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线粒体在运动保护心肌免受缺血再灌注损伤中的作用*

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摘要 线粒体是参与心肌缺血再灌注（myocardial ischemia and reperfusion，MI/R）损伤的关键细胞器，线粒体活性氧（reactive oxygen species，ROS）爆发、Ca^{2+}失调、线粒体通透性转换孔（mitochondrial permeability transition pore，mPTP）开放、线粒体肿胀、促凋亡蛋白释放等都会导致线粒体功能障碍，心肌功能受损。运动是预防MI/R损伤的有效干预手段，其保护作用可能通过线粒体来实现。运动保护MI/R损伤的线粒体机制由多种因素决定，如线粒体能量学、K_{ATP}通道、mPTP、线粒体跨膜电位（$\Delta\Psi_m$）、线粒体蛋白、线粒体脂质、线粒体质量控制、远程调控因子等。本文综述了MI/R产生的线粒体机制，运动对MI/R的保护作用以及线粒体在其中的作用，以期为MI/R损伤的线粒体治疗策略提供参考。

关键词 运动，线粒体，心肌缺血再灌注
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心血管疾病已成为致命疾病的关键风险因素，在全球范围内具有高发病率和致死率[1-2]。调查显示，急性心肌梗死已成为心血管疾病中致死的主要原因[3]。心肌缺血再灌注（myocardial ischemia and reperfusion，MI/R）发生在血供有限或缺乏后心肌血运重建时[4-5]，常发生在心肌梗死后，是急性心肌损伤的主要诱因[6]。

根据缺血时间的长短，会出现3种不同程度的MI/R损伤（图1）。缺血1~5 min后再灌注会促进室性心动过速或心室颤动，这种损伤往往与心律失常的发生相关，但不会引起心室收缩功能障碍或心肌细胞死亡。缺血5~20 min后再灌注会产生二级心肌损伤，称为“心肌顿抑”，其主要特征是可逆性心室收缩功能障碍，但没有心肌细胞死亡。通常，这种程度的损伤可持续24~72 h。缺血时间超过20 min再灌注时，心肌细胞受到不可逆的损伤，细胞凋亡和坏死造成细胞死亡，产生心肌梗死，这是最严重的MI/R损伤。事实上，心肌梗死的严重程度是导致心肌缺血再灌注损伤相关死亡的主要因素[7-8]。

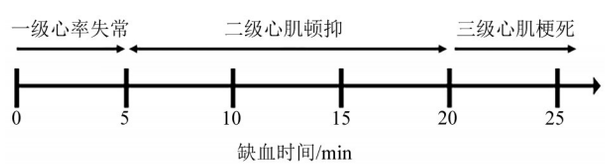

Fig. 1 Three degrees of myocardial ischemia−reperfusion injury

图1 心肌缺血再灌注损伤的三种程度

随着缺血时间的不断延长，MI/R损伤的程度不断加重，依次表现为心律失常、心肌顿抑、心肌梗死。

众所周知，运动有益于健康，运动可以预防和缓解MI/R损伤。心脏是一个高能量需求器官，线粒体约占成年心肌细胞体积的35%。当线粒体出现

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功能失调或发生缺陷时可通过细胞凋亡或坏死决定细胞的生死命运。鉴于线粒体功能障碍对细胞的严重后果，生物体已进化出多种机制来防止或修复线粒体的损伤，如果不能，则消除并替换线粒体以保证心脏的能量供应，防止心脏损伤。可见，线粒体在运动保护心肌缺血再灌注损伤中发挥着关键作用。

1　MI/R损伤产生的线粒体机制

尽管导致MI/R损伤的因素很复杂，但引起MI/R细胞死亡的关键因素已基本了解，线粒体在其中发挥了重要作用（图2）[9]。在MI/R期间，线粒体对细胞死亡至关重要，同时也对细胞存活至关重要。

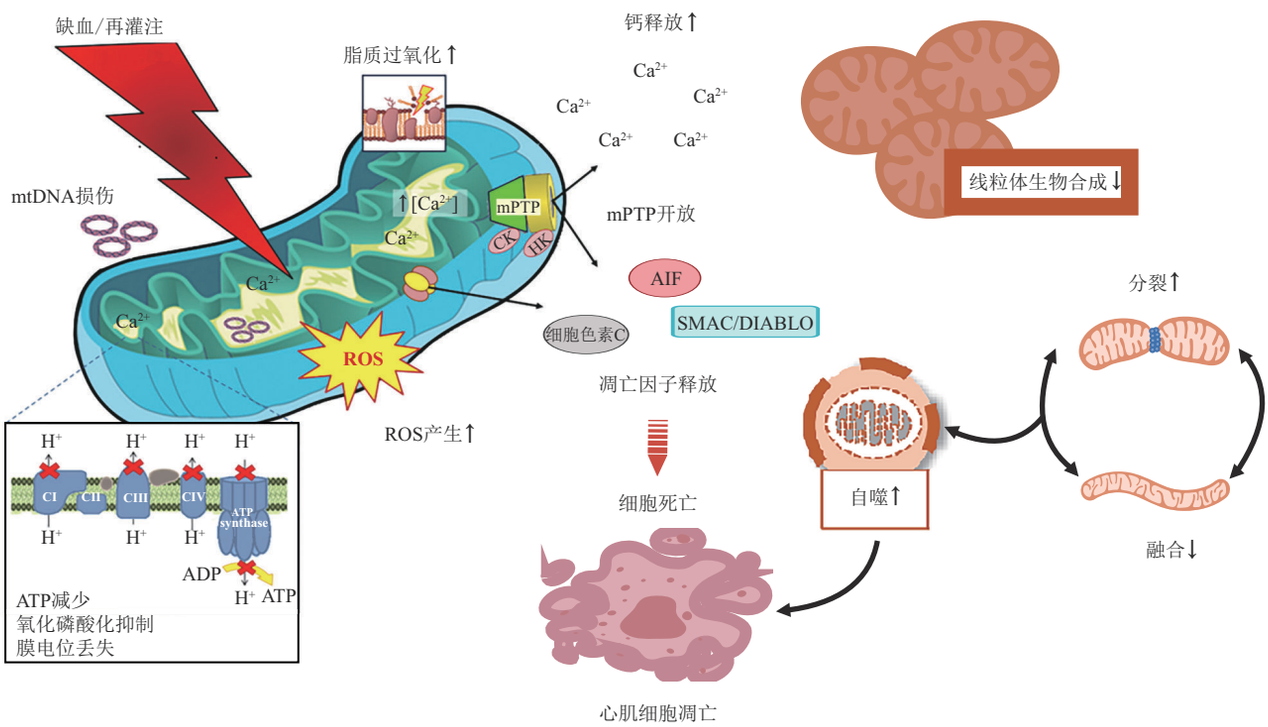

Fig. 2　Role of mitochondria in myocardial ischemia−reperfusion injury

图2　线粒体在心肌缺血再灌注损伤中的作用

缺血/再灌注诱导的线粒体功能障碍的特征是ROS的产生增加、氧化应激、mtDNA受损、氧化磷酸化障碍、跨膜电位的去极化、ATP储备的耗竭、线粒体Ca^{2+}超载、mPTP的激活和线粒体生物合成减少、分裂增强、融合受抑、自噬失衡及线粒体途径细胞凋亡。AIF：细胞凋亡诱导因子（apoptosis inducing factor，AIF）；SMAC/DIABLO：第二个线粒体衍生的半胱氨酸蛋白酶激活剂/低等电点的细胞凋亡抑制剂的直接结合蛋白（second mitochondrial-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI，SMAC/DIABLO）。

在心肌缺血期间，血供不足致使组织缺氧，导致线粒体氧化磷酸化中断，细胞内三磷酸腺苷（adenosine-triphosphate，ATP）和磷酸肌酸水平降低，损害心脏收缩力。此时，ATP的合成来源于无氧代谢，无氧代谢糖酵解中产物乳酸的积累和pH值的降低反过来又会抑制糖酵解。Na^+/H^+逆向转运蛋白被激活，试图恢复pH值，从而导致细胞内［Na^+］和［H^+］同时升高。反过来，细胞内［Na^+］的增加会减慢或逆转Na^+/Ca^{2+}交换的方向，使细胞内［Ca^{2+}］增加，最终造成线粒体内钙超载，呼吸链电子通量减少，在复合物I和III处形成超氧阴离子，并导致还原当量的积累[10-11]。

再灌注过程可能进一步导致不同程度的心肌损伤，占最终心肌损伤的50%[12]。再灌注开始时，心脏血流恢复，氧供应瞬间上升，缺血期累积的还原性代谢物提供电子供体，与氧结合，使线粒体呼吸链复合物I和III处的活性氧（reactive oxygen species，ROS）大量形成并释放，引起脂质过氧化水平升高，线粒体生物发生减弱，破坏线粒体DNA（mitochondrial DNA，mtDNA），最终导致线粒体功能障碍[11, 13]。最近有研究发现，在MI/R损伤模型中，ROS可引起运动性心绞痛[14]。

ROS产生的初始爆发可直接导致线粒体氧化损伤，破坏ATP的产生，并与Ca^{2+}的失调共同诱发线粒体通透性转换孔（mitochondrial permeability transition pore，mPTP）的持续开放，最终导致细胞坏死和凋亡[15]。研究发现，受损但功能尚存的线粒体可释放高达10倍的H_2O_2，占耗氧量的10%~20%[16]。增加的氧化应激可诱导促凋亡线粒体蛋白的同源二聚化和激活，导致线粒体基质重塑和内膜肿胀[17-18]。膜重排导致视神经萎缩蛋白1（optic atrophy 1，OPA1）复合物解体并从线粒体释放，干扰线粒体的分裂和融合[19]。肿胀的线粒体失去线粒体膜电位，启动自噬程序，然而再灌注可导致自噬失调，促进心肌细胞凋亡，损害心肌[20]。受损的线粒体还能够通过释放细胞色素C和凋亡诱导因子到细胞质中，启动细胞凋亡，诱导细胞死亡[21]。再灌注早期，mPTP的开放会使线粒体内膜对高达1 500 u的溶质具有渗透性[22]，使膜两侧的电化学梯度消散，膜电位去极化，并改变心脏动作电位持续时间，导致心律失常[23-26]。电化学梯度的丧失还会导致ATP合酶反向运转，消耗ATP，随后瞬间大量释放ROS和Ca^{2+}[27-29]。这种ROS释放信号会激活邻近线粒体ROS释放，最终激活钙依赖性蛋白酶和脂肪酶，导致坏死细胞死亡[30]。

可见，线粒体是参与MI/R损伤的关键细胞器。MI/R破坏线粒体呼吸链，并伴有ATP耗竭，导致线粒体ROS的积累[31]。由此产生一系列反应，最终导致心肌功能受损。

2 运动对MI/R损伤的保护作用

有规律的体育活动不仅是一种简单、经济高效的预防心血管疾病的措施，它还可以直接保护心脏免受急性MI/R或梗死的影响[32]。而运动对心脏的保护效应与运动强度的大小、运动时间的长短、运动类型及内在运动能力密切相关。

2.1 运动强度

运动训练可预防MI/R诱发的心律失常、心肌顿抑和心肌梗死[33-34]。当运动强度低于55%~60% VO_2max时，预期的MI/R损伤抵抗作用并未产生[35]。但最近有研究发现，低强度运动可以提高代谢综合征老年雌性大鼠对MI/R损伤的心脏耐受性[36]。中等强度的间歇训练可以减轻糖尿病大鼠的MI/R损伤[37]。Esposito等[38]比较了运动强度对MI/R心肌损伤的影响，发现高强度运动比中等强度和低强度运动更有效地降低心肌梗死面积。但也有研究发现，中等强度（即50% VO_2max）和相对高强度（即70% VO_2max）的运动对MI/R诱导的心肌顿抑产生的保护作用相似[39]。无论如何，可能存在一个运动强度阈值，超过该阈值即可实现心脏保护作用。

2.2 运动时间

持续有氧运动（如60 min）和高强度间歇训练（在≥VO_2max的强度下运动1 min）均会产生心脏保护表型[40]。先前的数据表明，大鼠在跑步机上进行4个月的有氧耐力训练后，心脏体外灌注缺血30 min再灌流2 h，心肌梗死面积减少[41]。多数研究发现，8~10周持续有氧或高强度间歇训练可减轻MI/R损伤[42-44]。当运动时间缩短到3周[45]，甚至2 d[46]或单次[47]，同样会对MI/R损伤产生心脏保护效应。Thijssen等[48]在综述中表明，单次或短期运动诱导的心脏保护作用在动物和人类身上都可以减轻长期缺血和再灌注造成的损伤。这种单次或短期运动的裨益可能归功于循环体液因子，包括腺苷和阿片类药物等[49-50]。

可见，不同时长的运动均可对MI/R损伤产生心脏保护作用。那么，运动时长是否会影响心脏保护的程度？Budiono等[32]对比短期（2 d）、中期（7~14 d）和长期（28 d）自愿轮跑对MI/R的反应，发现雄性小鼠对MI/R的耐受性提高了，且随着运动时间或运动量的增加，这种心脏保护作用没有进一步的改善。这提示，运动的心脏保护效应不是“剂量依赖性”的。

与手术诱导的短暂缺血产生的缺血预处理现象类似，运动诱导的心脏保护也是双相的。心脏保护的第一阶段出现在运动后即刻，并延续1~2 h[51]，第二阶段在运动后12~24 h后出现，持续48~72 h时，远比第一阶段保护窗口稳固[52]。研究发现，啮齿类动物在停止运动训练后，运动诱导的心脏保护作用会在9~18 d内迅速消失[52-53]。

2.3 运动类型

中等强度的有氧耐力持续运动训练可使心脏mRNA甲基化水平降低，减轻急性MI/R损伤[54]。有氧持续运动可能通过激活糖尿病大鼠腺苷酸活化蛋白激酶（adenosine monophosphate-activated protein kinase，AMPK）/沉默信息调节因子1（silent information regulator 1，SIRT1）/过氧化物酶体增殖物激活受体γ辅助活化因子1α（peroxisome proliferator-activated receptor-gamma coactivator 1α，PGC-1α）通路来减轻MI/R损伤，

抑制血栓形成[55]。除了传统的持续运动，高强度间歇训练（high-intensity interval training，HIIT）也属于有氧运动的范畴。研究发现，HIIT可以减小雄性年轻大鼠的心肌梗死面积[47]，且对于老年鼠，同样可减轻MI/R损伤，降低运动比赛损伤[56]。有学者将HIIT与持续训练的效果进行比较，发现短期（连续5 d）[57]和长期（4周）[58] HIIT对MI/R损伤的预处理作用大于中等强度的持续训练。Rankovic等[58]表明，与中等强度的持续训练相比，HIIT训练在再灌注期释放的ROS更少。

除了有氧运动，抗阻运动也可减轻心肌损伤。研究表明，12周的抗阻运动可以预防MI/R诱导的大鼠心肌梗死[59]。此外，垂直正弦全身振动训练对MI/R损伤心肌也产生了保护作用[60]。Eduardo等[61]综述了2010~2022年对MI/R作用的运动方案，包括强迫游泳、负重运动和跑步训练，其中有些运动方案是自愿运动。

2.4　运动能力

基于内在的有氧跑步运动能力表型进行育种，开发出一种新的大鼠模型，将运动能力的遗传成分与环境后天影响（如运动训练）区分开来。内在有氧跑步运动能力低（low-capacity endurance running，LCR）的大鼠较内在有氧跑步运动能力高（high-capacity endurance running，HCR）的大鼠心血管疾病相关危险因素发生率高[62]。与HCR者相比，LCR者在短期心肌缺血和再灌注后表现出更高的致心律失常性[63]。高内在有氧能力提供了心脏保护，但它不是无限的/连续的，当损伤足够大时这种保护作用也会消失[64]。这种内在运动能力的差异可能是由代谢驱动的[65-67]。有人认为，积极的运动可能改善LCR表型，但控制运动训练反应和内在运动能力的因素在基因上有不同的排序[65，68]。此外，研究发现，不论是LCR还是HCR，在应对短期（15 min/2 h）和长期（30 min/2 h）心肌缺血再灌注时都保持了性别差异，雄性心肌梗死的面积大于雌性[69]。

总之，尽管运动对MI/R有一系列有益的影响，但运动的强度、持续时间、方式和其他干预因素会导致不同的结果[64]。

3　运动通过线粒体减轻MI/R损伤

定期锻炼可提供可靠有效的心血管益处，如改善急性缺血性心脏损伤，包括MI/R损伤[70]。运动训练可以保护心脏肌下和肌纤维间线粒体，使其能够适应短暂缺氧并减少ROS的产生，提高其耐受高钙水平的能力，并防止MI/R引起的氧化损伤，以实现心脏保护[71]。可见，线粒体在运动介导的MI/R损伤保护中发挥着重要作用。

3.1　线粒体能量学

线粒体的主要功能是氧化磷酸化产生ATP，线粒体占据心肌细胞体积的30%以上，每天产生超过30 kg的ATP。在缺血期间，ATP水平降低会破坏控制心脏细胞离子稳态的关键泵蛋白的活性，导致Ca^{2+}超载，改变心肌细胞的稳态，增加ROS的产生、钙蛋白酶的激活、收缩蛋白的损伤，并最终导致细胞死亡。在MI/R后，ATP合成的恢复对恢复心脏稳态和功能至关重要。

已有研究表明，运动训练限制了体外缺氧条件下线粒体呼吸控制率的改变[72]。运动组动物较久坐不动组相比，在缺氧/再复氧后线粒体能量（氧气消耗率）的恢复有所改善，久坐组动物线粒体产生H_2O_2与消耗O_2的比率是运动组的2倍[73]。运动通过诱导线粒体呼吸链/三羧酸循环蛋白的表达，以及线粒体肌酸激酶的表达[74]，增强了线粒体氧化能力，有助于维持MI/R损伤期间的能量稳态，改善心脏功能[75]。

此外，运动可以限制MI/R期间mPTP的激活[76-77]，从而对线粒体能量学、线粒体跨膜电位（$\Delta\Psi_m$）和再灌注心律失常产生有益影响[73]。运动训练还可以通过ATP敏感的钾通道在MI/R期间实现对线粒体的保护作用[78]。下面将详细介绍。

3.2　线粒体K_{ATP}通道

K_{ATP}通道的活性由细胞内ATP和ADP浓度决定，高表达于肌膜（sarcoK_{ATP}）和线粒体（mitoK_{ATP}）。ATP水平稳定时，K_{ATP}通道保持关闭。当代谢应激（如缺氧或缺血）诱导ATP减少时，就会触发通道开放，使心肌细胞K^+外流，细胞超极化，动作电位数减少。这将限制钙离子通过L型通道进入，并防止细胞内钙超载和mPTP开放[79]。最终使心脏代谢需求和电子传输链活性降低，从而防止ROS的产生和坏死性细胞死亡。因此，K_{ATP}通道被认为是监测细胞离子和生物能量平衡的传感器[80]。

sarcoK_{ATP}和mitoK_{ATP}是心肌细胞功能的重要调节器[81]。sarcoK_{ATP}和mitoK_{ATP}通道均由两个蛋白质复合物组成，1个负责向内整流的钾通道孔和1个负责控制通道开关的磺酰脲类受体亚单位。当细胞ATP处于高水平时，K_{ATP}通道关闭，K^+电流受抑

制。在急性缺血、腺苷和二磷酸腺苷（adenosine diphosphate，ADP）增加、蛋白激酶Cε（protein kinase C，PKCε）激活时，K_{ATP}通道激活[82]。研究发现，MI/R损伤前sarcoK_{ATP}或mitoK_{ATP}通道的开放可保护心脏[83]。sarcoK_{ATP}通道的开放可通过加速复极化3期K^+的外流，缩短心脏动作电位持续时间，抑制Ca^{2+}通过L型Ca^{2+}通道进入细胞，避免Ca^{2+}超载，防止MI/R损伤[83]。sarcoK_{ATP}通道开放后还会触发mitoK_{ATP}通道的开放[81]，保护线粒体免受MI/R诱导的Ca^{2+}超载和损伤[83]。

研究显示，短期运动[79]和长期运动[84]增加了心肌细胞膜K_{ATP}的表达，而药物阻断mitoK_{ATP}和sarcoK_{ATP}会损害心脏的保护机制[85]。8周耐力训练可上调心肌细胞sarcoK_{ATP}的表达，改善组织氧合恢复，保护心脏免受MI/R损伤[84]。将sarcoK_{ATP}通道阻断后，运动对MI/R的心肌保护作用也会降低[86-87]。有报道称，耐力运动对心脏的保护作用是由sarcoK_{ATP}通道介导的，而非mitoK_{ATP}通道。mitoK_{ATP}通道激活可以保护心脏免受MI/R诱导的室性心律失常[88]，但不能防止MI/R诱导的梗死[86]。也有研究报道，长期运动可以产生预处理效果，对MI/R产生心脏保护作用，并且这种保护作用是由mitoK_{ATP}介导的[85]。

K_{ATP}通道表达具有性别特异性[89]，这表明不同性别之间运动诱导的心脏保护程度不同。由于雌激素的作用，雌性动物体内的K_{ATP}通道水平较高，从而在运动后对MI/R损伤提供更强的心脏保护[90]。但最近也有研究表明，运动减轻了衰老进程中心脏表现的性别差异[91]。

综上所述，运动对肌膜（sarcoK_{ATP}）和/或线粒体（mitoK_{ATP}）通道的激活诱导细胞和/或心肌超极化，然后在缺血再灌注期间保护线粒体和心肌。

3.3 mPTP

运动本身并没有诱导对mPTP开放的适应。运动通过恢复促生存通路和增加再灌注时mPTP开放的阻力来诱导心肌保护。PKC激活被证明可以通过抑制mPTP的开放来保护心脏线粒体[92]，而mPTP是细胞死亡的关键触发因子[93]。在$\Delta\Psi_m$缺失的情况下，ATP合成酶会主动水解而不是合成ATP，从而导致细胞死亡[94-95]。然而，运动对mPTP激活的有益影响仍存在争议[96]。

有规律的运动增强了参与心脏保护的促生存激酶——蛋白激酶B（protein kinase B，PKB，也称Akt）的磷酸化，并诱导PKCε从细胞质转位到线粒体。此外，运动降低了相应磷酸酶的表达，从而增强了磷酸化张力，降低了羟甾醇7β-羟基胆固醇（7βOH）的浓度，有助于再灌注损伤补救激酶（reperfusion injury salvage kinase，RISK）通路的激活，有助于心脏保护信号的传递。这种激活需要结合应激条件，即缺血-再灌注，就可以抑制再灌注开始时mPTP的开放[97]。

可见，在缺血后再灌注期间，经过训练的心脏能更好限制mPTP的激活，通过RISK通路的激活保护心脏。

3.4 线粒体膜电位

运动可以防止心律失常以及其他缺血后损伤，如心肌顿抑和心肌梗死。再灌注期间的高氧化环境破坏线粒体能量学，并改变心脏动作电位持续时间，这是已知的致心律失常因素。线粒体通过氧化还原反应参与ATP的产生和自由基的解毒，这两者最终都依赖于$\Delta\Psi_m$。

运动通过线粒体依赖机制减少心律失常，包括更好地维持$\Delta\Psi_m$和较低的ROS产量。在代谢压力的条件下，由于sarcoK_{ATP}通道电流的一过性增强，$\Delta\Psi_m$会出现波动。心动周期复极化阶段，K^+电流的不稳定性会改变心脏电活动的时空组织，并增加对异常心律的敏感性。维持$\Delta\Psi_m$是缺血再灌注损伤、细胞死亡和心律失常的重要决定因素。运动可保留$\Delta\Psi_m$，降低纤颤/心动过速的发生率。将完整心脏中分离的肌细胞暴露于体外缺氧-复氧环境，发现运动组大鼠的氧化还原控制能力增强，复氧期间持续输出$\Delta\Psi_m$[73]。最近有研究发现，运动可以通过运动诱导肽提高线粒体膜电位，保护线粒体功能，减轻MI/R损伤[98-99]。这提示，运动诱导的心律失常抵抗是由于线粒体膜电位的保存。

以上提示，在缺血后再灌注期间，经过训练的心脏能更好地维持线粒体$\Delta\Psi_m$，保护线粒体功能，保护心肌免受损伤。

3.5 线粒体蛋白表达

运动训练改变线粒体表型之所以能实现，究其缘由是由于线粒体蛋白表达的变化。据研究报道，反复的耐力运动导致肌间纤维线粒体内11种蛋白质的显著改变（7种增加，4种减少），肌层下线粒体中的两种蛋白质发生显著变化（1种增加，1种减少）[68]。耐力运动训练通过增加有益蛋白质的表达和减少具有潜在有害功能的蛋白质表达而有益于线粒体，这些变化提高了线粒体产生ATP、消除ROS和维持健康线粒体氧化还原平衡的能力。

肌酸激酶（creatine kinase，CK）主要存在于细胞质和线粒体中，是一个与细胞内能量运转、肌肉收缩、ATP再生有直接关系的重要激酶。一项研究表明，人类短期耐力训练会增加心脏线粒体CK的活性[74]。在MI/R损伤期间，运动诱导的线粒体CK增加也可能有益于心脏[100]。

线粒体含有一种称为锰超氧化物歧化酶（Mn-containing superoxide dismutase，MnSOD）的抗氧化酶，可以降低细胞内的氧化应激。运动训练后大鼠心肌细胞中MnSOD水平升高，抑制了细胞凋亡[101]。Judge等[102]报道，与久坐不动相比，终生自愿转轮活动减少了大鼠心肌线粒体中H_2O_2的产生。与MI/R损伤相关的抗氧化酶中，MnSOD活性的增加是运动有益效果的主要触发因素之一[103-104]。线粒体谷胱甘肽库是ROS解毒系统的另一个关键因素。运动训练对总谷胱甘肽库和还原性谷胱甘肽/氧化谷胱甘肽比值没有影响[102，105]。然而，运动训练动物的心脏在MI/R后还原性谷胱甘肽补充得到改善[33，105]。在离体心肌细胞中，复氧化过程中还原性谷胱甘肽的恢复与线粒体维持$\Delta\Psi_m$的能力相关[73]。总之，氧化还原调控在心脏对运动的反应中是核心的[106]，运动可以通过增加线粒体抗氧化蛋白的表达诱导心脏保护的作用。

内皮型一氧化氮合酶（endothelial nitric oxide synthases，eNOS）激活在运动诱导的MI/R保护中起着关键作用。运动训练增加线粒体中eNOS/一氧化氮（NO）/s-亚硝基化信号，这可能是运动诱导的心脏保护的关键机制[107]。运动训练可以增加NO在心血管系统中的生物利用度[108]。这种作用主要依赖于eNOS的激活[109]。在心脏中，运动对eNOS水平没有影响，但会增加Ser117位点的磷酸化及其二聚化[110]。基因敲除或药物抑制eNOS可消除运动诱导的心脏保护作用[110-111]。此外，Calvert等[111]证明，β3肾上腺素能受体的基因消融会消除运动激活eNOS的能力，导致心脏保护完全丧失。这种eNOS依赖性的心脏保护是通过缺血前一氧化氮代谢物储存（即亚硝酸盐和s-硝基硫醇）的增加和早期再灌注时更高的蛋白质s-亚硝基化来介导的，而cGMP水平没有明显变化[110]。s-亚硝基化在缺血预处理的心脏保护中起重要作用[112-113]。超过1 000种蛋白质在心脏中被s-亚硝基化，线粒体蛋白是NO依赖性心脏保护的关键靶点[113-114]。线粒体蛋白的s-亚硝基化影响许多线粒体功能，如Ca^{2+}处理、mPTP打开和线粒体呼吸[115-116]。此外，有研究发现，游泳训练以eNOS依赖的方式诱导线粒体生物发生[117]。尽管eNOS在运动诱导的心脏保护中的作用似乎是显而易见的，但eNOS-NO与线粒体之间的潜在机制和相互作用还有待进一步研究。总之，运动可以增加线粒体附近NO的生物利用度，通过蛋白质s-亚硝基化间接实现运动诱导的心肌保护。

综上所述，运动训练增加了有益于线粒体功能的蛋白质表达，以保护心脏，减少MI/R损伤。

3.6　线粒体脂质积累

心脏在代谢调控范围内能够利用脂肪酸、葡萄糖、酮体、丙酮酸、乳酸和氨基酸（按递减顺序）等多种能量物质。有研究发现，低强度游泳运动训练对患有代谢综合征的老年雌性大鼠离体再灌注心脏的具有保护作用，可以使患病鼠的血脂恢复到正常水平[36]。MI/R诱导线粒体积聚胆固醇和氧甾醇，这对细胞器有害。而抑制胆固醇和氧甾醇积累可防止线粒体在再灌注时损伤。在MI/R期间，有规律的跑步机运动可以抑制线粒体胆固醇的积累[118]。

在野生型小鼠和肥胖小鼠中，有规律的运动可以改善氧化磷酸化，通过增加抗氧化酶的表达来恢复心脏的抗氧化能力，并减少线粒体生成的甾醇。有规律的运动可以防止小鼠缺血心肌早期再灌注时线粒体胆固醇和氧甾醇的积累，起到保护心脏的作用[118]。

可见，在MI/R期间，运动可以抑制线粒体脂质积累实现对心脏的保护作用。

3.7　线粒体质量控制

线粒体质量控制系统包括线粒体动力学即线粒体融合和分裂、线粒体生物合线粒体自噬等。线粒体质量控制系统与MI/R损伤密切相关。

心脏在急性缺血和再灌流时会发生线粒体动力学的变化[119]。Brady等[120]首次证明，模拟缺血2 h可导致超过90%的HL-1细胞线粒体碎裂。在MI/R损伤过程中，线粒体过度分裂导致细胞凋亡激活[121]。MI/R过程中ROS产生和Ca^{2+}超载之间复杂的相互作用直接涉及线粒体过度裂变[122-123]。线粒体靶向抗氧化剂预处理可以限制缺血再灌注诱导的线粒体断裂[124]。此外，用毒胡萝卜素（Thapsigargin）孵育诱导肌浆网释放Ca^{2+}可导致新生大鼠心室心肌细胞线粒体分裂[122]。体育锻炼是调节钙稳态和改善抗氧化状态的有效策略[34，125]。两者都可能导致缺血再灌注期间线粒体裂变钝化。

有研究表明，调节线粒体动力学可能通过预防线粒体功能障碍和mPTP开放抑制来影响对缺血再灌注损伤的易感性[121]。研究发现，MI/R后运动训练大鼠心脏线粒体融合蛋白1（mitochondrial fusion protein 1，Mfn1）和Mfn2水平升高，动力相关蛋白1（dynamin-related protein 1，Drp1）水平降低[126]。同样，Jiang等[127]表明，心肌梗死后进行8周有氧间歇训练会上调Mfn2和OPA1水平，降低Drpl表达，改善线粒体功能，限制线粒体网络的病理性重构。因此，运动诱导线粒体融合和抑制分裂，改善线粒体动力学，参与心脏对MI/R损伤的保护作用[126]。

自噬是一种生理过程，细胞中受损的蛋白质或细胞器会被隔离在自噬体内，然后与溶酶体融合进行降解。线粒体自噬通过靶向清除功能失调的线粒体来维持细胞的动态平衡。线粒体自噬的前提条件是线粒体发生裂变[128]。自噬在MI/R中是把双刃剑：在缺血时，肿胀的线粒体失去线粒体膜电位，启动PTEN诱导激酶1（PTEN induced putative kinase 1，PINK1）-E3泛素连接酶Parkin通路进行自噬[20]，保护心肌。然而，再灌注时，自噬失调和持续的自噬会抑制细胞增殖，促进心肌细胞死亡和凋亡，损害心肌[129-131]。同时，功能失调的自噬也会加重线粒体氧化应激和损伤[132]。研究发现，上调线粒体自噬可以实现对心肌的保护作用[133]。

线粒体生物发生是改善神经元能量代谢，维护mtDNA，平衡机体内环境的重要途径。MI/R发生时，线粒体生物发生减弱[134]，mtDNA受损。小鼠MI/R梗死区中瞬时启动子驱动的线粒体生物发生相关基因PGC-1α下调[135]。研究发现，跑步可以改善MI/R损伤模型组小鼠mtDNA的复制和转录，上调SIRT3、PCG-1α等线粒体生物发生相关基因的表达，发挥其神经保护作用[32]。在健康运动员的血浆中也发现，运动会增加mtDNA复制和转录以及线粒体呼吸链的活动[136]。由此可见，运动调节心肌线粒体完整性和生物发生，对于再灌注后心肌细胞的损伤具有一定的缓解作用。

细胞凋亡，特别是线粒体途径细胞凋亡是与MI/R密切相关的生物学环节。MI/R后的线粒体功能障碍，线粒体凋亡发生因子细胞色素C释放到细胞质中以激活半胱氨酸天冬氨酸蛋白酶3（Caspase3）介导的细胞凋亡，诱导细胞死亡[21]。游泳运动可降低肿瘤坏死因子-α水平，抑制Caspase3激活，增强Bcl-2蛋白的表达，从而减少了心肌中凋亡细胞的数量，并提出游泳运动可以作为预防心肌损伤的有效方式[137]。最近研究发现，棕色脂肪组织分泌的细胞外小泡可以将具有心脏保护作用的微小RNA（microRNA）输送到心脏中，通过靶向信号级联中的一系列分子，协同抑制促凋亡MAPK（有丝分裂原相关蛋白激酶）途径，参与运动心脏保护[138]。miR-486可以减轻MI/R损伤，通过p53诱导的BCL-2相关线粒体凋亡途径调节心肌细胞凋亡，介导运动对心肌保护的有益作用[139]。最新研究发现，运动训练通过表观遗传学修饰调节，降低N6-甲基腺苷（m6A）转移酶的表达，降低细胞凋亡，阻止MI/R损伤[140-142]。然而，一项随机对照试验显示，与单纯进行冠状动脉搭桥术的患者相比，术前24 h进行一次适度运动反而使心肌细胞线粒体呼吸水平降低，且凋亡相关标志物Caspase3转录水平增加1.5倍[143]，这表明运动预处理并未在人体MI/R中发挥积极的保护作用。

综上所述，运动训练也可以通过防止线粒体分裂、促进线粒体融合和增加线粒体生物发生来影响MI/R过程中的线粒体动力学。运动训练还促进受损线粒体的自噬，减少线粒体途径的细胞凋亡，进而有助于维持线粒体库的功能性。

3.8 远程调控因子

运动是预防和治疗心血管疾病的有效而经济的方法。在实验性MI/R损伤模型中，慢性运动训练被证明能有效减少梗死面积。运动能够通过特定的分子和细胞过程发挥治疗作用，包括一系列肌肉因子、参与肌肉代谢的分子、肠道微生物组成成分等。有趣的是，一些运动调节分子也有发挥心肌保护作用的潜力。在运动中，肌肉产生几种细胞因子，这些细胞因子被认为是有效的远程心脏保护分子[144]。

McGinnis等[145]表明，运动通过源自骨骼肌的白介素-6（interleukin 6，IL-6）发挥心脏保护作用。IL-6增加线粒体膜内极化，防止再灌注引起的线粒体功能变化[146]。

鸢尾素（Irisin）作为一种肌细胞因子，在心脏缺血中的生物学作用和机制已部分确定[147]，其细胞保护作用涉及抗凋亡、促自噬和抗炎作用[148]。Irisin介导的产热和能量消耗与线粒体的生物功能密切相关[149-151]。缺血后处理可能通过影响MI/R过程中Irisin的水平来发挥线粒体保护作用[152]。Irisin通过AMPK信号通路减轻线粒体功能障碍[153]。心脏SOD1水平升高可以解释Irisin对心

脏线粒体的保护作用[154]。研究发现，有氧运动通过激活AMPK-PGC1-α-Irisin信号级联，缓解心肌梗死小鼠肾脏氧化应激引发的线粒体功能障碍和细胞凋亡[155]。这提示，Irisin可以通过改善线粒体健康、减少氧化应激和抑制炎症，潜在地介导运动对MI/R损伤的保护作用[156]。

肌连蛋白（myonectine）是一种运动诱导的肌肉因子，它通过减少MI/R期间心脏的细胞凋亡和炎症，从而表现出运动诱导的心脏保护[157]。Myonectine可以促进线粒体内外源游离脂肪酸的吸收、转运和氧化代谢，从而抑制肌肉内脂肪细胞中的脂质沉积[158]。

MG53又称TRIM72，在横纹肌中高表达，运动后作为肌因子分泌，与膜脂磷脂酰丝氨酸相互作用，对许多组织受损的质膜修复至关重要。MG53在缺血再灌注诱导的氧化应激中保护心肌细胞的线粒体完整性[159]。

除了肌肉因子外，在循环可转移因子中，红细胞是NO的重要来源，NO是一种众所周知的保护剂。运动期间增加的剪切应力刺激红细胞NO代谢活性，这可能有助于保护心脏免受MI/R的伤害[160]。此外，其他血液循环因子，也被描述为运动因子，如细胞外囊泡[161]、血浆microRNA、包括miR-1192[162]和miR-342-5p[163]，或脑源性神经营养因子[164]，可能是解释运动对心脏远程调节的良好候选者。然而，没有数据表明它们可能与线粒体相互作用，特别是在MI/R期间。

4 结　语

运动训练是减少心血管危险因素的有效策略。线粒体是MI/R过程中细胞死亡的最终效应器，也是心脏保护细胞器。本综述总结了线粒体与MI/R损伤的关系及运动对于MI/R保护与线粒体之间的潜在联系。围绕线粒体，探究运动对MI/R的调控机制及其在心脏保护中的作用，可以为心脏疾病诊断和治疗提供更多理论依据和新的治疗靶点，为药物研发提供新的作用靶标。未来临床治疗中，期待通过纳米颗粒包装等新技术手段，以线粒体靶向的运动药片，实现卧床无法运动人群或不想运动人群的MI/R损伤干预。

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Role of Mitochondria in Exercise Protecting Myocardium From Ischemia-reperfusion Injury*

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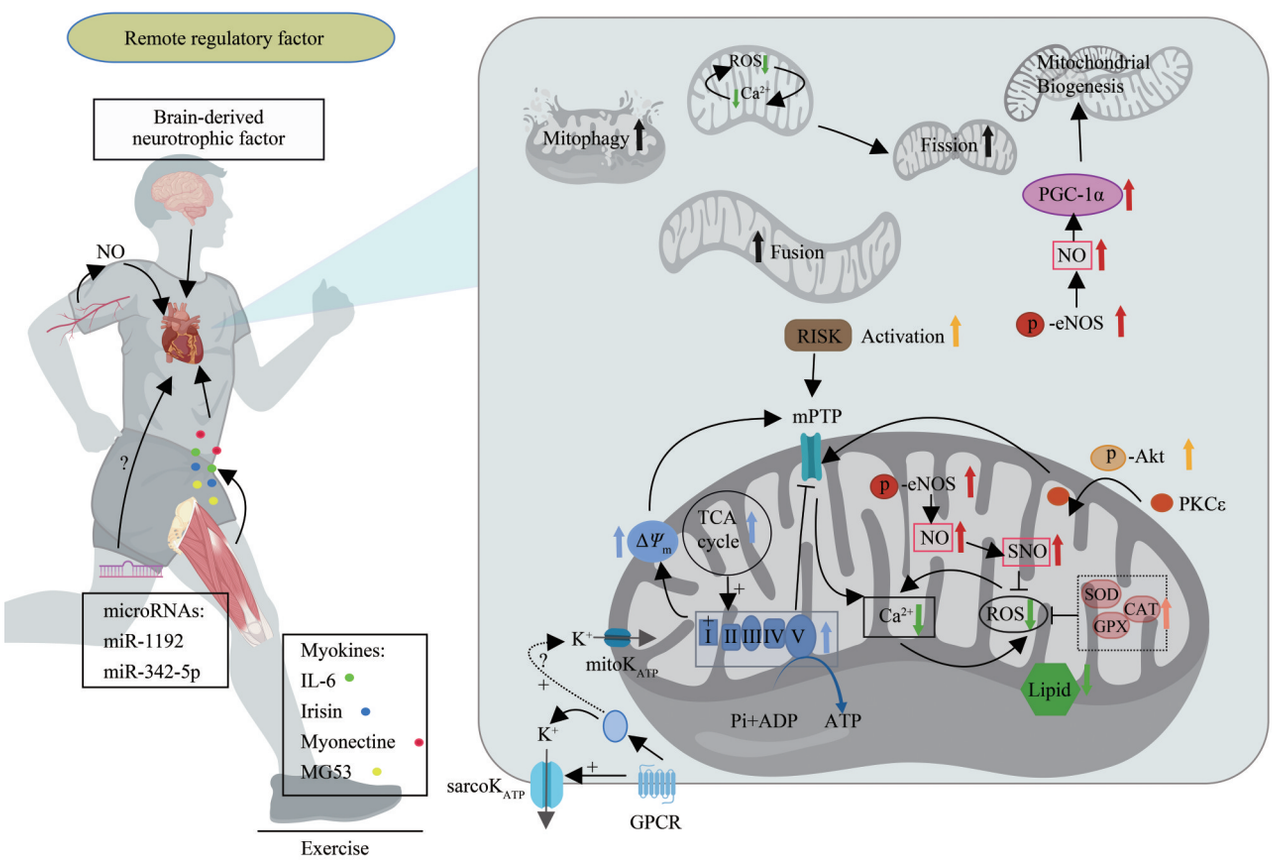
Graphical abstract



Abstract　Acute myocardial infarction (AMI) has become the leading cause of death in cardiovascular diseases. Myocardial ischemia and reperfusion (MI/R) occurs when myocardial blood circulation is reconstructed after blood supply is limited or lack, often after myocardial infarction, and is the main cause of acute myocardial injury. According to the length of ischemia time, arrhythmia, myocardial inhibition, and myocardial infarction may occur in sequence in MI/R. Mitochondria are the key organelles involved in MI/R injury. Mitochondrial ROS eruption,

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Ca^{2+} imbalance, mPTP opening, mitochondrial swelling, and release of pro-apoptotic proteins all lead to mitochondrial dysfunction and myocardial function impairment. Exercise is an effective intervention to prevent myocardial ischemia-reperfusion injury, and its protective effect is closely related to the intensity of exercise, the length of exercise time, the type of exercise and the internal exercise ability. The mitochondrial mechanism of exercise protection against myocardial ischemia-reperfusion injury is determined by many factors. During reperfusion, the heart after trained is better able to maintain energy homeostasis, maintain $\Delta\Psi_m$ and limit mPTP activation, maintain ATP synthesis. Activation of the sarcoK_{ATP} and/or mitoK_{ATP} channels by exercise induces cellular and/or myocardial hyperpolarization, protecting the mitochondria and myocardium during MI/R. Exercise-trained hearts can regulate calcium homeostasis during MI/R and limit mitochondrial Ca^{2+} overload. Exercise training can improve the activity of mitochondrial antioxidant enzymes to clear ROS and regulate mitochondrial Ca^{2+} concentration during MI/R. Exercise can increase the bioavailability of NO near mitochondria and indirectly achieve exercise-induced myocardial protection through protein S-nitrosylation and the eNOS-NO pathway is related to mitochondrial biogenesis after exercise training. Exercise training can also affect mitochondrial dynamics during MI/R by preventing mitochondrial division and promoting mitochondrial fusion. Exercise training can promote autophagy of damaged mitochondria and reduces apoptosis through mitochondria too, thus helping to maintain the function of mitochondrial bank. Besides these, exercise training leads to the production of motor factors (mainly from the muscles, but also from the brain, red blood cells, and other tissues) that contribute to remote regulation of the heart. This paper reviews the mitochondrial mechanism of MI/R, the protective effect of exercise on MI/R and the role of mitochondria in it, in order to provide more theoretical basis and new therapeutic targets for the diagnosis and treatment of heart disease, and provide new targets for drug research and development. In future clinical treatment, it is expected that sports pills targeted mitochondria can treat MI/R injury for bedridden people who cannot exercise or people who do not want to exercise through new technological means such as nanoparticle packaging.

Key words exercise, mitochondria, myocardial ischemia and reperfusion
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