·综 述·

Omega-3多不饱和脂肪酸抗心律失常作用及其机制研究进展

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【摘 要】越来越多的研究表明，n-3多不饱和脂肪酸（n-3PUFAs）能降低心率，提高心率变异性，减少室性心律失常的发生，预防心源性猝死及减少心房颤动复发等抗心律失常作用，也有研究发现n-3PUFAs具有致心律失常的作用。本文通过分析n-3PUFAs离子通道作用特点及其抗心律失常作用机制，发现n-3PUFAs干预方式不同，作用机制不完全一样，表明n-3PUFAs在抗心律失常方面具有两面性。

【关键词】n-3多不饱和脂肪酸；抗心律失常药物；心律失常

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Anti-arrhythmic effect of omega-3 polyunsaturated fatty acids and its underlying mechanism: a review of research progress

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【**Abstract**】 Much evidence shows that omega-3 polyunsaturated fatty acids (n-3PUFAs) protect the heart by reducing heart rate, increasing heart rate variability, decreasing atrial fibrillation, and preventing ventricular fibrillation arrhythmias and sudden cardiac death. However, some researches suggest that n-3PUFAs exert pro-arrhythmic action. The purpose of this review was to summarize the effects of n-3PUFAs on ion channels and anti-arrhythmic mechanism. Acute administration and long-term use of n-3PUFAs have quite different electrophysiological actions, indicating their anti- and pro-arrhythmic actions in different clinical settings.

【**Key words**】 omega-3 polyunsaturated fatty acids; anti-arrhythmic agent; arrhythmia

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n-3多不饱和脂肪酸（omega-3 polyunsaturated fatty acids，n-3PUFAs）包括二十碳五烯酸（eicosapentaenoic acid，EPA）、二十二碳六烯酸（docosahexaenoic acid，DHA）和α-亚麻酸(alpha-linolenic acid，ALA)，被认为是人体的必需脂肪酸[1]，具有广泛的抗心律失常作用。从目前有限的研究结果表明，n-3PUFAs各个成分抗心律失常作用的大小关系为DHA ≥ EPA > ALA[2]，但越来越多的研究表明，n-3PUFAs有抗心律失常及致心律失常的双重作用[2]。本文通过分析n-3PUFAs抗心律失常作用及其机制的多样性，阐明n-3PUFAs在抗心律失常方面具有两面性。

1 n-3PUFAs具有抗心律失常作用

n-3PUFAs在保护心血管作用过程中发挥多种作用，降低心率[3,4]及心率变异性[5]，减少恶性心律失常及心房颤动（简称：房颤）[6]发生，预防心源性猝死[7]（sudden cardiac death，SCD）。

1.1 减少室性心律失常发生，预防SCD

流行病学调查表明，红细胞膜上n-3PUFAs水平比例超过总脂肪酸的5%则心源性猝死风险减少75%。n-3PUFAs能使心肌梗死后人群的猝死率降低达45%[12]，能降低无心血管疾病的男性冠心病和SCD发生的风险[13]，减少急性心肌梗死患者室性心律失常的发生，特别是ALA上述作用更明显，而DHA + EPA的效果则不明显（$P = 0.06$）[14]。动物实验表明，n-3PUFAs能减少各种病因（急性心肌梗死[15]、心肌梗死后[16]、缺血-再灌注等）诱发的室性心律失

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常，也能提高室颤阈值或直接减少室颤发生。

1.2 预防房颤

n-3PUFAs可减少房颤发生率，降低全因死亡率及减少心肌梗死后房颤的发生率，可预防消融术后房颤的复发，也能降低持续性房颤的复发[18]和血液透析患者的房颤发生率[19]，减轻心力衰竭房颤导致的心房纤维化及心房传导异常，缩短房颤的持续时间[20]，DHA还能降低房颤敏感性而EPA不能[21]。动物房颤模型研究发现[22,20]，n-3PUFAs对持续性房颤有治疗作用，也能减轻炎症反应，但需在电生理或组织重构发生之前给予干预才有益于治疗或预防房颤复发[23]。

2 n-3PUFAs的抗心律失常作用尚存在不确定性

n-3PUFAs虽然在抗心律失常方面有惊人表现，但也存在不一致的结果。在预防室性心律失常及SCD方面，Hu等[24,25]对84 688名冠心病女性志愿者进行长达16年的随访调查发现，长期服用n-3PUFAs与预防SCD无相关性，也不能降低糖尿病女性SCD的发生率，也不能减少糖代谢异常人群的总体病死率及心血管病死率[26]，还可能增加心肌梗死后心肌细胞的舒张性钙波而诱发室性心律失常[27]。研究植入除颤器及心力衰竭患者发现，n-3PUFAs与其室性心律失常的发生率无相关性[28]，甚至可能增加其室性心律失常的发生[29,30]。因此，n-3PUFAs减少室性心律失常及预防SCD的有效性及安全性尚需进一步明确[2]。在预防房颤方面也有很多不一样的结果。Gronroos等[31]对14 222人（其中房颤1604人）进行长达17.6年的随访发现，不论直接食用海鱼或DHA + EPA，还是静脉给予DHA + EPA，均与房颤发生率无相关性，高水平的血清EPA[32]或组织EPA[33]可能增加房颤发生风险。单中心或多中心双盲对照试验研究结果表明，n-3PUFAs不能减少冠状动脉旁路移植术后房颤的发生[34−38]，两者呈U型关系，当DHA水平太高或太低均能促进术后房颤的发生[39]。

n-3PUFAs抗心律失常作用的不确定性还表现在，不同病因或动物的效果却不尽相同，甚至相反。研究缺血-再灌注大鼠模型发现，喂食n-3PUFAs 3个月后，心室颤动（简称室颤）的发生明显减少。但研究犬心肌梗死模型却发现，急性静脉给予EPA或DHA能减少致死性心律失常[40]，而长期给予n-3PUFAs在体研究未发现可以减少室颤发生，对照组和实验组室颤发生比例分别为9/17和22/45；细胞水平则发现，心肌细胞钙火花、舒张性钙波增多而可能促进室性心律失常发生[27]。在治疗不同病因所致的房颤方面，n-3PUFAs的表现也不尽如人意[31−39]，n-3PUFAs对阵发性房颤、电除颤复律的房颤复发无治疗作用[41,42]，而且也不能改善阵发性房颤的炎症反应。另外，n-3PUFAs抗心律失常作用的不确定性还表现在不同干预方式效果也不一样，不仅整体动物水平不一样，还表现在细胞水平各种电流及钙稳态方面。

3 n-3PUFAs抗心律失常作用机制的多样性

n-3PUFAs几乎对所有心脏离子通道或离子泵都有不同程度的影响，其中，对Na^+、Ca^{2+}电流影响最敏感[43]。目前研究发现，急性和慢性给予n-3PUFAs进行生理性干预所引起的电生理作用机制会有所不同，甚至截然相反[2]。

3.1 动作电位时程、膜兴奋性及传导的影响[44]

研究新生大鼠心室肌细胞发现，给予EPA（10μmmol/L）急性干预能缩短动作电位时程（action potential duration，APD），而成年大鼠心室肌细胞，给予低浓度n-3PUFAs（< 10μmol/L）时，APD随浓度增加而逐渐延长，高浓度n-3PUFAs（10～20μmol/L）急性处理APD则出现缩短，而在相同条件下研究豚鼠，2～20μmol/L n-3PUFAs使APD随浓度增加逐渐缩短。不同动物或不同发育阶段，相同干预方式结果不尽相同。长期给予n-3PUFAs进行干预，猪心肌细胞APD也缩短。兔长期喂食ALA后QT间期缩短，而直接用含ALA + EPA（1～20μmol/L）的灌流液对离体心脏进行灌注，QT间期则延长。用EPA + DHA（5～10μmol/L）急性处理单个心肌细胞可延长相对不应期，而表现出心肌细胞膜兴奋性降低。给予EPA + DHA（1～20μmol/L）急性处理兔离体心脏也发现，诱发室性期前收缩的阈值增加，且随着浓度增加而增加，纵向和横向传导速率均发生降低。而给予长期喂食n-3PUFAs后发现，猪心室肌细胞兴奋性及传导速度均无改变。因此，n-3PUFAs延长或缩短APD，取决于不同种属的动物、动物发育阶段及干预方式（含给药时间长短及浓度）。n-3PUFAs急性干预能降低膜兴奋性及传导速率，而长期慢性摄入对上述两者则无影响。

3.2 离子电流的影响

通过全细胞膜片钳技术发现，n-3PUFAs使钠通道的失活阈值左移，降低细胞的兴奋性，减弱晚钠电流[45]，通过抑制$I_{Ca\text{-}L}$通道及钠钙交换体减少钙离子内流，也相应地减少瞬时钙电流所引起的去极化振幅，

抑制I_{to}，I_{kr}及I_{kur}钾电流。急性干预的n-3PUFAs直接作用离子通道，而慢性摄入的n-3PUFAs往往嵌入到细胞膜,通过改变细胞膜的特性(如细胞膜的流动性) 间接影响离子电流发挥作用[46]。乙酯化的DHA抵抗DHA对血管平滑肌BK通道的刺激效应[47]。正是由于急性干预的n-3PUFAs与慢性摄入的具有完全不同的离子通道作用机制，因此对电流的影响也不一样[2]。例如，I_{Na}在n-3PUFAs急性干预时减小，而慢性摄入时，无论是大鼠还是猪的心肌细胞I_{Na}均未见明显改变。急性干预降低I_{to}和I_{kr}，明显增加I_{ks}（DHA，约增加32%），而长期干预时，I_{to}和I_{kr}未见变化，而I_{k1}激活，I_{ks}进一步增大（约增加70%）。长期摄入EPA也能通过稳定Kv1.5蛋白运输而增加I_{kur}。这个电流的激活可以缩短APD而促进房颤的发生。这也许能解释为何有研究表明EPA增加房颤发生的风险[48]。

3.3 钙转运的影响

n-3PUFAs介导心肌细胞的钙转运机制，影响肌浆网及其受体功能调节细胞内钙离子水平[49]，n-3PUFAs干预方式不一样产生的作用也不尽相同。急性干预可降低$I_{Ca\text{-}L}$，而慢性干预则没有影响[16]，或通过抑制动作电位平台期，该通道重新激活，也降低该电流。后者这样的变化可减弱早后除极而预防尖端扭转型室性心动过速[50]。慢性给予而嵌入细胞膜的n-3PUFAs也能阻止急性干预进一步缩短APD的作用[51]。当急性分离的大鼠心肌细胞在n-3PUFAs直接干预下，肌浆网钙摄取和钙释放均降低，继而引起自发性钙波发生频率减少。还有研究发现，单独给予EPA干预时，钙火花减少更明显。这有利于减少心律失常的发生。n-3PUFAs长期干预则结果完全不一样。研究犬心肌梗死后模型发现，长期补充n-3PUFAs不能改善心肌梗死后心肌细胞的Ca^{2+}循环重构，增加钙火花和舒张性钙波发生，诱发心律失常。这表明，长期摄入n-3PUFAs对于预防心肌梗死后恶性心律失常发生无益，可能反而增加风险[27]。

4 总结与展望

缩短APD或降低心脏兴奋性的药物能改善触发活动增加导致的心律失常，但可能促进折返的发生；延长APD的药物能改善折返所致的心律失常，但可能会增加早后除极的发生，甚至引发尖端扭转型室性心动过速。长期摄入n-3PUFAs能缩短APD，急性干预则降低心室传导性，因此，折返所致的心律失常在n-3PUFAs存在时（不论急性或长期干预所致）则更容易发生。n-3PUFAs抗心律失常的效果取决于干预对象种属、发育阶段、用药时间长短及浓度，更重要的是与心律失常发生的机制密切相关[52]。n-3PUFAs发挥抗/致心律失常作用是其各种机制综合作用的结果，而心律失常的发生既有折返激动也有触发活动或自律性异常的因素，所以，n-3 PUFAs对心律失常的影响具有多样性也就不足为奇了[53,54]。因此，临床应用n-3PUFAs治疗心律失常还需谨慎，有必要依据心律失常发生机制进一步研究，选择最优的干预方式，发挥最大的抗心律失常作用。

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