

射血分数保留性心力衰竭患者血清 miR-146a, IRAK-1 表达水平与血管内皮功能、心室重构的相关性分析

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摘要: **目的** 探讨射血分数保留性心力衰竭 (heart failure with preserved ejection fraction, HFpEF) 患者血清微小 RNA (micro RNA, miR) -146a、白介素 1 受体相关激酶 1 (interleukin-1 receptor-associated kinase 1, IRAK-1) 表达水平及其与血管内皮功能、心室重构的相关性。**方法** 选择 2021 年 6 月~2022 年 3 月在内蒙古医科大学附属医院收治的 93 例 HFpEF 患者为观察对象, 选择同期门诊体检健康者 (无心血管病史) 90 例为对照组, 收集患者资料, 采用实时荧光定量 PCR (quantitative real-time PCR, qRT-PCR) 检测血清 miR-146a 和 IRAK-1 mRNA 表达, 采用酶联免疫吸附试验 (enzyme linked immunosorbent assay, ELISA) 法检测血清内皮素-1 (endothelin-1, ET-1) 水平, 化学发光法检测血清一氧化氮 (nitric oxide, NO) 水平, 超声心动图检查左室射血分数 (LVEF)、二尖瓣口舒张早期最大血流速度 E 峰与舒张晚期最大血流速度 A 峰的比值 (E/A)、左心室舒张末期径 (LVEDD)、左心房内径 (LAD) 和左室质量指数 (LVMI)。Pearson 法分析 HFpEF 患者血清 miR-146a 和 IRAK-1 mRNA 表达水平的相关性及 miR-146a, IRAK-1 与血管内皮功能、心室重构相关性指标的相关性, ROC 曲线分析血清 miR-146a 和 IRAK-1 对 HFpEF 的诊断价值。**结果** 与对照组比较, HFpEF 组血清 miR-146a (2.13 ± 0.35 vs 1.05 ± 0.21) 表达水平升高, IRAK-1 mRNA (0.65 ± 0.10 vs 1.03 ± 0.12) 表达水平降低, 差异有统计学意义 ($t=25.209, 23.302$, 均 $P < 0.05$); HFpEF 患者血清 miR-146a 与 IRAK-1 mRNA 水平呈负相关 ($r=-0.473, P < 0.001$), 血清 miR-146a 与 ET-1, LVEDD, LAD, LVMI 呈正相关 ($r=0.501, 0.556, 0.391, 0.601$, 均 $P < 0.001$), 与血清 NO, LVEF, E/A 呈负相关 ($r=-0.453, -0.623, -0.613$, 均 $P < 0.001$); IRAK-1 mRNA 与血清 ET-1, LVEDD, LAD, LVMI 呈负相关 ($r=-0.369, -0.478, -0.551, -0.457$, 均 $P < 0.001$), 与血清 NO, LVEF, E/A 呈正相关 ($r=0.447, 0.605, 0.567$, 均 $P < 0.001$)。血清 miR-146a, IRAK-1 联合诊断 HFpEF 的 AUC 显著高于 miR-146a, IRAK-1 单独诊断 ($Z=2.122, 2.067, P=0.033, 0.038$)。**结论** HFpEF 患者血清 miR-146a 表达水平升高, IRAK-1 表达水平降低, 与血管内皮功能、心室重构相关, 可能成为 HFpEF 诊断与病情评估的指标。

关键词: 射血分数保留性心力衰竭; 微小核糖核酸-146a; 白介素 1 受体相关激酶 1; 血管内皮功能; 心室重构
中图分类号: R541.6; R392.11 **文献标识码:** A **文章编号:** 1671-7414 (2023) 03-109-06

doi:10.3969/j.issn.1671-7414.2023.03.019

Correlation Analysis of Serum miR-146a, IRAK-1 Expression Levels with Vascular Endothelial Function and Ventricular Remodeling in Patients with Ejection Fraction Preserved Heart Failure

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Abstract: Objective To investigate the expression levels of serum microRNA (miR) -146a and interleukin-1 receptor-associated kinase 1 (IRAK-1) in patients with heart failure with preserved ejection fraction (HFpEF) and their correlation with vascular endothelial function and ventricular remodeling. **Methods** 93 HFpEF patients admitted to the Affiliated Hospital of Inner Mongolia Medical University from June 2021 to March 2022 were selected as observation objects. A total of 90 healthy people (with no history of cardiovascular disease) were selected as the control group. The data of patients were collected, Quantitative Real-time PCR (qRT-PCR) was used to detect the expression of serum miR-146a and IRAK-1 mRNA, Enzyme linked immunosorbent assay (ELISA) was used to detect the level of serum endothelin-1 (ET-1), chemiluminescent immunoassay methods were used to detect the level of serum nitric oxide (NO), echocardiography was used to examine left ventricular ejection fraction (LVEF), the ratio of the maximum early diastolic flow velocity of the mitral valve E-peak to the maximum late-diastolic flow velocity of the A-peak (E/A), the left ventricular end-diastolic diameter (LVEDD), left atrial

基金项目: 2022 年度内蒙古自治区卫生健康科技计划项目 (编号: 202201239): 沙库巴曲缬沙坦对射血分数保留性心力衰竭患者心肌纤维化和血管内皮功能的影响。

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diameter (LAD), and left ventricular mass index (LVMI). Pearson was used to analyze the correlation of serum miR-146a and IRAK-1 mRNA expression levels in HFpEF patients and the correlation of miR-146a and IRAK-1 with vascular endothelial function and ventricular remodeling-related indicators, ROC curve was used to analyze the diagnostic value of serum miR-146a and IRAK-1 for HFpEF. **Results** Compared with the control group, the expression level of miR-146a (2.13 ± 0.35 vs 1.05 ± 0.21) in serum of HFpEF group was increased, and the expression level of IRAK-1 mRNA (0.65 ± 0.10 vs 1.03 ± 0.12) was decreased, with statistical significance ($t=25.209, 23.302$, all $P<0.05$). Serum miR-146a and IRAK-1 levels in HFpEF patients were negatively correlated ($r=-0.473$, $P<0.001$). Serum miR-146a was positively correlated with ET-1, LVEDD, LAD and LVMI ($r=0.501, 0.556, 0.391, 0.601$, all $P<0.001$), negatively correlated with serum NO, LVEF and E/A ($r=-0.453, -0.623, -0.613$, all $P<0.001$), IRAK-1 mRNA was negatively correlated with serum ET-1, LVEDD, LAD and LVMI ($r=-0.369, -0.478, -0.551, -0.457$, all $P<0.001$), and positively correlated with serum NO, LVEF and E/A ($r=0.447, 0.605, 0.567$, all $P<0.001$). The AUC of serum miR-146a and IRAK-1 in the diagnosis of HFpEF was significantly higher than that of miR-146a and IRAK-1 alone ($Z=2.122, 2.067$, $P=0.033, 0.038$). **Conclusion** The expression level of serum miR-146a in HFpEF patients was increased, and the expression level of IRAK-1 was decreased, and may become an indicator of diagnosis and disease evaluation of HFpEF.

Keywords: heart failure with preserved ejection fraction; microRNA-146a; interleukin-1 receptor-related kinase 1; vascular endothelial function; ventricular remodeling

射血分数保留性心力衰竭 (heart failure with preserved ejection fraction, HFpEF) 以老年患者为主要人群, 占心力衰竭总发病率的 60% 左右, 多数患者伴发基础疾病, 以高血压居多, 发病率与死亡率居高, 常规治疗效果不理想, 严重影响患者身心健康, HFpEF 病因复杂, 研究认为 HFpEF 发病机制与心肌纤维化和血管内皮功能障碍有关^[1-2]。微小 RNA (micro RNA, miR) -146a 可通过调节免疫炎症反应、血管形成等在冠心病、心肌病、缺血再灌注损伤等心血管疾病中发挥重要作用^[3]。研究显示, miR-146a 在心力衰竭大鼠心肌组织中表达水平升高, 其作用机制可能与其通过抑制磷脂酰肌醇 3-激酶/蛋白激酶 B(phosphatidylinositol 3-kinase/protein kinase B, PI3K/AKT) 信号通路, 促进心肌细胞凋亡有关^[4]。有报道显示, HFpEF 患者血清 miR-146a 表达水平升高^[5]。白细胞介素 1 受体相关激酶 1 (interleukin-1 receptor-related kinase 1, IRAK-1) 是 miR-146a 靶基因, 是炎症调控相关因子, IRAK-1 可激活核因子- κ B (Nuclear Factor-kappaB, NF- κ B) 通路, 诱导炎症因子表达^[6]。本研究探索 HFpEF 患者血清 miR-146a, IRAK-1 表达与血管内皮功能、心室重构的相关性, 为 HFpEF 的临床诊治提供新思路。

1 材料与方法

1.1 研究对象 本研究已获医院医学伦理委员会批准, 选择 2021 年 6 月 ~ 2022 年 3 月内蒙古医科大学附属医院收治的 93 例 HFpEF 患者为观察对象 (HFpEF 组), 其中男性 57 例, 女性 36 例, 年龄 60~78 (69.30 ± 3.70) 岁。选择同期门诊体检健康者 (无心血管病史) 90 例为对照组, 其中男性 50 例, 女性 40 例, 年龄 60~80 (68.90 ± 4.23) 岁。HFpEF 组与对照组年龄、性别、吸烟史、糖

尿病、高血压史等基线资料比较差异无统计学意义 ($t=0.681, \chi^2=0.619, 1.705, 0.520, 0.085$, 均 $P>0.05$)。纳入标准: ①符合《中国心力衰竭诊断和治疗指南 2018》中 HFpEF 诊断标准^[5]; ②年龄 60 岁以上; ③患者基本资料完整。排除标准: ①先天性心脏病、严重瓣膜疾病、缩窄性心包炎、肥厚型心肌病等心包疾病; ②恶性肿瘤、血液系统疾病等非心源性因素引起的心力衰竭; ③严重肝肾功能不全患者; ④感染性疾病; ⑤妊娠期或哺乳期妇女。

1.2 仪器与试剂 人内皮素 1 (ET-1) 酶联免疫吸附测定试剂盒 (E-EL-H0064c) 及一氧化氮 (NO) 测试盒 (化学发光法, A013-1) (内蒙古劲恩生物科技有限公司); 总 RNA 抽提试剂 (R1010) 及 Maxima First Strand cDNA Synthesis Kit for RT-qPCR (K1642) (呼和浩特市双志商贸有限公司); $2 \times$ SYBR Green PCR Mastermix (SR1110) (索莱宝生物科技有限公司); miR-146a, IRAK-1 及 U6, β -actin 引物 (广州锐博生物科技有限公司); 荧光定量 PCR 仪 (Light Cycler 480 II, 瑞士罗氏)。

1.3 研究方法

1.3.1 RT-qPCR 检测血清 miR-146a, IRAK-1 水平: 采集患者入院 48h 内清晨空腹外周静脉血 5 ml, 对照组人员采集体检当日空腹静脉血 5 ml, 离心后收集血清, -80°C 保存, 采用 TRzol 法提取血清总 RNA, 使用 Maxima First Strand cDNA Synthesis Kit 逆转录合成 cDNA, 采用 RT-qPCR 法检测血清 miR-146a, IRAK-1 表达, 按照试剂盒说明书进行操作。miR-146a 上游引物序列: 5'-GAGAACTGAATTCC ATGG-3', 下游引物序列: 5'-GAACATGTCTGCG TATCTC-3'; U6 上游引物序列: 5'-GCTTCGGCAG CACATATACTAAAAT-3', 下游引物序列: 5'-CGCTT CACGAATTTGCGTGTTCAT-3'; IRAK-1 上游引物序

列: 5'-GCACCCACAACCTTCTCGGAG-3', 下游引物序列: 5'-CACCGTGTTCCTCATCACCG-3'; β -actin 上游引物序列: 5'-GCTTCGGCAGCACATATACT-3', 下游引物序列: 5'-GCAGGGTCCGAGGTATTC-3'。分别以 U6, β -actin 为内参, 采用 $2^{-\Delta\Delta Ct}$ 法计算 miR-146a, IRAK-1 水平相对表达量。

1.3.2 其他资料收集: 记录各研究对象一般资料, 包括年龄、性别、吸烟史及病史资料(高血压、糖尿病), 血脂水平(TC, TG, HDL-C, LDL-C)及血清 C 反应蛋白(CRP)、N 端脑钠肽前体(NT-proBNP)水平, 超声心动图检查左室射血分数(LVEF)、二尖瓣口舒张早期最大血流速度 E 峰与舒张晚期最大血流速度 A 峰的比值(E/A)、左心室舒张末期内径(LVEDD)、左心房内径(LAD)和左室质量指数(LVMI)。采用 ELISA 法检测血清 ET-1 水平, 化学发光法检测血清 NO 水平, 具体操作严格按照试剂说明书进行。

1.4 统计学分析 计量资料符合正态分布以均数 \pm 标准差($\bar{x} \pm s$)表示, 采用 SPSS 25.0 统计分析, 两组间比较采用 t 检验, 计数资料采用 $[n(\%)]$ 表示, 采用卡方检验, Pearson 分析 HFpEF 患者血清 miR-146a, IRAK-1 水平的相关性及 miR-146a, IRAK-1 与心室重构、血管内皮功能指标的相关性, ROC 曲线分析血清 miR-146a, IRAK-1 对 HFpEF 的诊断价值, 以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 HFpEF 组与对照组一般资料及血清指标比较 见表 1。与对照组比较, HFpEF 组血清 CRP, NT-proBNP 和 ET-1 水平显著升高, NO 水平显著降低, 差异有统计学意义(均 $P < 0.05$), 血脂水平比较差异无统计学意义(均 $P > 0.05$)。

表 1 HFpEF 组与对照组血清指标比较($\bar{x} \pm s$)

项目	对照组 ($n=90$)	HFpEF 组 ($n=93$)	t 值	P 值
TC (mmol/L)	4.26 \pm 0.53	4.31 \pm 0.62	0.586	0.559
TG (mmol/L)	1.43 \pm 0.35	1.39 \pm 0.41	0.709	0.479
LDL-C (mmol/L)	2.45 \pm 0.64	2.51 \pm 0.52	0.697	0.487
HDL-C (mmol/L)	1.54 \pm 0.39	1.48 \pm 0.37	1.068	0.237
CRP (mg/L)	3.34 \pm 0.85	8.73 \pm 2.51	19.326	< 0.001
NT-proBNP (ng/L)	158.34 \pm 24.37	1 843.73 \pm 252.38	63.064	< 0.001
ET-1 (pg/ml)	34.21 \pm 7.34	75.31 \pm 12.05	27.755	< 0.001
NO (μ mol/L)	47.26 \pm 10.53	23.15 \pm 6.81	18.451	< 0.001

2.2 HFpEF 组与对照组超声心动图指标比较 见表 2。与对照组比较, HFpEF 组患者 LVEDD, LAD, LVMI 显著升高(均 $P < 0.05$), LVEF 及

E/A 显著降低, 差异有统计学意义(均 $P < 0.05$)。

表 2 HFpEF 组与对照组超声心动图指标比较($\bar{x} \pm s$)

项目	对照组 ($n=90$)	HFpEF 组 ($n=93$)	t 值	P 值
LVEDD (mm)	46.79 \pm 6.78	58.30 \pm 8.59	10.040	< 0.001
LAD (mm)	35.59 \pm 7.32	50.36 \pm 6.42	14.525	< 0.001
LVMI (g/m^2)	103.49 \pm 25.42	125.46 \pm 26.51	5.719	< 0.001
LVEF (%)	63.23 \pm 5.61	58.35 \pm 5.14	6.139	< 0.001
E/A	1.13 \pm 0.21	0.82 \pm 0.14	11.785	< 0.001

2.3 HFpEF 组与对照组血清 miR-146a, IRAK-1 水平比较 HFpEF 组患者血清 miR-146a 表达水平高于对照组(2.13 \pm 0.35 vs 1.05 \pm 0.21), 血清 IRAK-1 mRNA 表达水平低于对照组(0.65 \pm 0.10 vs 1.03 \pm 0.12), 差异有统计学意义($t=25.209$, 23.302, 均 $P < 0.001$)。

2.4 HFpEF 患者血清 miR-146a 与 IRAK-1 mRNA 表达水平的相关性 相关性分析显示, HFpEF 患者血清 miR-146a 与 IRAK-1 mRNA 水平呈负相关($r=-0.473$, $P < 0.001$)。

2.5 HFpEF 患者血清 miR-146a, IRAK-1 水平与心室重构指标的相关性 见表 3。相关性分析显示, HFpEF 患者血清 miR-146a 与 LVEDD, LAD, LVMI 呈正相关($P < 0.001$), 与 LVEF, E/A 呈负相关($P < 0.001$), IRAK-1 mRNA 与 LVEDD, LAD, LVMI 呈负相关($P < 0.001$), 与 LVEF, E/A 呈正相关($P < 0.001$)。

表 3 HFpEF 患者血清 miR-146a, IRAK-1 水平与心室重构指标的相关性

项目	miR-146a		IRAK-1	
	r	P	r	P
LVEDD	0.556	< 0.001	-0.478	< 0.001
LAD	0.391	< 0.001	-0.551	< 0.001
LVMI	0.601	< 0.001	-0.457	< 0.001
LVEF	-0.623	< 0.001	0.605	< 0.001
E/A	-0.613	< 0.001	0.567	< 0.001

2.6 HFpEF 患者血清 miR-146a, IRAK-1 水平与血管内皮功能指标的相关性 相关性分析显示, HFpEF 患者血清 miR-146a 表达与血清 ET-1 水平呈正相关($r=0.501$, $P < 0.001$), 与 NO 呈负相关($r=-0.453$, $P < 0.001$), IRAK-1 mRNA 与血清 ET-1 水平呈负相关($r=-0.369$, $P < 0.001$), 与 NO 呈正相关($r=0.447$, $P < 0.001$),

2.7 血清 miR-146a, IRAK-1 对 HFpEF 的诊断价值 见图 1。miR-146a 诊断 HFpEF 的曲线下面积(AUC)为 0.816 (95%CI=0.752 ~ 0.869, $P < 0.001$), 截断

值为1.66,敏感度和特异度分别为74.19%,86.67%;IRAK-1诊断HFpEF的AUC为0.838(95%CI=0.788~0.897, $P < 0.001$),截断值为0.85,敏感度和特异度分别为83.87%,74.44%;血清miR-146a,IRAK-1联合诊断HFpEF的AUC为0.901(95%CI=0.848~0.940, $P < 0.001$),敏感度和特异度分别为82.80%,85.56%,联合诊断AUC显著高于miR-146a,IRAK-1单独诊断($Z=2.122, 2.067$; $P=0.033, 0.038$)。

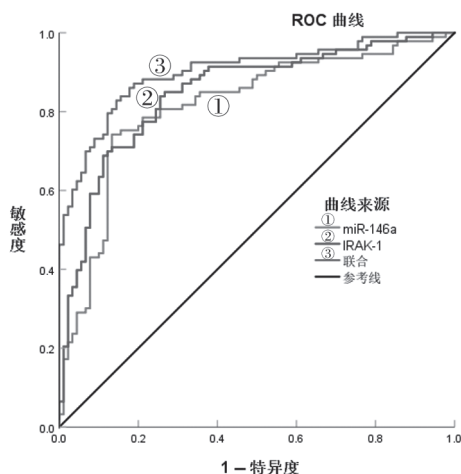


图1 血清miR-146a,IRAK-1诊断HFpEF的ROC曲线分析

3 讨论

HFpEF主要表现为心肌肥厚、心肌纤维化、心脏舒张功能障碍,目前对HFpEF尚缺乏有效的治疗手段,早期诊断显得尤为重要,NT-proBNP是由心室细胞分泌,可用于诊断心力衰竭,但仍有一定局限性,因此需要更加准确的标志物,用于HFpEF的诊断^[8-9]。

miRNAs参与许多疾病的病理生理过程,通过调控细胞增殖、分化、凋亡与自噬等过程,在心力衰竭、冠心病、心律失常等心血管疾病的发生发展中起着重要作用^[10]。据报道显示,多种miRNA的异常表达与心力衰竭的心功能和心室重构有关^[11]。miR-146a属于miRNAs的一种,在冠状动脉内皮细胞、心肌细胞、血管平滑肌细胞等均有表达,可通过Toll样受体4(Toll-like receptor 4,TLR4)/NF- κ B通路靶向多个基因,参与调节炎症反应,还可通过调节转化生长因子 β (transforming growth factor- β 1,TGF- β 1)表达调节血管生成^[12]。研究显示,miR-146a在急性冠状动脉综合征(acute coronary syndrome,ACS)患者血清中表达水平升高,且与冠脉病变程度相关^[13]。研究显示,在心力衰竭模型大鼠中,抑制miR-146a可改善心力衰竭大鼠的心脏功能障碍和心脏重塑^[14]。IRAK-1是促炎因子,是Toll样受体/白介素1受体(Toll-like

receptor/Interleukin 1 receptor,TLR/IL-1R)炎症信号通路的重要介质,与多种炎症疾病有关^[15]。本研究结果显示,HFpEF组患者血清miR-146a表达水平显著升高,IRAK-1表达水平显著降低,提示miR-146a,IRAK-1与HFpEF的发生有关。HFpEF发病机制复杂,涉及系统性炎症、心肌缺血、组织纤维化、肌细胞肥大等多种病理生理机制。有研究显示,miR-146a可通过靶向IRAK-1抑制NF- κ B信号通路和氧化应激,减少炎症因子的表达,保护心脏功能^[16]。本研究经相关性分析显示,miR-146a与IRAK-1表达水平呈负相关,也证实miR-146a与IRAK-1的靶向负调控关系,推测miR-146a通过靶向调控IRAK-1表达,影响心肌细胞功能,进而影响HFpEF发生发展。

HFpEF的病理学过程主要为舒张功能障碍,HFpEF超声心动图表现为左心室肥厚、左心房扩大、舒张功能不全,E/A为左室舒张功能异常的早期指标,HFpEF心功能发生异常,心肌细胞由于炎症浸润、细胞间质胶原沉积等造成心肌重构,LVEDD,LAD,LVMI和LVEF是反映心室重构的指标^[17-18]。本研究显示,HFpEF组患者LVEDD,LAD,LVMI显著升高,LVEF及E/A显著降低,与以往报道一致。HFpEF患者血清miR-146a与LVEDD,LAD,LVMI呈正相关,与LVEF,E/A呈负相关,IRAK-1 mRNA与LVEDD,LAD,LVMI呈负相关,与LVEF,E/A呈正相关,提示miR-146a,IRAK-1可能与HFpEF患者心肌重构有关,检测miR-146a,IRAK-1水平对评估HFpEF患者病情有一定指导意义。

HFPEF患者中存在内皮功能障碍,血管的舒张功能部分依赖内皮的功能完整,血管内皮通过释放ET-1,NO等各种因子调节血管张力,维持血管稳态^[19]。本研究显示,HFpEF组血清ET-1水平升高,NO水平降低,相关性分析显示,miR-146a表达与血清ET-1水平呈正相关,与NO呈负相关,IRAK-1 mRNA与血清ET-1水平呈负相关,与NO呈正相关,提示miR-146a,IRAK-1与HFpEF患者内皮功能损伤有关。ET-1具有收缩血管的作用,是常用的内皮评价指标,NO为内源性血管舒张因子,内皮功能发生障碍时,NO释放减少,收缩因子增加,使血管收缩/舒张功能失调。因此通过检测miR-146a,IRAK-1水平可反映HFpEF患者的内皮功能障碍。ROC曲线分析显示,血清miR-146a,IRAK-1联合诊断HFpEF的AUC为0.901,敏感度和特异度分别为82.80%,85.56%,提示miR-146a,IRAK-1对HFpEF有一定诊断价值,且联合诊断AUC显著高于miR-146a,IRAK-1单独诊断,提示miR-146a,IRAK-1可能成为诊断HFpEF的标

志物,可为HFpEF的诊断提供一定临床参考。

综上所述, HFpEF患者血清miR-146a表达水平升高, IRAK-1表达水平降低,与血管内皮功能、心室重构相关,可能成为HFpEF诊断与病情评估的指标。本研究纳入样本量较少,实验结果可能存在一定偏颇,此为本研究不足之处,miR-146a与IRAK-1的具体作用机制尚不清楚,仍需结合动物模型做更深入的研究。

参考文献:

- [1] CUNNINGHAM J W, CLAGGETT B L, O' MEARA E, et al. Effect of sacubitril/valsartan on biomarkers of extracellular matrix regulation in patients with HFpEF[J]. Journal of the American College of Cardiology, 2020, 76(5): 503-514.
- [2] NAIR N. Epidemiology and pathogenesis of heart failure with preserved ejection fraction[J]. Reviews in Cardiovascular Medicine, 2020, 21(4): 531-540.
- [3] GUO Hui, ZHANG Yongxin, LIAO Zifang, et al. MiR-146a upregulates FOXP3 and suppresses inflammation by targeting HIPK3/STAT3 in allergic conjunctivitis[J]. Annals of Translational Medicine, 2022, 10(6): 344.
- [4] 程璐, 时学昆, 张超, 等. miR-146a调控PI3K/Akt信号通路促进心力衰竭大鼠心肌细胞凋亡[J]. 生物技术通讯, 2020, 31(3): 275-280.
CHENG Lu, SHI Xuekun, ZHANG Chao, et al. MiR-146a regulates PI3K/Akt signaling pathway and promotes cardiomyocyte apoptosis in rats with heart failure[J]. Letters in Biotechnology, 2020, 31(3): 275-280.
- [5] 张文婧, 洪海波, 胡文倩, 等. 静脉血NT-proBNP联合miR-146a对射血分数保留性心力衰竭诊断及预后的影响[J]. 长寿, 2020, 1(12): 82.
ZHANG Wenjing, HONG Haibo, HU Wenqian, et al. Effect of venous blood NT-proBNP combined with miR-146a on diagnosis and prognosis of heart failure with ejection fraction retention[J]. Longevity, 2020, 1(12): 82.
- [6] LI Yatan, ZHAO Jun, SHAO Hua, et al. Preventive effect of total flavonoids of Trollius altaicus on a chronic obstructive pulmonary disease rat model based on the TLR4/NF- κ B pathway[J]. Annals of Translational Medicine, 2022, 10(4): 222.
- [7] 中华医学会心血管病学分会心力衰竭学组, 中国医师协会心力衰竭专业委员会, 中华心血管病杂志编辑委员会. 中国心力衰竭诊断和治疗指南2018[J]. 中华心血管病杂志, 2018, 46(10): 760-789.
Heart Failure Group of Chinese Society of Cardiology of Chinese Medical Association, Chinese Heart Failure Association of Chinese Medical Doctor Association, Editorial Board of Chinese Journal of Cardiology. Chinese guidelines for the diagnosis and treatment of heart failure 2018 [J]. Chinese Journal of Cardiology, 2018, 46(10): 760-789.
- [8] UPADHYA B, KITZMAN D W. Heart failure with preserved ejection fraction: New approaches to diagnosis and management[J]. Clinical Cardiology, 2020, 43(2): 145-155.
- [9] 高婉琴, 李小丹, 杨朋康, 等. 血清Galectin-3和sST2水平检测用于保留射血分数心力衰竭的生物标记物的研究[J]. 现代检验医学杂志, 2019, 34(6): 54-59.
GAO Wanqin, LI Xiaodan, YANG Pengkang, et al. Study on Galectin-2 and sST2 used as biomarker for heart failure patient with preserved ejection fraction[J]. Journal of Modern Laboratory Medicine, 2019, 34(6): 54-59.
- [10] ZHANG Bei, MAO Shanyong, LIU Xingde, et al. MiR-125b inhibits cardiomyocyte apoptosis by targeting BAK1 in heart failure[J]. Molecular Medicine, 2021, 27(1): 72.
- [11] 杨萍, 代天, 张苏川. 慢性收缩性心力衰竭患者血清miR-129表达与心功能的关系[J]. 中国动脉硬化杂志, 2021, 29(4): 312-316.
YANG Ping, DAI Tian, ZHANG Suchuan. The relationship between serum miR-129 expression and cardiac function in patients with chronic systolic heart failure [J]. Chinese Journal of Arteriosclerosis, 2021, 29(4): 312-316.
- [12] LIU Wei, WU Yuanhao, ZHANG Lei, et al. MicroRNA-146a suppresses rheumatoid arthritis fibroblast-like synoviocytes proliferation and inflammatory responses by inhibiting the TLR4/NF- κ B signaling[J]. Oncotarget, 2018, 9(35): 23944-23959.
- [13] 牛君义, 陈凤英, 狄祥龙, 等. 血清miR-146a与miR-34a表达水平对ACS冠脉病变及预后评估价值[J]. 临床心血管病杂志, 2020, 36(9): 815-818.
NIU Junyi, CHEN Fengying, DI Xianglong, et al. Clinical value of serum levels of miR-146a and miR-34a to the severity and prognosis in patients with acute coronary syndrome [J]. Journal of Clinical Cardiology, 2020, 36(9): 815-818.
- [14] HE Junjie, LU Ying, SONG Xiaozheng, et al. Inhibition of microRNA-146a attenuated heart failure in myocardial infarction rats[J]. Bioscience Reports, 2019, 39(12): BSR20191732.
- [15] 杨柳, 党永康, 乌兰, 等. miR-146a-5p靶向IRAK-1调控DVT患者内皮祖细胞的增殖及炎症[J]. 重庆医学, 2021, 50(17): 2906-2911.
YANG Liu, DANG Yongkang, WU Lan, et al. MiR-146a-5p regulating proliferation and inflammation of endothelial progenitor cells of DVT patients by targeting IRAK-1 [J]. Chongqing Medicine, 2021, 50(17): 2906-2911.
- [16] HE Liang, WANG Zhuoran, ZHOU Rui, et al. Dexmedetomidine exerts cardioprotective effect through miR-146a-3p targeting IRAK1 and TRAF6 via inhibition of the NF- κ B pathway[J]. Biomedicine & Pharmacotherapy, 2021, 133: 110993.
- [17] 朱明娜, 张丽华, 蒋友旭, 等. 高血压患者动态动脉硬化指数与射血分数保留性心力衰竭严重程度的相关性研究[J]. 中国全科医学, 2021, 24(20): 2568-2572.
ZHU Mingna, ZHANG Lihua, JIANG Youxu, et al. Correlation between ambulatory arterial stiffness index and severity of heart failure with preserved ejection fraction in patients with hypertension[J]. Chinese General Practice, 2021, 24(20): 2568-2572.

- [4] 中华医学会围产医学分会, 中华医学会妇产科学分会产科学组. 预防围产期B族链球菌病(中国)专家共识[J]. 中华围产医学杂志, 2021, 24(8): 561-566.
Society of Perinatal Medicine, Chinese Medical Association, Obstetrics Subgroup, Society of Obstetrics and Gynecology, Chinese Medical Association. Chinese experts consensus on prevention of perinatal group B *Streptococcal* disease [J]. Chinese Journal of Perinatal Medicine, 2021, 24 (8): 561-566.
- [5] LEE H T, KIM S Y, PARK P W, et al. Detection and genomic analysis of genital group B *Streptococcus* in pregnant Korean women [J]. J Obstet Gynaecol Res, 2019, 45(1): 69-77.
- [6] GUO Huiwu, FU Maozhang, PENG Qing, et al. Antimicrobial resistance and molecular characterization of *Streptococcus agalactiae* from pregnant women in Southern China [J]. J Infect Dev Ctries, 2019, 13(9): 802-809.
- [7] 徐守宁, 王仁存. 胎膜早破孕妇感染常见病原菌类型及耐药性分析[J]. 国际医药卫生导报, 2018, 24 (2): 262-264.
XU Shouning, WANG Rencun. Common pathogenic bacteria types in pregnant women with premature rupture of membranes and the drug resistance [J]. International Medicine and Health Guidance News, 2018, 24 (2): 262-264.
- [8] 马靖杰, 唐丽, 郭瑶珊. 孕妇生殖道B族链球菌感染与胎膜早破的关系及对母婴预后的影响[J]. 国际医药卫生导报, 2021, 27(12): 1845-1847.
MA Jingjie, TANG Li, GUO Yaoshan. The relationship between genital tract group B *Streptococcus* infection and premature rupture of membranes in pregnant women and its effect on maternal and infant prognosis [J]. International Medicine and Health Guidance News, 2021, 27(12): 1845-1847.
- [9] 林雅茵, 林新祝. 围产期B族链球菌感染血清型研究进展[J]. 中华围产医学杂志, 2018, 21(12): 836-839.
LIN Yayin, LIN Xinzhu. Advances in serotypes of perinatal group B *Streptococcus* infection [J]. Chinese Journal of Perinatal Medicine, 2018, 21(12): 836-839.
- [10] PERME T, GOLPARIAN D, IHAN M B, et al. Genomic and phenotypic characterisation of invasive neonatal and colonising group B *Streptococcus* isolates from Slovenia, 2001-2018[J]. BMC Infectious Diseases, 2020, 20(1): 958.
- [11] 林新祝, 吴佳音, 祝珪, 等. 孕晚期阴道定植B族链球菌的血清型特点及其与新生儿早发型感染的相关性[J]. 中华围产医学杂志, 2020, 23(4): 232-238.
LIN Xinzhu, WU Jiayin, ZHU Yao, et al. Serotype features of group B *Streptococcus* vaginal colonization in late pregnant women and their correlation with early-onset neonatal infection [J]. Chinese Journal of Perinatal Medicine, 2020, 23 (4): 232-238.
- [12] SHABAYEK S, SPELLERBERG B. Group B *Streptococcal* colonization, molecular characteristics, and epidemiology[J]. Frontiers in Microbiology, 2018, 9: 437.
- [13] DO NASCIMENTO C S, DOS SANTOS N F B, FERREIRA R C C, et al. *Streptococcus agalactiae* in pregnant women in Brazil: prevalence, serotypes, and antibiotic resistance[J]. Brazilian Journal of Microbiology, 2019, 50(4): 943-952.
- [14] FURFARO L L, CHANG B J, PAYNE M S. Perinatal *Streptococcus agalactiae* epidemiology and surveillance targets[J]. Clinical Microbiology Reviews, 2018, 31(4): e00049-18.
- [15] WANG Jing, ZHANG Yan, LIN Miao, et al. Maternal colonization with group B *Streptococcus* and antibiotic resistance in China: systematic review and meta-analyses [J]. Ann Clin Microbiol Antimicrob, 2023, 22(1): 5.
- [16] HAYES K, O'HALLORAN F, COTTER L. A review of antibiotic resistance in group B *Streptococcus*: the story so far [J]. Crit Rev Microbiol, 2020, 46(3): 253-269.
- [17] MOTALLEBIRAD T, FAZELI H, AZADI D, et al. Determination of capsular serotypes, antibiotic susceptibility pattern, and molecular mechanism of erythromycin resistance among clinical isolates of group B *Streptococcus* in Isfahan, Iran [J]. Adv Biomed Res, 2021, 10: 27.
- [18] ZHU Dekang, ZHENG Mingyu, XU Jing, et al. Prevalence of fluoroquinolone resistance and mutations in the *gyrA*, *parC* and *parE* genes of *Riemerella anatipestifer* isolated from ducks in China [J]. BMC Microbiol, 2019, 19(1): 271.
- 收稿日期: 2022-12-29
修回日期: 2023-02-16

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- [18] 李俐, 肖俊会, 毕健成, 等. 老年慢性心力衰竭患者血浆BNP、TNF- α 和血清cTnI水平与心室重构指标及心功能的相关性[J]. 中国老年学杂志, 2019, 39(5): 1031-1034.
LI Li, XIAO Junhui, BI Jiancheng, et al. Correlation of plasma BNP, TNF- α and serum cTnI levels with ventricular remodeling index and cardiac function in elderly patients with chronic heart failure[J]. Chinese Journal of Gerontology, 2019, 39(5): 1031-1034.
- [19] 王玉华, 佟士骅, 居海宁, 等. 有氧康复运动对慢性心力衰竭患者心室重构及血管内皮功能的影响[J]. 现代生物医学进展, 2018, 18(11): 2118-2121.
WANG Yuhua, TONG Shihua, JU Haining, et al. Influence of aerobic rehabilitation exercise on the ventricular remodeling and endothelial function of patients with chronic cardiac failure[J]. Progress in Modern Biomedicine, 2018, 18(11): 2118-2121.
- 收稿日期: 2022-12-01
修回日期: 2022-12-16