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收稿日期:2015-10-29

线粒体能量代谢异常与病理性心肌肥大的研究进展

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【摘要】 病理性心肌肥大是临床常见的适应性改变过程,伴随着能量代谢类型的转变及线粒体生物学功能的衰退,是心血管疾病发生率和病死率增高的独立危险因素。肥大心肌细胞能量代谢异常与多条信号通路异常关系密切,改善能量代谢异常有望成为逆转心肌肥大和延缓心力衰竭进程治疗的新靶点。

【关键词】 线粒体;能量代谢;心肌肥大
【中图分类号】 R542.2 **【文献标志码】** A **【DOI】** 10.16806/j.cnki.issn.1004-3934.2016.03.008

Mitochondrial Energy Metabolism and Pathological Cardiac Hypertrophy

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【Abstract】 Pathological cardiac hypertrophy is a coadaptive process accompanied by metabolic profile change and mitochondrial bioenergetic decline, and is an independent predictor of higher rate of cardiovascular events and mortality. Many signaling pathways are involved in the maladaptive metabolism of hypertrophied hearts, and targeting abnormal metabolism is likely the new therapy of hypertrophic prevention and reversion.

【Key words】 Mitochondria; Energy metabolism; Cardiac hypertrophy

心肌是体内耗能最多的组织,腺苷三磷酸(adenosine-triphosphate,ATP)是其直接利用的能量形式。正常心肌产生的 ATP 95% 以上来自线粒体的氧化磷酸化,少量来源于糖酵解。哺乳动物胚胎期心脏主要以葡萄糖和乳酸作为能源,出生后则以脂肪酸氧化为主;但在病理性心肌肥大时脂肪酸氧化降低,糖酵解增加,心肌能量代谢发生"胚胎型转换"[1]。

生理性心肌肥大多发于运动员和孕妇,是可以逆转的,对心脏功能无损伤。病理性心肌肥大大多数是心肌细胞对心脏压力负荷增加的适应性反应,常见于

基金项目:国家自然科学基金青年科学基金项目(81300169)
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主动脉瓣狭窄或肥厚型心肌病。虽然代偿期心肌肥大可增加心脏的收缩能力及泵血功能,但最终会发展为心室扩张、心力衰竭。研究表明,心肌肥大是临床上多种心血管疾病发生率和病死率增高的一个独立危险因素[2-4]。心肌肥大涉及包括基因表达、凋亡,细胞及生长因子释放和能量代谢信号通路调控在内的一系列生理病理变化。现就肥大心肌能量代谢的变化及特点、肥大心肌细胞能量代谢异常的病理学机制和改善肥大心肌细胞能量代谢异常的临床指导价值三个方面进行综述。

1　肥大心肌细胞能量代谢的变化及特点

心肌肥大过程伴随着代谢底物利用的改变、产能结构变化及耗能结构的转变,存在慢性能量缺乏。肥大心肌 ATP 的产生主要依赖于葡萄糖,而不是脂肪酸,心肌能量代谢的胚胎型转换与心肌肥大及心室重塑过程中胚胎型基因重新表达增加有关[5-6]。有学者采用碳同位素标记技术发现肥厚心脏的葡萄糖代谢主要表现为糖酵解速率增加,而丙酮酸的三羧酸循环产生 ATP 的效率减低[7-8]。心肌肥大的动物模型亦提示肥大心肌具有更高的葡萄糖摄取率,但是糖酵解代谢相关酶的表达水平及活性并没有增加[9-10]。这一现象可能与苹果酸-天冬氨酸穿梭活性增加和酮戊二酸表达增加有关[11]。

心肌肥大向心力衰竭的演变亦伴随着线粒体生物学功能的衰退及氧化磷酸化能力的降低。Dai 等[12]的研究揭示血管紧张素Ⅱ和线粒体 DNA 缺失所致心肌肥大的线粒体生物学功能上调,但在发展至心力衰竭的进程中,线粒体生物学功能明显降低。在胸主动脉缩窄的兔子心肌肥大模型中,尽管呼吸链复合体Ⅰ和复合体Ⅱ的表达量不变,而活性却明显降低[13]。在代偿性心室肥厚向左室心力衰竭的进展过程中,呼吸链复合体Ⅰ的氧化活性呈现先增加后降低的双相改变[14]。亦有研究证实在鼠类动物的主动脉缩窄左室肥厚模型中,呼吸链复合体Ⅰ、Ⅲ、Ⅳ和Ⅴ的数量增加,但缺乏复合体活性的检测[15-16]。线粒体氧化磷酸化能力的降低加速左室收缩功能障碍的发展进程,为满足心肌的能量消耗,衰竭心肌更大程度地依赖糖酵解。

2　肥大心肌细胞能量代谢异常的病理学机制

目前关于肥大心肌细胞能量代谢异常的病理学机制尚未完全阐明,其中比较公认的为 AMPK/ERK1/2/PPARα/SCAD 信号途径。心肌过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)是一类由配体激活的核转录因子,属于细胞核激素受体超家属成员,有 α、β 和 γ 三种亚型,其中 PPARα 和 PPARγ 是脂肪酸氧化酶和线粒体功能基因的主要转录调控子。研究表明,苯肾上腺素诱导的乳鼠心肌细胞肥大模型和主动脉缩窄术建立的左室肥厚模型小鼠心肌肥大过程中伴随着 PPARα 的下调[17-18]。相反,PPARα 激动剂可预防肥大心肌缺血后的收缩功能障碍[19]。进一步的机制研究表明,磷酸化腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)的激活通过抑制细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK1/2),进而增加 PPARα 的活性达到逆转心肌肥大表型的目的[20]。国内学者提出,ERK1/2 /PPARα 进一步通过下调短链脂酰辅酶 A 脱氢酶(short-chain acyl-CoA dehydrogenase, SCAD) mRNA 及蛋白表达水平,导致心肌细胞脂肪酸 β 氧化能力减弱,参与病理性心肌肥大的调控[21]。

AMPK/mTORC1/PPARγC1a 信号途径被证实参与卵泡素基因缺失所致的小鼠心肌肥大模型心脏能量代谢过程。卵泡素基因缺失小鼠 AMPK 活性降低,下游信号 mTORC1 活性增加,最终导致 PPARγ 辅激活因子 1a 表达增加,肥大心肌线粒体数量及 ATP 产生增加;抑制 PPARγC1a 活性后肥厚表型减轻,发展至心力衰竭过程中线粒体能量代谢失衡[22]。线粒体 Sirt3 蛋白去乙酰化与中药厚朴预防及逆转苯肾上腺素、血管紧张素Ⅱ药物诱导及主动脉缩窄的压力负荷增加所致小鼠心肌肥大关系密切[23]。其他信号途径包括参与线粒体功能调控的 A-激酶相互作用蛋白 1(A-kinase-interacting protein 1, AKIP1)及核酸内切酶 G1(endonuclease G-like-1, EXOG)蛋白异常[24-25]。

其他途径如胰岛素抵抗、氧化应激以及细胞凋亡亦有报道与病理性心肌肥大线粒体能量代谢异常有关。研究表明,胰岛素敏感性葡萄糖转运体-4 基因敲除小鼠接受压力负荷时肥厚表型更加明显,心肌收缩障碍出现更早,预后更差[26]。心肌肥大向心力衰竭的发展进程中不仅伴随线粒体 ATP 产生减少,还导致活性氧的大量产生,加重线粒体功能障碍并形成恶性循环。不仅如此,衰竭心肌抗氧化剂清除防御作用减弱,过量的活性氧族将触发线粒体诱发的心肌细胞凋亡及心肌代谢重构[27-28]。

3　改善肥大心肌细胞能量代谢异常的临床指导价值

通过临床观察和建立心肌肥大模型的研究,已经证明改善能量代谢异常可以预防或逆转病理性的心肌肥大。这一发现为人类预防、治疗病理性心肌肥大提供了新的思路和靶点。沉默线粒体激酶相关蛋白 AKIP1 基因可以减轻苯肾上腺素诱导的乳鼠原代心肌细胞肥大模型的线粒体耗氧率,过表达 AKIP1 基因可

增强线粒体呼吸功能,这一现象与呼吸链密度及耦联程度增加有关[28]。活性氧清除剂可减少 EXOG 基因(与线粒体 DNA 修复及心脏收缩功能关系密切)缺失心肌细胞过度产生的活性氧,改善线粒体呼吸功能,减轻肥厚表型[29]。胰高血糖素样肽可降低循环脂肪酸水平,增强心肌细胞对葡萄糖的摄取及利用,有利于心力衰竭的治疗[29]。曲美他嗪通过抑制脂肪酸氧化,增强葡萄糖的利用与氧化磷酸化,改善缺血心肌功能[30]。

国内实验研究表明,中药成分具有潜在的纠正能量代谢异常的功能,在调节脂质和糖代谢供能、改善心肌产能及耗能结构方面显示了较好的效果。黄芪甲苷可加强心肌细胞对脂肪酸的氧化利用,改善能量供应不足的同时也抑制了糖酵解,进而抑制大鼠心肌肥大及改善心肌能量代谢[31]。亦有学者报道川芎嗪及心复康口服液分别在逆转血管紧张素Ⅱ诱导的原代培养乳鼠心肌细胞肥大过程中和腹主动脉缩窄的压力超负荷大鼠模型中具有保护心肌细胞线粒体结构和功能的作用[32-33]。

综上所述,病理性肥大心肌脂肪酸氧化减少,能量消耗主要来源于葡萄糖。心肌肥大向心力衰竭的演变伴随着线粒体生物学功能的衰退及氧化磷酸化能力的降低。AMPK/ERK1/2/PPARα/SCAD 信号途径及 AMPK/mTORC1/PPARγC1a 信号途径等多条信号通路参与肥大心肌细胞能量代谢变化。优化心肌能量代谢有望成为预防和逆转心肌肥大新的治疗靶点;但动物模型研究结果向临床治疗决策的转化尚需大量实验研究的证实。

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收稿日期:2015-12-21 修回日期:2016-01-11

预防非瓣膜性心房颤动性脑卒中的治疗新进展

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【摘要】 心房颤动是临床最常见的心律失常,所致的脑卒中具有高致死率和致残率的特点。近年来非瓣膜性心房颤动患者脑卒中的预防已得到高度关注,但收效不明显。最经典的预防心房颤动性脑卒中的方法为口服华法林抗凝治疗,但因其治疗窗窄,需频繁监测国际标准化比值等,使用受限。新型口服抗凝药弥补了华法林的部分不足,但并非所有患者都能耐受或有效。对于不能口服或口服药物无效的患者,需要新方法来预防脑卒中,经皮左心耳封堵术为其带来了新希望。现就预防非瓣膜性心房颤动性脑卒中的各种方法进行综述。

【关键词】 心房颤动;脑卒中;华法林;新型口服抗凝药;经皮左心耳封堵术;左心耳封堵系统

【中图分类号】 R541.7;R743.3 **【文献标志码】** A **【DOI】** 10.16806/j.cnki.issn.1004-3934.2016.03.009

New Progress in the Treatment for Cerebral Apoplexy of Nonvalvular Atrial Fibrillation

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【Abstract】 Atrial fibrillation is the most common arrhythmia in clinic, and easily leads to stroke, which has high mortality and morbidity. In recent years, we have attached great importance to the prevention of stroke in patients with atrial fibrillation, but the effect was not obvious. The gold standard in prevention is oral warfarin anticoagulant therapy, and its use is limited for warfarin's narrow therapeutic window, and frequent monitoring of INR values. New oral anticoagulants (NOAC) make up for the inadequacy of warfarin, but not all patients are effective. For these patients, the percutaneous left atrial appendage occlusion has brought us new hope. This paper reviews the therapeutic advances of preventing the stroke in patients with atrial fibrillation .

【Key words】 Atrial fibrillation; Stroke; Warfarin; New oral anticoagulants; Percutaneous left atrial appendage occlusion; WATCHMAN

基金项目: 国家重点基础研究发展计划(2014CB542400);国家自然科学基金面上项目(81170112, 81270210);重庆市科委课题(CSTC2012JJA10143);国家临床重点专科建设项目经费资助[财社(2011)170 号]

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