似性最高[27]； RC 损伤后与人类一样显现出关节外展活动度变小的现象[28]； 广泛应用于各种影响急性 RC 损伤及修复生物学效应的研究，尤其是促进肌腱-骨愈合的修复重建过程的机制研究 There are coracoacromial arch and obvious SS tendon attachment point in the larger tubercle of the proximal humerus, which has the highest similarity with human anatomy[27]. After RC injury, the abduction activity of the joint decreased like that of human beings[28]. It is widely used in various studies that affect the biological effects of acute RC injury and repair, especially the mechanism of the repair and reconstruction process of promoting tendon-bone healing.	自愈能力很强； 不适合评估修复技术的优劣势[29]； RC 损伤可伴有肱骨头和关节盂软骨退化[30]； 肩部形态不算大，有一定操作难度，术后观察困难 The self-healing ability is very strong; It is not suitable to evaluate the advantages and disadvantages of repair technology[29]. RC injury may be accompanied by degeneration of humeral head and articular glenoid cartilage[30]. There is a certain degree of difficulty in surgical operation and postoperative observation because the shape of the shoulder is not large.
兔 New Zealand White Rabbit, Japanese Short-eared Rabbit	细胞组织学水平接近人类，体型中等； SS 肌腱的形态与人类较为相似[31]； 但 SSc 肌腱的走行与人类 SS 肌腱更为类似，肌腱离断后存在与人类相似的脂肪浸润过程，术后愈合方式也大体一致[32]； 多用于与 RC 撕裂相关的肌肉变化、肌腱-骨愈合的研究 The level of cytohistology is close to that of humans, and the somatotype is medium. The shape of the SS tendon is similar to that of human beings[31]. But the distribution of SSc tendon is more similar to that of human SS tendon, the process of fat infiltration after tendon amputation is similar to that of humans, and the mode of postoperative healing is generally the same[32]. It is mainly used in the study of muscle changes and tendon-bone healing related to RC tear.	自愈能力较强； 双前肢站立机会较多； 肩部解剖结构相对简单； 易遭受惊吓或腹泻，造成二次受伤和死亡[33] Strong self-healing ability There are more opportunities to stand on both forelegs. The anatomical structure of the shoulder is relatively simple. It is vulnerable to shock or diarrhea, resulting in secondary injuries and death[33].
犬 Beagle	RC 承受机械载荷与人类相当，具有相似的生物力学环境； 多用于探讨某些内在因素介导 RC 损伤修复效果以及术后康复方案 RC bears the same mechanical load as human beings and has a similar biomechanical environment. It is mainly used to explore the repair effect of RC injury mediated by some internal factors and postoperative rehabilitation plan.	解剖学结构与人类有较大差异，稳定性较差； 有自发的 RC 退行性病变的情况，不利于控制变量[34]； 购买和饲养成本较高，难以展开大样本实验研究； The anatomical structure is quite different from that of human beings, and its stability is poor. There are spontaneous RC degenerative diseases, which is not conducive to the control of variables[34]. The cost of purchase and feeding is high, so it is difficult to carry out large sample experimental research.
绵羊 Sheep	IS 肌腱包括形态大小和微脉管系统在内是与人类 SS 极为相似的； 多用于慢性 RC 损伤和各种降低术后不良状况缝合技术的研发[35] IS tendons, including shape, size, and microvascular system, are very similar to human SS. It is mainly used for the research and development of various suture techniques for chronic RC injury and reducing postoperative adverse condition[35].	饲养和管理成本不低； 偶蹄类动物术后会立即使用双前肢，有 RC 损伤手术修复失败的潜在风险 The cost of feeding and management is not low. Cloven-hoofed animals will use both forelimbs immediately after the operation, and there is a potential risk of failure in surgical repair of RC injury.
灵长类动物 Primate	肩部结构在解剖学、生物力学及免疫学方面与人类极为相似； 狒狒可能是研究 RC 损伤最佳的动物[36] The structure of the shoulder is very similar to that of humans in anatomy, biomechanics, and immunology. Baboons may be the best animals to study RC damage[36].	购买和围手术期饲养设施管理成本极高 The cost of purchasing and managing perioperative feeding facilities is extremely high.

围度和体积等。除此之外步态分析依旧是评定动物运动行为的有效方式,虽然啮齿类动物的四足步态和人类双足步态之间存在明显差异,但患病后二者均表现出相似的补偿性步态模式。有研究曾描述了一种新开发的步态分析方法,该方法可以轻松量化大量运动参数。通过使用墨水标记测量单个爪印的特征和爪印之间的距离,以提供时间和空间步态数据。健康的啮齿类动物以平衡对称的步态行走,步长的缩短表明外展能力可能受损。步幅宽度的减少表明,啮齿类动物通过重新分配,将体重转移到其他三条腿来保护受伤的肢体,从而对受伤的肢体进行补偿。这类似于在两足动物中观察到的跛行。爪印之间角度的改变是由过度的旋前或旋后引起的,这可能表明关节的活动障碍[40-41]。

5　总结

目前没有任何一种动物模型能够完全模拟临床上的 RC 病变,大鼠和兔仍是最常用的两种造模动物。人类与大型动物(尤其是灵长类动物)由于在解剖学上的相似性,可以对手术技术和相关问题进行有力的评估,而小型动物更适合研究影响 RC 损伤和修复的多种生物学因素。单一的从撞击或缺血退变病因的角度探讨 RC 损伤机制可能较为局限。RC 撕裂的发生发展也可能导致肱骨头上半脱位,最终导致整个肩部的功能障碍。慢性 RC 撕裂与肌肉本身结构变化关系更为密切,例如肌肉体积的丧失和脂肪的堆积,同时也受 RC 肌腱微血管供应的影响。因此对于 RC 损伤动物模型的研究应注重整体与局部的联系,临床生物力学模型的开发为 RC 损伤提供了一定思路,具有较好的应用前景。进一步了解肩袖肌腱损伤的细胞和分子途径、肌腱生理病理学以及关节生物力学,有利于以后开发出更为成熟的动物模型。

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[收稿日期] 2020-03-05