

阿霉素诱导大鼠心肌纤维化的性别及剂量差异性比较

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摘要 本研究旨在探讨阿霉素(doxorubicin, DOX)诱导SD大鼠心肌纤维化的性别差异及剂量的依赖性。实验选取56只6~8周龄SD大鼠(雌雄各半), 按性别及阿霉素累积剂量[0(生理盐水对照)、12、15、18 mg/kg]分为8组, 通过腹腔注射构建心肌纤维化模型。该研究构建了腹腔注射诱导的心肌纤维化动物模型。为全面评估该模型, 该实验分别从功能、分子及形态学层面进行检测: 通过心电图和超声心动图评价心脏功能; 通过检测血清脑钠肽(B-type natriuretic peptide, BNP)和雌二醇(estradiol, E2)水平反映相关病理生理变化; 通过心脏组织病理学分析直接判定心肌纤维化的程度。结果显示在相同阿霉素剂量下, 雄性大鼠较雌性表现出更显著的心率降低($P<0.001$)、QT间期延长($P<0.05$)、左心室射血分数与缩短分数下降($P<0.05$), 同时血清脑钠肽水平($P<0.01$)和心肌胶原沉积面积($P<0.01$)显著增加, 且血清雌二醇降低幅度更大($P<0.01$)。剂量依赖性分析表明, 随着阿霉素累积剂量增加, 所有组别均出现心脏功能恶化及心肌纤维化程度加重, 其中雄性大鼠在15 mg/kg时已出现显著损伤, 而雌性需达18 mg/kg才出现明显损伤。组织病理学进一步证实同阿霉素剂量下雄性心肌炎症浸润和心肌纤维化程度更严重。实验结果显示阿霉素诱导SD大鼠心肌纤维化存在剂量依赖性和性别差异, 雄性敏感性高于雌性, 雌性相对耐受可能与雌激素的保护作用相关。

关键词 SD大鼠; 阿霉素; 心肌纤维化; 性别差异; 剂量依赖性

Comparison of Sex and Dose Differences in Doxorubicin-Induced Myocardial Fibrosis in Rats

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Abstract This study investigated gender-related and dose-related differences in the sensitivity of SD (Sprague-Dawley) rats to doxorubicin-induced cardiac fibrosis. Fifty-six 6- to 8-week-old SD rats (equal numbers of males and females) were divided into 8 groups based on sex and cumulative DOX doses [0 (saline control), 12, 15, or 18 mg/kg] to establish a myocardial fibrosis model via intraperitoneal injection. In this study, the present experiment established an animal model of myocardial fibrosis induced by intraperitoneal injection. To comprehensively evaluate the model, assessments were conducted at multiple levels: cardiac function was assessed by ECG (electrocardiography) and echocardiography; relevant pathophysiological changes were reflected by measuring se-

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rum levels of BNP (B-type natriuretic peptide) and E2 (estradiol); and the extent of myocardial fibrosis was directly determined by cardiac histopathological analysis. Results display under equivalent DOX doses, male rats exhibited significantly greater reductions in heart rate ($P<0.001$), prolonged QT intervals ($P<0.05$), decreased left ventricular ejection and fractional shortening ($P<0.05$), elevated serum BNP ($P<0.01$), increased myocardial collagen deposition ($P<0.01$), and more pronounced reductions in serum E2 ($P<0.01$) compared to females. Dose-dependent analysis revealed progressive cardiac dysfunction and aggravated myocardial fibrosis across all groups with increasing DOX doses. Male rats showed significant myocardial damage at 15 mg/kg, whereas females required 18 mg/kg to manifest comparable injury. Histopathology confirmed more severe inflammatory infiltration and fibrotic lesions in males at identical doses. The conclusion shows DOX-induced myocardial fibrosis in SD rats demonstrates both dose dependence and sex dimorphism, with males exhibiting higher susceptibility than females. The relative resistance in females may be attributed to estrogen-mediated cardioprotective mechanisms.

Keywords Sprague-Dawley rats; doxorubicin; cardiac fibrosis; gender differences; dose-dependence

心肌纤维化是多种心血管疾病的典型病理改变,其特征是伴随心肌细胞炎症、变性和坏死,成纤维细胞过度活化并增殖为肌成纤维细胞,后者产生的大量细胞外基质蛋白在细胞间隙过度沉积。这一病理过程可导致心脏结构重塑、顺应性下降,进而引发心功能减退和心律失常等,最终进展为不可逆性心力衰竭甚至猝死^[1-2]。

阿霉素(doxorubicin, DOX)作为蒽环类抗生素的代表性药物,因其广谱强效的抗肿瘤活性,已成为临床多种恶性肿瘤治疗方案的核心组分^[3]。然而,DOX对心肌组织的亲和力显著高于其他组织,阿霉素进入心肌细胞后,炎症因子产生增多进而诱导心肌细胞凋亡坏死,最终导致心肌细胞被纤维组织取代,形成以肌成纤维细胞增多为特征的心肌纤维化,值得注意的是,该病变的严重程度与阿霉素累积剂量呈明确的剂量依赖性关系^[4]。因此,建立标准化的动物模型剂量方案至关重要。但以SD大鼠为例,不同研究中DOX诱导心肌纤维化的用量存在显著差异^[5-7]。此外,DOX诱导的心脏毒性涉及多方面的生化途径^[8-9],近年研究发现,性别因素是独立于剂量之外的关键风险变量^[10]。例如,JENKINS等^[11]利用B6C3F1小鼠模型系统揭示了雄性小鼠对DOX心脏毒性的易感性更大;DESAI等^[12]同样利用B6C3F1小鼠模型系统揭示了这种性别差异可能与apelin-APJ通路有关;GAWAD等^[13]利用C57BL/6小鼠模型表明抗炎标志物IL-10水平仅在DOX处理的雄性小鼠心脏中显著降低。

尽管SD大鼠作为阿霉素诱导心肌纤维化的常用动物模型已被广泛应用^[14-16],但关于其性别差异

及剂量依赖性反应的系统性研究仍相对匮乏。本研究聚焦阿霉素对SD大鼠诱导心肌纤维化的性别及剂量的差异性,旨在为阿霉素诱导心肌纤维化的动物模型提供实验依据。

1 材料与方法

1.1 材料

1.1.1 实验动物 6~8周龄SPF级SD大鼠56只,雌雄各半,体质量(200±20)g,购于成都达硕实验动物有限公司,生产许可证号:SCXK(川)2020-0030。所有动物均饲养于陕西中医药大学实验动物中心[SYXK(陕)2021-001],昼夜节律12 h/12 h,饮水摄食自由,温度(20±2)°C,湿度50%~70%。所有动物实验经陕西中医药大学实验动物伦理委员会审核并批准(SUCMDL20241011021)。

1.1.2 主要试剂与仪器 阿霉素(货号D70017)购自北京普西唐生物科技有限公司;氯化钠(国药准字H37020764)注射液购自山东齐鲁药业有限公司;HE染色试剂盒(货号G1003)、Masson三色染色试剂盒(货号G1006)和4%多聚甲醛通用固定液(货号G1101)购自武汉赛维尔生物科技有限公司;Mouse BNP ELISA Kit(货号WS09V2226013)和QuicKey-ProRatE2 ELISA Kit(货号E-OSEL-R0001)购自武汉伊莱瑞特科技股份有限公司;异氟烷购自瑞沃德生命科技公司(兽药生产证字15198)。

小动物麻醉机(型号R640-S1)购自瑞沃德生命科技公司;小动物超声仪(型号VINNO6)购自飞依诺科技股份有限公司;生物信号采集与分析系统(型号BL-420N)购自成都泰盟软件有限公司;数字

病理切片扫描系统(型号为PRECICE510)购自优纳科技有限公司;大容量冷冻离心机(型号为ST16R)购自美国ThermoFisher Scientific公司。

1.2 方法

1.2.1 动物分组与模型构建 SD大鼠按体质量和性别随机分为雌-生理盐水(f-SAL)组、雌-4周(f-4w)组、雌-5周(f-5w)组、雌-6周(f-6w),雄-生理盐水(m-SAL)组、雄-4周(m-4w)组、雄-5周(m-5w)组、雄-6周(m-6w),共8组,每组7只。各组大鼠每周腹腔注射3 mg/kg DOX或同等体积的生理盐水,连续4、5或6周。生理盐水组累积剂量为0 mg/kg;4周累积剂量为12 mg/kg;5周累积剂量为15 mg/kg;6周累积剂量为18 mg/kg。

1.2.2 样本采集 阿霉素末次给药后禁食不禁水12 h,大鼠称重后,采用5%异氟烷诱导麻醉,腹主动脉采血,常温静置2 h,4 °C、3 500 r/min离心15 min,吸取上清。取出心脏放入生理盐水清洗,常温固定于4%多聚甲醛48 h。

1.2.3 心电图检测 在实验第0天和4、5、6周DOX给药后进行心电图(electrocardiogram, ECG)检测。大鼠采用3%异氟烷初始麻醉,之后1.5%异氟烷维持麻醉,仰卧位固定于检测台上,将电极针连接在四肢上,采用生物信号采集与分析系统记录ECG。

1.2.4 超声心动图检测 在实验第0天和4、5、6周DOX给药后进行超声心动图检测。大鼠采用3%异氟烷初始麻醉,之后用1.5%异氟烷维持麻醉,仰卧位固定于检测台上,用刮毛器将毛刮除,暴露胸部皮肤^[7]。将耦合剂置于探头上使用M波记录超声心动图,检测左心室射血分数(left ventricular ejection fraction, LVEF)、左心室缩短分数(left ventricular fractional shortening, LVFS)。

1.2.5 心脏组织病理学观察 提取心脏组织样本,4%多聚甲醛常温固定48 h,脱水并用石蜡包埋,制备切片进行HE染色和Masson染色,使用数字切片扫描系统观察大鼠心脏组织炎症浸润程度和纤维化改变。Masson染色通过ImageJ分析胶原面积评估大鼠心肌纤维化程度。

1.2.6 血清脑钠肽(BNP)、雌二醇(E2)检测 4 °C、3 500 r/min离心15 min,离心后的血清放入4 °C冰箱保存,24 h之内用ELISA试剂盒检测血清中脑钠肽、雌二醇的含量。

1.3 统计学分析

实验数据用GraphPad Prism 10.1.2统计学软件进行分析,结果以 $\bar{x}\pm s$ 表示。多组间比较使用单因素方差分析,两组间比较采用独立样本 t 检验, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 各组大鼠心电图比较

用心电图评价大鼠的一般情况,实验开始前同性别大鼠各组之间心率、QT间期无明显差异。第4、5、6周末检测大鼠心电图发现,随着阿霉素剂量的增加雌雄大鼠组与SAL组相比均出现不同程度的心率降低、QT间期延长($P<0.01$, $P<0.001$),进一步研究发现DOX累积剂量相同时,雄性大鼠心率降低程度及QT间期延长程度均高于雌性大鼠($P<0.05$, $P<0.01$, $P<0.001$)(图1)。

2.2 各组大鼠超声心动图比较

超声心动图评价各组大鼠心脏的结构和功能,结果显示随着阿霉素剂量的增加,雌雄大鼠组与SAL组相比出现不同程度的EF、FS下降($P<0.01$, $P<0.001$)。超声心动图发现,当阿霉素累积剂量相同时雄性大鼠组与雌性大鼠组相比雄性组大鼠EF和FS下降显著($P<0.05$, $P<0.001$)(图2)。

2.3 各组大鼠心脏组织HE染色比较

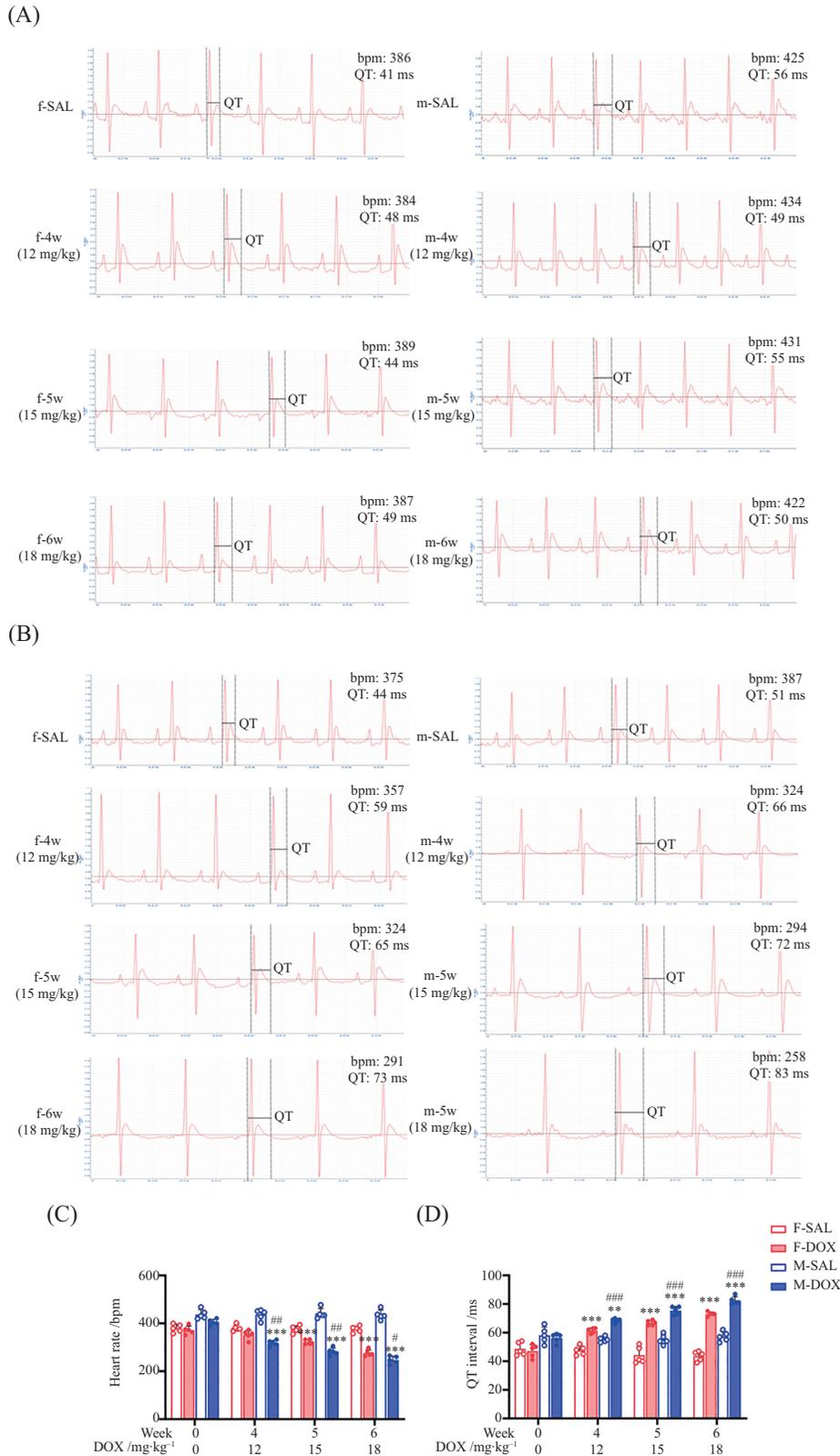
HE结果显示,随着阿霉素剂量增加雌雄组大鼠与SAL组相比心脏横截面积出现不同程度萎缩、心肌排列紊乱、心肌排列不齐和炎症细胞浸润等。当DOX累积剂量相同时,雄性组大鼠比雌性组大鼠心脏损伤更严重(图3)。

2.4 各组大鼠血清脑钠肽(BNP)、雌二醇(E2)含量比较

结果显示随着阿霉素剂量增加,雌雄组大鼠与SAL组相比血清脑钠肽出现不同程度的升高($P<0.01$, $P<0.001$),当阿霉素累积剂量相同时,雄性组大鼠与雌性组大鼠相比雄性组大鼠血清脑钠肽升高明显($P<0.001$)(图4A)。结果显示, m-SAL组与f-SAL组相比血清雌二醇含量低($P<0.01$),当阿霉素累积剂量相同时,雄性组大鼠与雌性组大鼠相比雌性组大鼠血清雌二醇降低明显($P<0.001$)(图4B)。

2.5 各组大鼠心脏组织Masson染色比较

Masson结果显示,随着阿霉素剂量增加雌雄大鼠与SAL组相比出现不同程度的胶原纤维沉积($P<0.05$,

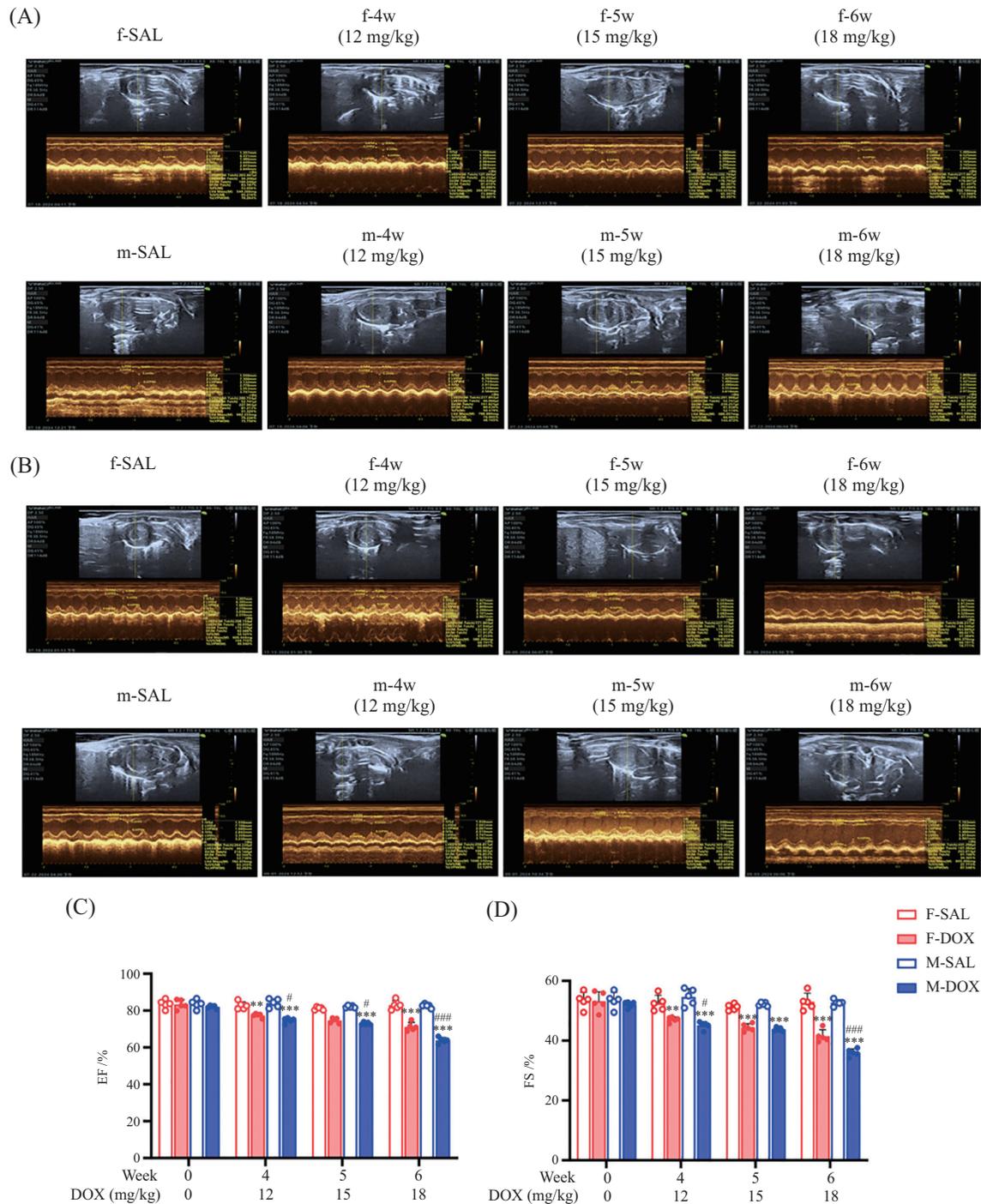


A: 实验开始前大鼠心电图; B: 实验结束后大鼠心电统计图; C: 大鼠心电统计图; D: 大鼠QT间期统计图。n=5; **P<0.01, ***P<0.001, 同性别SAL组与DOX组相比; #P<0.05, ##P<0.01, ###P<0.001, DOX同剂量雄性组与雌性组相比。

A: baseline electrocardiogram (ECG) of rats before experiment; B: post-experimental statistical chart of rat heart rate; C: statistical chart of rat heart rate; D: statistical chart of rat QT interval. n=5; **P<0.01, ***P<0.001, comparisons were made between the same-sex SAL and DOX groups; #P<0.05, ##P<0.01, ###P<0.001, male DOX groups compared with female DOX groups at same dosage.

图1 各组大鼠心电图

Fig.1 The ECG results of each rat group



A: 实验开始前大鼠超声心动图; B: 实验结束后大鼠超声心动图; C: 左心室射血分数(LVEF); D: 左心室短轴缩短(LVFS)。n=5; **P<0.01, ***P<0.001, 同性别SAL组与DOX组相比; #P<0.05, ###P<0.001, DOX同剂量雄性组与雌性组相比。

A: baseline echocardiography of rats before experiment; B: post-experimental echocardiography of rats; C: left ventricular EF (ejection fraction); D: left ventricular FS (fractional shortening). n=5; **P<0.01, ***P<0.001, comparisons were made between the same-sex SAL and DOX groups; #P<0.05, ###P<0.001, male DOX groups compared with female DOX groups at same dosage.

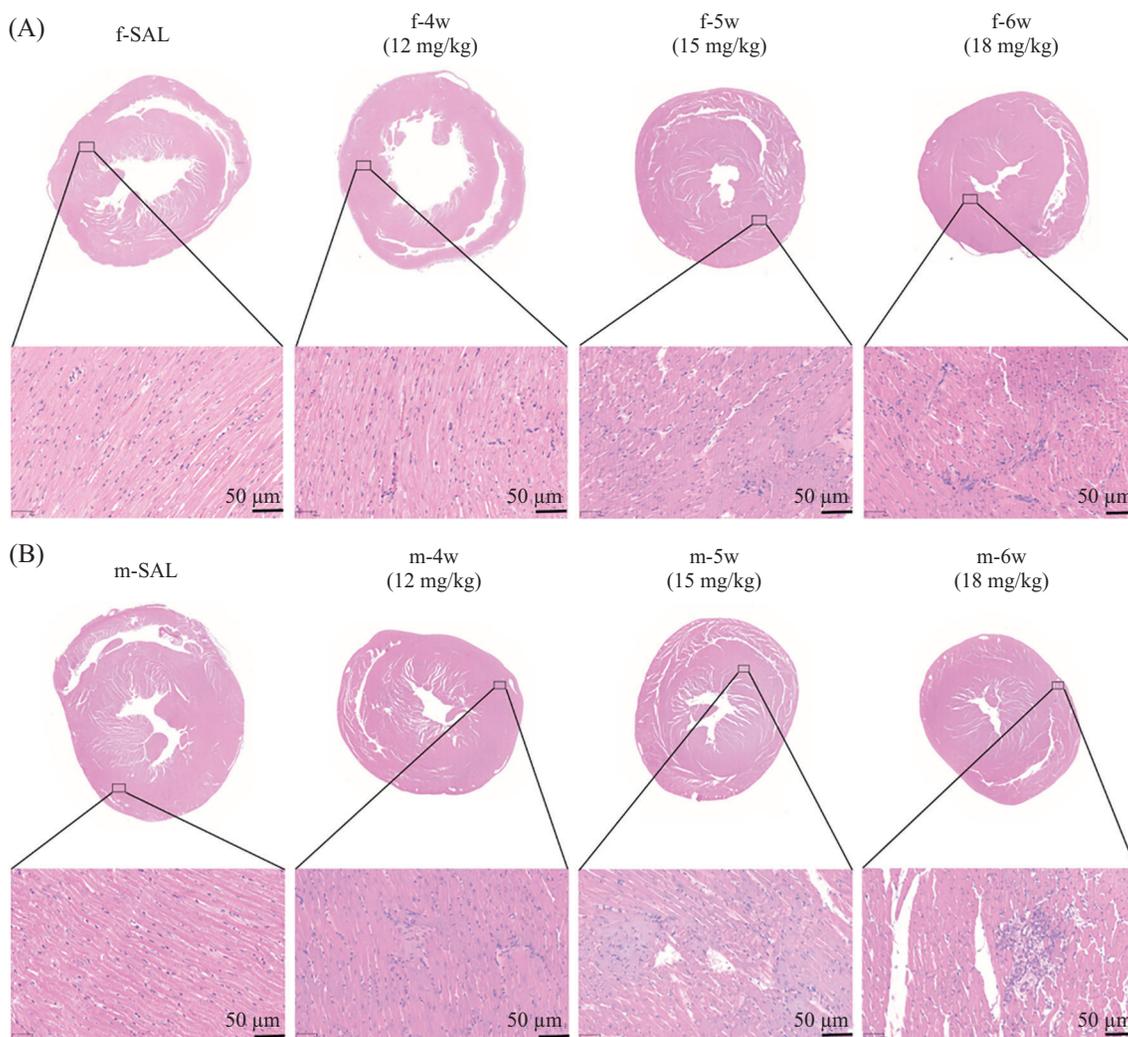
图2 各组大鼠超声心动图

Fig.2 Effects of DOX on rat echocardiographic parameters

P<0.01, P<0.001)且大多沉积在血管周围, 当DOX累积剂量相同时雄性组大鼠与雌性组大鼠相比雄性组大鼠胶原纤维沉积显著(P<0.01, P<0.001)(图5)。

3 讨论

阿霉素通过氧化应激、炎症反应及TGF-β信号通路的激活等多种诱导心肌纤维化且纤维化大多集



$n=5$.

图3 各组大鼠心脏组织HE染色比较

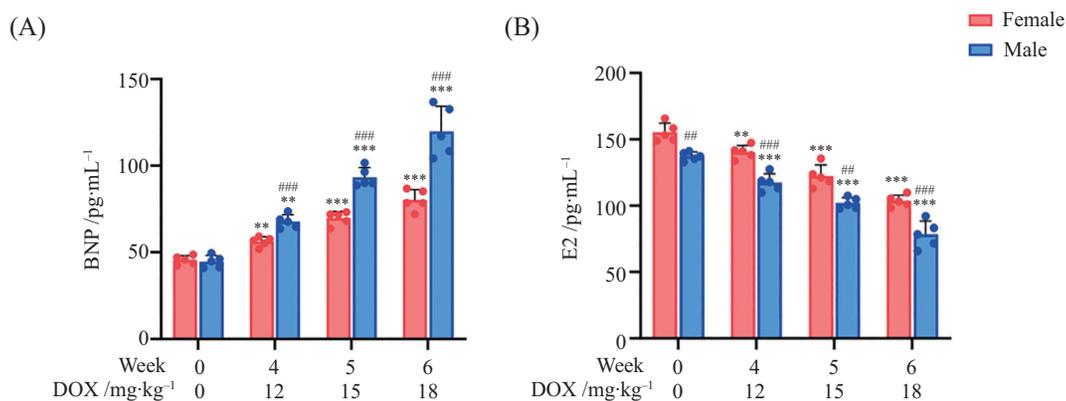
Fig.3 Comparison of HE staining in cardiac tissues of rat groups

中在心血管周围,这些机制已被广泛研究和验证^[18-19]。SD大鼠是近交系大鼠,具有稳定的遗传背景,且对阿霉素敏感,模型构建成熟,成本效益高^[20]。基于此,本研究采用SD大鼠为实验对象。

阿霉素作为蒽环类抗生素,因其抗肿瘤作用强、疗效确切,已成为临床上许多常见肿瘤的一线化疗药物^[21],但其导致的心脏毒性死亡风险常超过肿瘤复发风险^[22]。右雷佐生是唯一被批准有效干预蒽环类药物的心脏毒性的药物^[23],但由于骨髓抑制等副作用,在临床使用中存在诸多争议^[24]。因此,如何应对阿霉素引起的心脏损害已成为肿瘤治疗中的一大难题。当前,采用阿霉素诱导大鼠心肌纤维化作为动物模型的相关研究较多,但文献报道的阿霉素累积剂量存在差异^[25]。查阅大量文献发现,DOX

的累积剂量多集中在12~18 mg/kg^[26-27]。因此,本研究设置12 mg/kg、15 mg/kg和18 mg/kg三个剂量梯度,以观察大鼠心肌纤维化的严重程度。此外,多项研究表明阿霉素诱导的心肌纤维化存在显著的性别差异^[28-29],但针对SD雌性大鼠心肌纤维化诱导剂量的研究较少^[30]。因此,本研究设置雌、雄对照旨在明确SD大鼠对阿霉素诱导心肌纤维化的剂量敏感性及性别差异。

本研究从心电图、超声心动图、BNP水平检测、E2水平检测和心脏病理学等方面对6组大鼠进行全面比较。本次实验中f-4w组、f-6w组、m-4w组、m-5w组各死亡1只,m-6w组死亡2只,共死亡6只大鼠。实验结果显示,在同剂量阿霉素作用下,雄性SD大鼠较雌性个体呈现出更为显著的心功能损伤和心肌纤



A: 各组大鼠血清脑钠肽(BNP)比较; B: 各组大鼠血清雌二醇(E2)。n=5; ** $P<0.01$, *** $P<0.001$, 同性别SAL组(DOX 0 mg/kg)与DOX组相比; # $P<0.01$, ### $P<0.001$, DOX同剂量雄性组与雌性组相比。

A: comparison of serum BNP (brain natriuretic peptide) levels across experimental groups; B: comparison of serum E2 levels among treatment groups. n=5; ** $P<0.01$, *** $P<0.001$, comparisons were made between the same-sex SAL (DOX 0 mg/kg) and DOX groups; # $P<0.01$, ### $P<0.001$, male DOX groups compared with female DOX groups at same dosage.

图4 各组大鼠脑钠肽(BNP)、雌二醇(E2)含量统计图

Fig.4 Statistics of BNP (brain natriuretic peptide) and E2 (estradiol) in different rat groups

维化进程。心电图显示雄性大鼠的心率降低明显、QT间期延长显著,提示阿霉素的毒性作用导致了心肌细胞的损伤、凋亡和纤维化,心肌纤维化常引起心肌电生理学的改变,导致心肌复极过程延迟,进而引发QT间期延长。超声心动图显示雄性大鼠左心室射血分数和缩短分数下降更明显,收缩和舒张功能明显降低提示雄性大鼠心功能损伤更明显。血清脑钠肽结果显示雄性大鼠血清脑钠肽水平升高显著,提示心室压力负荷增加,表明雄性大鼠在阿霉素处理后心肌细胞受损更为严重。病理染色是最直观反映造模效果的指标,HE染色和Masson染色结果一致,雄性大鼠心肌组织中的炎症细胞浸润和胶原纤维沉积更为显著,且纤维化大多沉积在血管周围,这是因为内皮-间质转化参与阿霉素诱导的心肌纤维化^[31]。此外,心脏横截面积分析显示,随着阿霉素剂量增加,心脏萎缩程度逐渐加剧,这一现象与先前的研究一致^[32-34],主要归因于阿霉素诱导的心肌细胞死亡萎缩,值得注意的是这种萎缩性病理改变与传统压力超负荷性心肌肥大的机制截然不同,因此可部分解释为何常规抗心肌肥大药物对阿霉素心脏毒性的干预效果有限^[35]。然而,也有报道称阿霉素治疗导致心肌肥大^[36],这可能与实验设计、阿霉素累积用量、给药方式不一致有关。病理染色进一步证实了雄性大鼠对阿霉素心脏毒性更加敏感。有研究表明,性激素水平可能是阿霉素心脏毒性性别差异的重要原因,其中雌激素具有一定的心脏保护作用,可减轻阿霉素诱导的心肌

损伤^[12,29],雌二醇是人体内最重要的雌激素之一,主要由卵巢、睾丸和胎盘分泌,血清雌二醇结果显示雌雄SAL组雌二醇本身存在差异,阿霉素给药后雌雄大鼠雌二醇水平显著降低,且雄性大鼠降幅更为明显。结合雌性大鼠心肌损伤程度较轻的结果,提示雌激素可能通过其心脏保护作用,部分缓解阿霉素诱导的心肌纤维化。

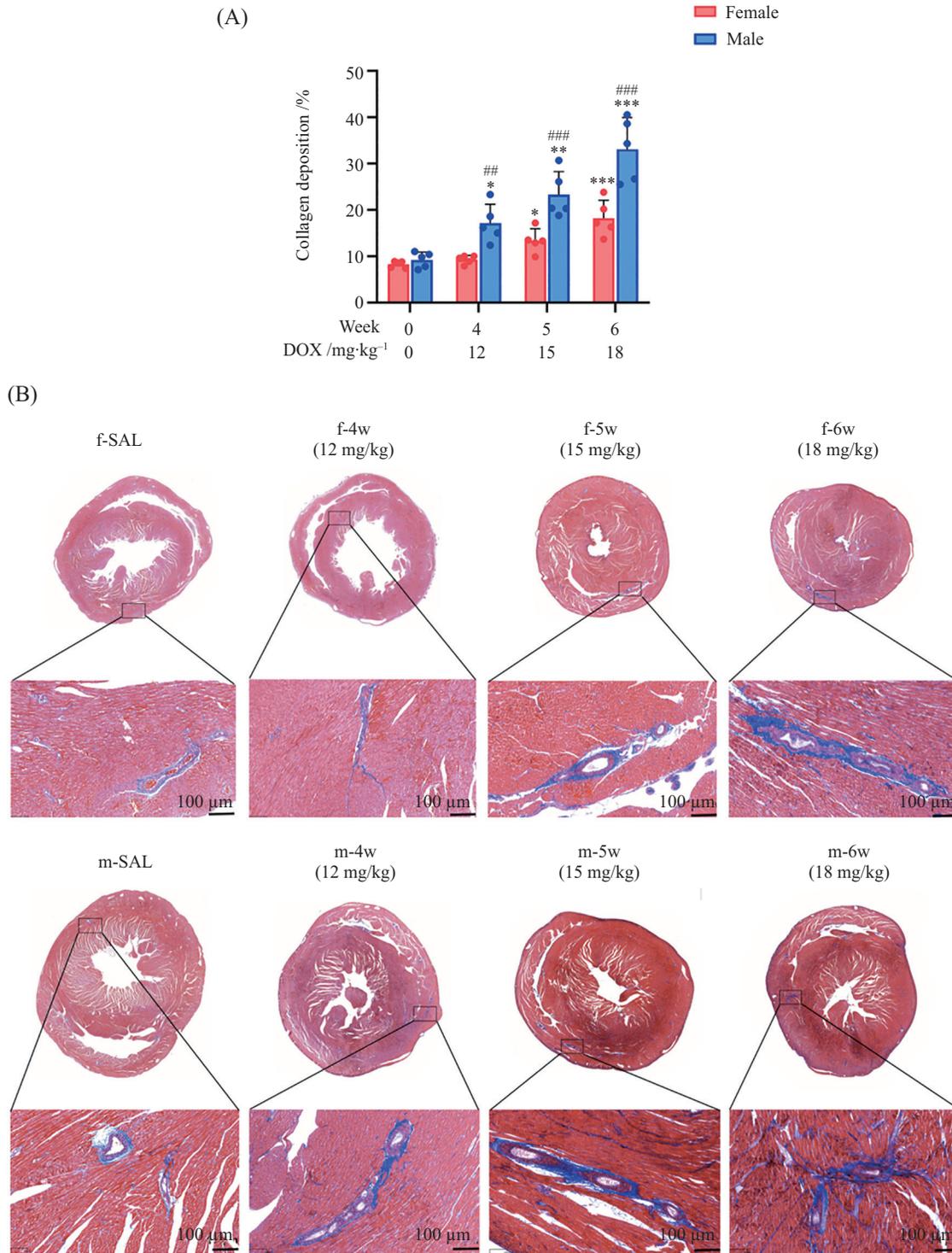
本研究中,随阿霉素累积剂量增加,大鼠心脏功能受损和心肌纤维化程度逐渐加重。在4、5和6周阿霉素处理组中心脏状态逐渐恶化,表明阿霉素诱导的心脏毒性和心肌纤维化呈明显剂量依赖性。

综合各项结果,本研究成功构建了以15 mg/kg或18 mg/kg DOX诱导的雄性SD大鼠心肌纤维化模型。其中,18 mg/kg诱导的心脏损伤和心肌纤维化更加明显,但15 mg/kg剂量下大鼠的存活率更佳。雌性SD大鼠在累积剂量达到18 mg/kg时才可能出现明显的心肌纤维化。

本研究主要侧重于造模效果的评价,而对于造模机制的探讨相对较少。下一步将通过分子水平的分析,如基因表达、蛋白质修饰和信号通路的变化,以进一步探索阿霉素引起心肌纤维化雌雄差异的分子机制。

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A: Masson染色胶原沉积面积统计图; B:大鼠心脏组织Masson染色图像。n=5; *P<0.05, **P<0.01; ***P<0.001, 同性别SAL组(DOX 0 mg/kg)与DOX组相比; ^{##}P<0.01, ^{###}P<0.001, DOX同剂量雄性组与雌性组相比。

A: quantitative analysis of collagen deposition area by Masson's trichrome staining; B: representative Masson's trichrome-stained images of rat cardiac tissues. n=5; *P<0.05, **P<0.01, ***P<0.001, comparisons were made between the same-sex SAL (DOX 0 mg/kg) and DOX groups; ^{##}P<0.01, ^{###}P<0.001, male compared with female DOX groups at same dosage.

图5 各组大鼠心脏组织Masson染色

Fig.5 Comparison of Masson staining in cardiac tissues of rat groups

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