

持续性心房颤动患者血清 miR-133a-3p 和 miR-324-3p 表达与射频消融术后房颤复发的关系

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摘要: 目的 探讨血清 miR-133a-3p、miR-324-3p 在持续性心房颤动患者血清中的表达以及与射频消融术后房颤复发的关系。方法 收集 2019 年 7 月~2022 年 7 月于沧州市人民医院住院诊治并接受射频消融术治疗的 180 例持续性心房颤动患者(持续性心房颤动组)作为研究对象,根据房颤是否复发,分为无复发组($n=116$)和复发组($n=64$),另选取同期在该院体检的 180 例健康人作为对照组。比较各组血清 miR-133a-3p, miR-324-3p 表达水平;多因素 Logistic 回归分析持续性心房颤动患者射频消融术后房颤复发的影响因素;ROC 曲线分析血清 miR-133a-3p, miR-324-3p 水平对持续性心房颤动患者射频消融术后房颤复发的预测价值。结果 持续性心房颤动组血清 miR-133a-3p (0.76 ± 0.25), miR-324-3p (0.68 ± 0.21) 水平显著低于对照组 (1.03 ± 0.32 , 1.05 ± 0.30), 差异具有统计学意义 ($t=8.921$, 13.556 , 均 $P<0.05$)。复发组血清 miR-133a-3p (0.58 ± 0.19), miR-324-3p 水平 (0.50 ± 0.16) 均显著低于无复发组 (0.86 ± 0.27 , 0.78 ± 0.25), 差异具有统计学意义 ($t=7.349$, 8.087 , 均 $P<0.055$)。多因素 Logistic 回归分析, 结果显示, 血清 miR-133a-3p [OR (95%CI): $0.673 (0.534-0.848)$], miR-324-3p [OR (95%CI): $0.756 (0.629-0.909)$] 为持续性心房颤动患者射频消融术后房颤复发的保护因素 (均 $P<0.05$), 心率 [OR (95%CI): $2.143 (1.265-3.631)$]、LAD [OR (95%CI): $1.756 (1.159-2.661)$] 为持续性心房颤动患者射频消融术后房颤复发的独立危险因素 (均 $P<0.05$)。miR-133a-3p, miR-324-3p 二者联合预测持续性心房颤动患者射频消融术后房颤复发的 AUC 为 0.901, 敏感度和特异度分别为 82.81%, 86.21%, 优于各自单独预测 ($Z=4.210$, 2.804 , 均 $P<0.05$)。结论 持续性心房颤动患者血清 miR-133a-3p, miR-324-3p 表达显著降低, 二者联合对预测持续性心房颤动患者射频消融术后房颤复发有较好的参考价值。

关键词: 持续性心房颤动; 微小 RNA-133a-3p; 微小 RNA-324-3p; 射频消融术; 房颤复发

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Relationship between the Expressions of Serum miR-133a-3p and miR-324-3p in Patients with Persistent Atrial Fibrillation and the Recurrence of Atrial Fibrillation after Radiofrequency Ablation

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Abstract: Objective To investigate the expression of serum miR-133a-3p and miR-324-3p in patients with persistent atrial fibrillation and their relationship with recurrence of atrial fibrillation after radiofrequency ablation. **Methods** A total of 180 patients with persistent atrial fibrillation (persistent atrial fibrillation group) who were hospitalized in Cangzhou City People's Hospital from July 2019 to July 2022 and received radiofrequency ablation were collected as research objects. According to whether atrial fibrillation recurred, they were assigned into a non recurrence group ($n=116$) and a recurrence group ($n=64$). Meanwhile, another 180 healthy individuals who underwent physical examination at the hospital were regarded as the control group. The expression levels of serum miR-133a-3p and miR-324-3p of each group were compared. Multivariate Logistic regression was applied to analyze the factors influencing the recurrence of persistent atrial fibrillation after radiofrequency ablation, and ROC curve analysis was applied to analyze the predictive value of serum miR-133a-3p and miR-324-3p levels for the recurrence of atrial fibrillation in patients with persistent atrial fibrillation after radiofrequency ablation. **Results** Compared with the control group, the levels of serum miR-133a-3p (0.76 ± 0.25) and miR-324-3p (0.68 ± 0.21) in the persistent atrial fibrillation group were lower than the control group (1.03 ± 0.32 , 1.05 ± 0.30), and the differences were statistically significant ($t=8.921$, 13.556 , all $P<0.05$). The serum levels of miR-133a-3p (0.58 ± 0.19) and miR-324-3p (0.50 ± 0.16) in the recurrent group were obviously lower than those in the non recurrent group (0.86 ± 0.27 , 0.78 ± 0.25), and the differences were statistically significant ($t=7.349$, 8.087 , all $P<0.05$). Multivariate Logistic regression analysis showed that serum miR-133a-3p [OR(95%CI):

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0.673(0.534~0.848)] and miR-324-3p [OR(95%CI): 0.756(0.629~0.909)] were protective factors for atrial fibrillation recurrence after radiofrequency ablation in patients with persistent atrial fibrillation, while heart rate [OR(95%CI): 2.143(1.265~3.631)] and LAD [OR(95%CI): 1.756(1.159~2.661)] were independent risk factors for atrial fibrillation recurrence after radiofrequency ablation in patients with persistent atrial fibrillation (all $P < 0.05$). The AUC of the combination of miR-133a-3p and miR-324-3p in predicting atrial fibrillation recurrence after radiofrequency ablation in patients with persistent atrial fibrillation was 0.901, with the sensitivity and specificity were 82.81% and 86.21%, respectively, which was better than those of their respective prediction alone ($Z=4.210, 2.804$, all $P < 0.05$). **Conclusion** The expressions of serum miR-133a-3p and miR-324-3p in patients with persistent atrial fibrillation are reduced, and the combination of the two has a good reference value in predicting the recurrence of atrial fibrillation in patients with persistent atrial fibrillation after radiofrequency ablation.

Keywords: persistent atrial fibrillation; miRNA-133a-3p; miRNA-324-3p; radiofrequency ablation; recurrence of atrial fibrillation

心房颤动是常见的心律失常,患病率占总人口的1.5%,随着人口老龄化,其发病率呈增加的趋势,目前,该病影响到全球3300多万人,预计在未来40年,这一数字将增加两倍以上^[1]。心房颤动也是一种进行性疾病,每年进展率为7%~15%,有50%以上的阵发性心房颤动将在10年内进展为持续性心房颤动,会导致心肌梗死、血栓栓塞、心力衰竭急性失代偿和中风的风险增加^[2-3]。射频消融术是目前治疗持续性心房颤动的重要有效方法,但术后复发一直是医生面临的难题^[4]。因此,寻找与持续性心房颤动患者射频消融术后房颤复发相关的生物标志物,对持续性心房颤动患者的治愈具有重要意义。微小RNA(microRNA, miRNAs, miR)是一种小的非编码RNA,参与多种生理、病理过程的调节,在心肌细胞凋亡、血管生成和心房纤维化的过程中发挥重要作用^[5]。miR-133a-3p是一种抑癌基因,在肺癌、肝癌、乳腺癌、食管鳞状细胞癌等多种癌症中发挥抑癌作用,可以介导AKT下游信号通路促进血管生成、改善增殖、抑制细胞凋亡、减少纤维化等过程在体外和体内发挥心脏保护作用^[6-7]。miR-324-3p在不同类型的癌症中作用不同,在急性淋巴细胞白血病、肺炎、缺血性中风等非癌疾病中发挥保护作用^[8]。目前miR-133a-3p, miR-324-3p在持续性心房颤动患者血清中的表达以及与射频消融术后房颤复发的关系,尚不明晰。因此本研究通过检测持续性心房颤动患者血清miR-133a-3p和miR-324-3p表达,分析其与射频消融术后房颤复发的关系,为持续性心房颤动患者的预后改善提供一定的参考依据。

1 材料与方法

1.1 研究对象 选取2019年7月~2022年7月于沧州市人民医院住院诊治并接受射频消融术治疗的180例持续性心房颤动患者(持续性心房颤动组)作为研究对象,其中男性100例,女性80例,平均年龄 50.08 ± 7.35 岁。术后服用抗心律失常药3个月,并在术后1, 3, 6个月进行随访,进行常规

心电图及24h动态心电图检查,若患者有心悸等症状及时记录心电图。术后3个月空白期后,24h动态心电图记录到 $\geq 30s$ 的快速房性心律失常则为复发^[9]。根据房颤是否复发,分为无复发组($n=116$)和复发组($n=64$)。纳入标准:①符合人民卫生出版社第九版《内科学》指定的房颤诊断标准^[10];②第一次进行射频消融术;③研究对象本人详知此项研究内容,并自愿签署同意书。排除标准:①瓣膜性房颤患者;②既往接受过心脏外科手术史的患者;③消融失败患者;④自身免疫功能障碍者。本研究遵循《世界医学协会赫尔辛基宣言》。另选取同期在本院体检的与持续性心房颤动患者临床资料相匹配的180例健康人作为对照组,其中男性96例,女性84例,平均年龄 49.63 ± 7.27 岁。两组基本临床资料差异无统计学意义,具有可比性($P > 0.05$)。

1.2 仪器与试剂 逆转录试剂盒、荧光定量试剂盒(货号:R211-01, Q221-01 南京诺唯赞生物科技股份有限公司);酶标仪(型号:ELX-808IU,美国宝特公司);东芝120FR全自动生化分析仪。

1.3 方法

1.3.1 样本收集:持续性心房颤动患者入院次日,对照组体检当日清晨,经肘采集空腹静脉血8~10ml,3000r/min离心10min,分离血清后 -80°C 冰箱保存备用。

1.3.2 血清miR-133a-3p, miR-324-3p水平检测:采用TRIzol法提取持续性心房颤动组和对照组血清总RNA,使用南京诺唯赞生物科技股份有限公司逆转录试剂盒合成cDNA。根据荧光定量试剂盒,在ABI 7500 Fast系统上进行实时荧光定量聚合酶链式反应(Quantitative Real-time PCR, qRT-PCR),扩增条件为 95°C 10 min 1个循环, 95°C 15s, 60°C 60s进行40个循环,检测血清中miR-133a-3p, miR-324-3p的相对表达量。以U6作为内参,根据 $2^{-\Delta\Delta\text{Ct}}$ 计算miR-133a-3p, miR-324-3p基因的相对表达量。基因引物由上海生工生物工程有限公司合成,序列见表1。

表1 qRT-PCR 引物序列

基因	上游引物	下游引物
miR-133a-3p	5'-ACACTCCAGCTGGGTTTGTCCCTTCAAC-3'	5'-TGGTGTCGTGGAGTTCG-3'
miR-324-3p	5'-ACTGCCCCAGGTGCTG-3'	5'-CAGTGGCTGCTCGTGGACT-3'
U6	5'-GACCTCTATGCCAACACAGT-3'	5'-ACTACTTGGCTCAGGAGGA-3'

1.3.3 患者血清指标的检测：采用东芝 120FR 全自动生化分析仪检测血清中三酰甘油（TG）、总胆固醇（TC）、高密度脂蛋白-胆固醇（HDL-C）、低密度脂蛋白-胆固醇（LDL-C）、空腹血糖（FBG）。

1.3.4 采用索诺声（美国）Edge II 床边彩色超声诊断系统，检测患者左心室射血分数（left ventricular ejection fraction, LVEF）、左室舒张末期内径（left ventricular end diastolic diameter, LVESD）、左房内径（left atrial diameter, LAD）。

1.4 统计学分析 数据以 SPSS 25.0 软件进行统计学分析，计量资料 miR-133a-3p, miR-324-3p 等经正态性检验，符合正态分布，以均数 ± 标准差 ($\bar{x} \pm s$) 描述，采用独立样本 *t* 检验进行组间比较；对高血压、糖尿病等计数资料以 *n* (%) 表示，采用 χ^2 检验进行组间比较；多因素 Logistic 回归分析持续性心房颤动患者射频消融术后房颤复发的影响因素；

ROC 曲线分析血清 miR-133a-3p, miR-324-3p 水平对持续性心房颤动患者射频消融术后房颤复发的预测价值，*P*<0.05 为差异有统计学意义。

2 结果

2.1 两组血清 miR-133a-3p, miR-324-3p 水平比较 持续性心房颤动组血清 miR-133a-3p (0.76 ± 0.25), miR-324-3p (0.68 ± 0.21) 水平显著低于对照组 (1.03 ± 0.32 , 1.05 ± 0.30)，差异具有统计学意义 ($t=8.921$, 13.556 , 均 *P*<0.05)。

2.2 无复发组和复发组患者一般资料比较 见表 2。复发组心率、LAD 显著高于无复发组，差异具有统计学意义 (均 *P*<0.05)；两组之间年龄、性别、BMI, 高血压、糖尿病、冠心病、吸烟、FBG, TC, TG, HDL-C, LDL-C, LVEF, LVEDD 差异无统计学意义 (均 *P*>0.05)。

表2 无复发组和复发组患者一般资料比较 [$\bar{x} \pm s$, *n* (%)]

项目	无复发组 (<i>n</i> =116)	复发组 (<i>n</i> =64)	<i>P</i> 值
年龄 (岁)	49.56 ± 5.14	51.02 ± 5.38	0.074
性别			0.205
男	63 (54.31)	37 (57.81)	
女	53 (45.69)	27 (42.19)	
BMI (kg/m ²)	23.28 ± 2.83	24.01 ± 0.105	1.630
高血压			3.202
有	21 (18.10)	19 (29.69)	
无	95 (81.90)	45 (70.31)	
糖尿病			2.421
有	18 (15.52)	16 (25.00)	
无	98 (84.48)	48 (75.00)	
冠心病			1.297
有	16 (13.79)	13 (20.31)	
无	100 (86.21)	51 (79.69)	
吸烟			2.910
有	36 (31.03)	28 (43.75)	
无	80 (68.97)	36 (56.25)	
心率 (次/min)	90.83 ± 9.52	105.54 ± 10.96	<0.001
FBG (mmol/L)	5.24 ± 1.23	5.47 ± 1.31	0.242
TC (mmol/L)	4.98 ± 1.52	5.16 ± 1.63	0.460
TG (mmol/L)	1.16 ± 0.34	1.25 ± 0.36	0.098
HDL-C (mmol/L)	1.49 ± 0.42	1.61 ± 0.49	0.086
LDL-C (mmol/L)	2.42 ± 0.65	2.58 ± 0.78	0.143
LVEF (%)	62.79 ± 6.85	60.84 ± 6.64	0.066
LVEDD (mm)	47.52 ± 5.14	47.96 ± 5.23	0.673
LAD (mm)	34.65 ± 3.82	38.74 ± 4.13	<0.001

2.3 无复发组与复发组血清 miR-133a-3p, miR-324-3p 水平比较 复发组血清 miR-133a-3p (0.58 ± 0.19), miR-324-3p (0.50 ± 0.16) 水平显著低于无复发组 ($0.86 \pm 0.27, 0.78 \pm 0.25$), 差异具有统计学意义 ($t=7.349, 8.087$, 均 $P<0.05$)。

2.4 多因素 Logistic 回归分析持续性心房颤动患者射频消融术后房颤复发的影响因素 见表3。以持续性心房颤动患者射频消融术后房颤是否复发为因变量 (复发=1, 无复发=0),

表3 多因素 Logistic 回归分析持续性心房颤动患者射频消融术后房颤复发的影响因素

因素	β 值	SE 值	Wald 值	P 值	OR 值	95%CI
miR-133a-3p	-0.396	0.118	11.263	0.001	0.673	0.534~0.848
miR-324-3p	-0.279	0.094	8.855	0.003	0.756	0.629~0.909
心率	0.762	0.269	8.029	0.005	2.143	1.265~3.631
LAD	0.563	0.212	7.053	0.008	1.756	1.159~2.661

2.5 血清 miR-133a-3p, miR-324-3p 水平对持续性心房颤动患者射频消融术后房颤复发的预测价值

见表4和图1。以血清 miR-133a-3p 和 miR-324-3p 分别预测持续性心房颤动患者射频消融术后房颤复发的曲线下面积 (area under curve, AUC) 为 0.772

表4 血清 miR-133a-3p, miR-324-3p 水平对持续性心房颤动患者射频消融术后房颤复发的预测价值

项目	AUC	截断值	95%CI	敏感度 (%)	特异度 (%)	Youden 指数
miR-133a-3p	0.772	0.78	0.704~0.831	87.50	56.03	0.435
miR-324-3p	0.866	0.60	0.796~0.904	73.44	83.62	0.571
二者联合	0.901		0.848~0.941	82.81	86.21	0.690

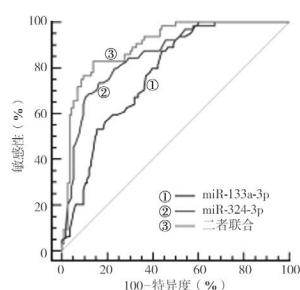


图1 血清 miR-133a-3p, miR-324-3p 水平预测持续性心房颤动患者射频消融术后房颤复发的 ROC 曲线

3 讨论

持续性心房颤动是一种发病机制复杂的疾病, 左心房纤维化被认为是需要房颤治疗的主要因素, 且随着年龄的增长, 发病率上升, 严重威胁人类生存及健康^[11]。尽管目前射频消融术已经成为持续性心房颤动的重要治疗手段, 但仍存在残余纤维化程度高导致患者术后疗效差等问题, 射频消融术后复发率在 33% ~ 60.7%, 是影响其康复的一个重要挑战^[12]。因此, 找到与射频消融术后房颤复发的特异

以血清 miR-133a-3p, miR-324-3p, 心率、LAD (均为连续变量) 为自变量进行多因素 Logistic 回归分析, 结果显示, 血清 miR-133a-3p [OR (95%CI): 0.673 (0.534~0.848)], miR-324-3p [OR (95%CI): 0.756 (0.629~0.909)] 为持续性心房颤动患者射频消融术后房颤复发的保护因素, 心率 [OR (95%CI): 2.143 (1.265~3.631)], LAD [OR (95%CI): 1.756, (1.159~2.661)] 为持续性心房颤动患者射频消融术后房颤复发的独立危险因素 ($P<0.05$)。

和 0.866, 二者联合预测持续性心房颤动患者射频消融术后房颤复发的 AUC 为 0.901。二者联合预测优于血清 miR-133a-3p, miR-324-3p 各自单独预测 ($Z=4.210, 2.804$, 均 $P<0.05$)。

度高的生物标志物, 对改善持续性心房颤动患者的预后具有重要意义。

miRNA 以非常稳定的形式大量存在于体液中, 包括不含细胞的血清、血浆和尿液, 可以通过其在体液中的表达反映机体的病理生理状态^[13]。miR-133a-3p 在各种癌症中起抑制肿瘤的作用, 也可以缓解其他类型细胞的胁迫诱导的凋亡^[14]。GUO 等^[15]发现, miR-133a-3p 通过增加超氧化物歧化酶和谷胱甘肽过氧化物酶的活性, 降低活性氧和丙二醛水平, 保护心肌细胞免受氧化应激和细胞凋亡, 可为子癲前期的治疗提供依据。HIRMAN 等^[16]发现, miR-133a-3p 在烫伤小鼠瘢痕组织中表达水平明显下降, miR-133a-3p 高表达可减轻烫伤小鼠瘢痕组织中胶原蛋白的过度沉积, 有效抑制成纤维细胞的增殖、迁移、活化, 可作为治疗病理性瘢痕的一个靶点。YAO 等^[17]发现, 房颤患者外周血白细胞中 miR-133a-3p 表达水平显著降低, 可以抑制房颤引起的纤维化, 有效地降低了房室纤维化的发生。

ZHU 等^[18]发现, miR-133a-3p 通过靶向下游基因抑制细胞焦亡来减弱血管紧张素 II 诱导的心肌细胞肥大, 可能是心脏肥厚治疗的一种有前途的策略。本研究发现, 持续性心房颤动组血清 miR-133a-3p 水平显著降低, 且在患者复发组表达水平显著低于未复发组, 提示 miR-133a-3p 可能通过增加抗氧化酶的活性, 降低活性氧和丙二醛水平, 抑制成纤维细胞的增殖, 抑制房颤引起的纤维化, 以及心肌细胞肥大, 其在持续性心房颤动患者和复发组中低表达, 可能是患者发生房颤和预后不良的原因。

miR-324-3p 可根据在不同的病理学进程和不同的恶性肿瘤发挥不同的作用, 目前 miR-324-3p 的研究多集中在癌症中, 但有研究表明 miR-324-3p 在心肌细胞的增殖、纤维化、凋亡等过程中发挥着重要的作用^[19]。HOU 等^[20]发现, miR-324-3p 可以通过靶向谷胱甘肽过氧化物酶 4, 抑制乳腺癌细胞的增殖。LIU 等^[21]发现, miR-324-3p 在体外通过降低 TERM27 的表达, 抑制了心血管病的感染, 降低了细胞病理效应和病毒斑块的形成; 在体内 miR-324-3p 降低了 TERM27 下游基因的表达, 减少了心脏病毒的复制和负荷, 从而减弱了病毒性心肌炎相关的心脏损伤和炎症。XU 等^[22]发现, 房颤大鼠模型中发现 miR-324-3p 表达减少, miR-324-3p 通过靶向 TGF-受体 1 抑制成纤维细胞增殖。本研究发现, miR-324-3p 在持续性心房颤动组血清表达水平显著降低, 在复发组的表达水平显著降低, 提示 miR-324-3p 可能通过抑制心肌炎症、心肌纤维化等过程, 抑制持续性心房颤动的病情进展。ROC 曲线显示血清 miR-133a-3p, miR-324-3p 二者联合预测持续性心房颤动患者射频消融术后房颤复发优于各自单独预测, 提示 miR-133a-3p, miR-324-3p 均可能通过抑制心肌细胞凋亡、心肌纤维化等过程抑制射频消融术后房颤复发, 可作为其预后的生物标志物。多因素 Logistic 回归分析, 结果显示, 血清 miR-133a-3p, miR-324-3p, 心率、LAD 为持续性心房颤动患者射频消融术后房颤复发的影响因素, 提示 miR-133a-3p, miR-324-3p 的表达可能影响持续性心房颤动的心率、LAD 等生理表型, 临床上应积极关注这些指标, 及时干预。

综上所述, 持续性心房颤动患者血清 miR-133a-3p, miR-324-3p 表达显著降低, 二者联合对预测持续性心房颤动患者射频消融术后房颤复发有较好的参考价值。然而 miR-133a-3p, miR-324-3p 参与预测持续性心房颤动的具体机制仍需进一步探究。

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