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miR-181b 在冠心病慢性心力衰竭患者血清中的表达及其临床意义*

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摘要 目的:探讨 miR-181b 在冠心病慢性心力衰竭患者血清中的表达及其临床意义。**方法:**选取 2017 年 3 月到 2018 年 10 月期间在我院接受治疗的冠心病慢性心力衰竭患者 103 例作为心衰组,另选取同期在我院收治的单纯冠心病患者 60 例作为冠心病组,另选取同期在我院体检的健康志愿者 60 例作为对照组。比较三组研究对象的血清 miR-181b、炎症因子、心功能指标。另根据美国纽约心脏病协会(NYHA)分级标准将 103 例冠心病慢性心力衰竭患者分为 I-II 级组(38 例)、III 级组(32 例)、IV 级组(33 例)。比较不同心功能分级的冠心病慢性心力衰竭患者的血清 miR-181b、炎症因子、心功能指标。分析冠心病慢性心力衰竭患者的血清 miR-181b 与炎症因子、心功能指标的相关性。**结果:**心衰组的肿瘤坏死因子- α (TNF- α)、白介素-6(IL-6)、超敏 C 反应蛋白(hs-CRP)、左室舒张末期内径(LVEDD)均高于冠心病组和对照组,miR-181b、左室射血分数(LVEF)低于冠心病组和对照组($P<0.05$)。冠心病组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于对照组,miR-181b、LVEF 低于对照组($P<0.05$),IV 级组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于 III 级组和 I-II 级组,miR-181b、LVEF 低于 III 级组和 I-II 级组($P<0.05$),III 级组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于 I-II 级组,miR-181b、LVEF 低于 I-II 级组($P<0.05$),Pearson 分析结果显示,冠心病慢性心力衰竭患者血清 miR-181b 与 TNF- α 、hs-CRP、IL-6 呈负相关,与 LVEF 呈正相关($P<0.05$),与 LVEDD 无明显的相关性($P>0.05$)。**结论:**miR-181b 在冠心病慢性心力衰竭患者血清中呈异常低表达,且表达水平与炎症反应程度和 LVEF 存在一定相关性。

关键词:慢性心力衰竭;冠心病;miR-181b;炎症因子;心功能

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Expression of miR-181b in Serum of Patients with Chronic Heart Failure Due to Coronary Heart Disease and Its Clinical Significance*

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ABSTRACT Objective: To investigate the expression and clinical significance of miR-181b in serum of patients with chronic heart failure due to coronary heart disease. **Methods:** A total of 103 patients with chronic heart failure due to coronary heart disease who were treated in our hospital from March 2017 to October 2018 were enrolled as the heart failure group. 60 patients with coronary heart disease admitted to our hospital in the same period were selected as the coronary heart disease group. Another 60 healthy volunteers who were examined in our hospital during the same period were selected as the control group. Serum miR-181b, inflammatory factors and cardiac function were compared between the three groups. According to the New York Heart Association (NYHA) grading standard, 103 patients with chronic heart failure of coronary heart disease were divided into group I-II (38 cases), group III (32 cases) and group IV (33 cases). Serum miR-181b, inflammatory factors and cardiac function were compared in patients with chronic heart failure due to coronary heart disease with different cardiac function grades. The correlation between serum miR-181b and inflammatory factors and cardiac function in patients with chronic heart failure due to coronary heart disease were analyzed. **Results:** The tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP) and left ventricular end diastolic diameter (LVEDD) in the heart failure group were higher than those in the coronary heart disease group and control group, miR-181b and left ventricular ejection fraction (LVEF) were lower than those in the coronary heart disease group and the control group ($P<0.05$). The levels of serum TNF- α , hs-CRP, IL-6 and LVEDD were higher in the coronary heart disease group were higher than those in the control group, miR-181b and LVEF were lower than those in the control group($P<0.05$). The levels of serum TNF- α , hs-CRP, IL-6 and LVEDD in group IV were higher than those in group III and I-II, miR-181b and LVEF were lower than those in group III and group I-II ($P<0.05$). The levels of serum TNF- α , hs-CRP, IL-6 and LVEDD in group III were higher than those in group I-II, and miR-181b and LVEF were lower than those in group I-II ($P<0.05$). Pearson analysis showed that serum miR-181b was negatively correlated with TNF- α , hs-CRP, IL-6, and positively correlated with LVEF in patients with chronic heart failure due to coronary heart disease ($P<0.05$), and had no significant correlation with LVEDD ($P>0.05$). **Conclusion:** miR-181b is abnormally low expressed in the serum of patients with chronic heart failure due to coronary heart disease, and the expression level is related to the degree of inflammatory reaction and LVEF.

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Key words: Chronic heart failure; Coronary heart disease; miR-181b; Inflammatory factors; Cardiac function**Chinese Library Classification(CLC):** R541.61; R541.4 **Document code:** A**Article ID:** 1673-6273(2020)11-2110-04

前言

慢性心力衰竭是指患者在原有慢性心脏疾病基础上逐渐出现心衰症状、体征,其主要病因有冠心病、高血压、风湿性心脏瓣膜病等,其中冠心病是最常见的病因^[1-3]。慢性心力衰竭的发病机制复杂,至今尚未完全阐明,除了已知的肾素-血管紧张素-醛固酮系统过度激活以外,炎症反应也在慢性心力衰竭的发生、发展中起到重要的作用^[4-6]。微小RNA(miRNAs)是长约22nt的单链非编码RNA,具有广泛的生物学功能,近年来有大量研究发现,多种miRNAs参与了慢性心力衰竭的发生、发展,如miR-132^[7]、miR-423-5p等^[8]。miR-181b是miR-181的一种亚型,含有23个核苷酸,其可抑制核转录因子- κ B(NF- κ B)信号通路介导的炎症反应^[9],且Gao等人的研究显示^[10],miR-181b具有抑制心肌细胞凋亡的作用。目前关于miR-181b与心力衰竭的研究较少,尚不清楚miR-181b是否与心力衰竭的疾病进展有关,值得进行研究探讨。本研究检测了冠心病慢性心力衰竭患者血清中miR-181b的表达,并分析了其与炎症因子和心功能指标的关系,现将研究结果整理如下。

1 资料与方法

1.1 临床资料

选取2017年3月到2018年10月期间在我院接受治疗的冠心病慢性心力衰竭患者103例作为心衰组,诊断标准参考《中国心力衰竭诊断和治疗指南2014》^[11],且经临床诊断病因为冠心病。另选取同期在我院收治的单纯冠心病患者60例作为冠心病组,均通过冠状动脉造影确诊。另选取同期在我院体检的健康志愿者60例作为对照组。病例的纳入标准:(1)所患疾病均经过了临床确诊,且参与了所有研究指标的检测;(2)病历资料完整;(3)近3个月未接受经皮冠状动脉介入治疗或其他外科手术治疗;(4)对本次研究内容知情同意。排除标准:(1)风湿性心脏瓣膜病、心肌病等疾病所致的慢性心力衰竭;(2)合并有恶性肿瘤者;(3)存在肝肾功能不全者;(4)合并严重感染者;(5)合并有甲状腺功能亢进或减退症、哮喘、慢性阻塞性肺疾病者。三组研究对象的一般资料比较无明显差异($P>0.05$),可作组间比较,见表1。本次研究内容通过了我院伦理委员会的批准。

表1 三组研究对象的一般资料比较

Table 1 Comparison of general data of the three groups

Indexes	Control group (n=60)	Coronary heart disease group(n=60)	Heart failure group (n=103)	F/ χ^2	P
Male/n(%)	36(60.00)	33(55.00)	60(58.25)	0.320	0.852
Age(years old)	63.51 $\pm$ 5.26	62.14 $\pm$ 5.94	64.08 $\pm$ 5.45	2.487	0.085
Body mass index(kg/m ²)	21.92 $\pm$ 2.53	21.25 $\pm$ 3.01	20.88 $\pm$ 3.02	2.266	0.106
History of smoking/n(%)	18(30.00)	20(33.33)	36(34.95)	0.420	0.811
Alanine aminotransferase(U/L)	25.62 $\pm$ 9.43	24.76 $\pm$ 12.54	25.15 $\pm$ 11.63	0.075	0.928
Glutamic oxaloacetic transaminase(U/L)	24.87 $\pm$ 10.36	25.95 $\pm$ 11.48	26.48 $\pm$ 10.96	0.403	0.669
Urea(mmol/L)	6.86 $\pm$ 3.68	7.15 $\pm$ 3.97	7.40 $\pm$ 3.69	0.394	0.675

1.2 检测方法

1.2.1 血清miR-181b的检测 抽取所有研究对象的空腹静脉血5mL,以3000r/min的速度离心10min,提取血清,采用实时荧光定量聚合酶链反应检测血清中miR-181b的相对表达情况,采用Trizol提取总RNA(试剂购于Invitrogen公司),测定RNA浓度及纯度(A_{260}/A_{280})后,进行逆转录反应,采用逆转录试剂盒合成cDNA(试剂盒购于大连宝生物工程有限公司),之后进行PCR扩增,miR-181b正向引物为:5'-AA-CATTCATTGCTGTCGGTGGG-3',miR-181b反向引物为:5'-GCGAGCACAGAATTAATACGACTCAC-3',反应条件:95℃,30s;95℃,30s;60℃,34s;74℃,30s,循环38次。以U6为内参,采用 $2^{-\Delta\Delta C_T}$ 计算mRNA的相对表达量。

1.2.2 血清炎症因子及心功能指标检测 采用酶联免疫吸附试验检测血清肿瘤坏死因子- α (Tumor necrosis factor- α ,

TNF- α)、白介素-6(Interleukin-6,IL-6)的水平,采用免疫透射比浊法检测超敏C反应蛋白(High-sensitivity C-reactive protein, hs-CRP)(试剂盒购于武汉博士德生物工程有限公司)。采用飞利浦IE33彩色超声诊断仪测量左室射血分数(Left ventricular ejection fraction,LVEF)、左室舒张末期内径(Left ventricular end diastolic diameter,LVEDD),均取3个心动周期的平均值。

1.3 观察指标

比较三组研究对象的血清miR-181b、炎症因子、心功能指标。另根据美国纽约心脏病协会(New York Heart Association, NYHA)分级标准将113例冠心病慢性心力衰竭患者进行分组,其中NYHA I-II级38例,NYHA III级32例,NYHA IV级33例。比较不同心功能分级的冠心病慢性心力衰竭患者的血清miR-181b、炎症因子、心功能指标。分析冠心病慢性心力衰竭患者的血清miR-181b与炎症因子、心功能指标的相关性。

1.4 统计学方法

采用 SPSS22.0 软件进行统计分析,以率的形式表示计数资料,进行卡方检验,计量资料经检验均符合正态分布,以均值±标准差表示,多组间比较采用单因素方差分析,两两比较采用 LSD-t 检验,采用 Pearson 进行相关性分析,检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 三组研究对象的血清 miR-181b 及相关指标的比较

三组研究对象的血清 miR-181b 及相关指标的整体比较均有统计学差异 ($P<0.05$),心衰组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于冠心病组和对照组,miR-181b、LVEF 低于冠心病组和对照组 ($P<0.05$),冠心病组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于对照组,miR-181b、LVEF 低于对照组 ($P<0.05$),见表 2。

表 2 三组研究对象的血清 miR-181b 及相关指标的比较($\bar{x}\pm s$)

Table 2 Comparison of serum miR-181b and related indicators of the three groups($\bar{x}\pm s$)

Indexes	Control group(n=60)	Coronary heart disease group(n=60)	Heart failure group (n=103)	F	P
miR-181b	2.06± 0.24	1.57± 0.21 [#]	1.21± 0.18 ^{**}	324.976	0.000
TNF- α (pmol/L)	4.83± 1.28	7.56± 3.48 [#]	15.29± 5.12 ^{**}	152.087	0.000
hs-CRP(mg/L)	0.97± 0.52	5.39± 2.47 [#]	18.69± 4.65 ^{**}	331.869	0.000
IL-6(ng/L)	56.87± 18.63	118.53± 29.75 [#]	142.88± 43.46 ^{**}	117.279	0.000
LVEF(%)	61.33± 5.22	49.36± 6.94 [#]	41.85± 5.36 ^{**}	215.010	0.000
LVEDD(mm)	49.42± 1.31	54.87± 1.29 [#]	57.34± 2.62 ^{**}	290.717	0.000

Note: Compared with control group, [#] $P<0.05$; Compared with coronary heart disease group, ^{*} $P<0.05$.

2.2 不同心功能分级的患者血清 miR-181b 及相关指标的比较

各组的血清 miR-181b 及相关指标的整体比较均有统计学差异 ($P<0.05$),IV 级组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于 III 级组和 I-II 级组,miR-181b、LVEF 低于 III 级组和 I-II

级组 ($P<0.05$),III 级组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于 I-II 级组,miR-181b、LVEF 低于 I-II 级组 ($P<0.05$),见表 3。

表 3 不同心功能分级的患者血清 miR-181b 及相关指标的比较($\bar{x}\pm s$)

Table 3 Comparison of serum miR-181b and related indicators in patients with different cardiac function grades($\bar{x}\pm s$)

Indexes	Group I-II(n=38)	Group III(n=32)	Group IV(n=33)	F	P
miR-181b	1.36± 0.18	1.20± 0.16 [#]	1.05± 0.14 ^{**}	75.076	0.000
TNF- α (pmol/L)	9.63± 3.97	14.65± 5.32 [#]	22.43± 6.48 ^{**}	105.546	0.000
hs-CRP(mg/L)	14.18± 4.36	18.09± 6.47 [#]	24.47± 8.26 ^{**}	45.078	0.000
IL-6(ng/L)	129.56± 20.68	143.48± 35.16 [#]	157.64± 45.09 ^{**}	12.732	0.000
LVEF(%)	46.33± 5.22	41.36± 6.94 [#]	37.17± 5.36 ^{**}	47.272	0.000
LVEDD(mm)	55.42± 1.31	57.15± 1.29 [#]	59.74± 2.62 ^{**}	90.231	0.000

Note: Compared with group I-II, [#] $P<0.05$; Compared with group III, ^{*} $P<0.05$.

2.3 冠心病慢性心力衰竭患者血清 miR-181b 与相关指标的相关性

Pearson 分析结果显示,冠心病慢性心力衰竭患者血清

miR-181b 与 TNF- α 、hs-CRP、IL-6 呈负相关,与 LVEF 呈正相关 ($P<0.05$),与 LVEDD 无明显的相关性 ($P>0.05$),见表 4。

表 4 冠心病慢性心力衰竭患者血清 miR-181b 与相关指标的相关性

Table 4 The correlation between serum miR-181b and related indexes in patients with chronic heart failure due to coronary heart disease

Indexes	miR-181b	
	r	P
TNF- α	-0.367	0.008
hs-CRP	-0.452	0.000
IL-6	-0.398	0.001
LVEF	0.326	0.017
LVEDD	0.205	0.104

3 讨论

慢性心力衰竭是多种心血管疾病的终末阶段,患者的预后较差,有较高的病死率^[12,13]。近年来,随着冠心病、高血压等慢性心力衰竭常见原发性疾病的发病率上升,导致慢性心力衰竭的发病率也一直居高不下,据《中国心血管病报告 2017》报道^[14],我国心血管病患者大约有 2.9 亿人,其中高血压有 2.7 亿、冠心病有 1100 万,而心力衰竭也有 450 万,由此可见心血管疾病仍是我国重大的公共卫生问题。随着对慢性心力衰竭研究的不断深入,人们发现炎症反应在慢性心力衰竭的发生、发展中起到重要的作用,动脉粥样硬化是冠心病、慢性心力衰竭等多种心血管疾病的病理基础,而炎症反应引起的内皮功能障碍、斑块稳定性下降等是促进动脉粥样硬化进展的重要原因^[15-17]。此外,有研究显示^[18,19],炎症反应可通过抑制左心室收缩功能、促进心室重塑等多个方面参与慢性心力衰竭的发展。TNF- α 、IL-6 均是常见的炎症因子,其中 TNF- α 可损伤血管内皮细胞,促进 IL-6 等炎症因子的分泌,级联放大炎症反应^[20-22];IL-6 可通过促进基质金属蛋白酶的释放降低斑块的稳定性,并可通过介导 TGF- β 1/Smad3 信号通路参与心室重塑^[23]。hs-CRP 是机体受到炎症性刺激时分泌的急性相蛋白,其表达水平可反映机体的炎症反应程度^[24,25]。

本研究结果显示,心衰组的血清 TNF- α 、hs-CRP、IL-6、LVEDD 均高于冠心病组和对照组,LVEF 低于冠心病组和对照组,这说明冠心病慢性心力衰竭患者心功能和结构均发生了明显的病理改变,且炎症因子在患者血清中呈异常高表达。另一方面,心衰组的血清 miR-181b 低于冠心病组和对照组,说明 miR-181b 在冠心病慢性心力衰竭患者血清中呈异常低表达。李晓丽等人的研究显示^[26],miR-181b 在动脉粥样硬化患者血清中呈低表达,并通过细胞实验证实 miR-181b 可阻断血管内皮细胞中 NF- κ B 信号途径,并能抑制血管平滑肌细胞的增殖和迁移,具有抗动脉粥样硬化的作用。谢岩等人的研究显示^[27],miR-181b 在冠心病患者血浆中呈低表达,且其表达水平与患者病情严重程度有关。进一步分析显示,冠心病慢性心力衰竭患者血清 miR-181b 与 TNF- α 、hs-CRP、IL-6 呈负相关,与 LVEF 呈正相关,提示冠心病慢性心力衰竭患者血清中 miR-181b 的水平与患者的炎症反应和左心肌收缩能力有关。已有大量研究证实 miR-181b 与炎症反应密切相关,Zhang 等人的研究证实脂多糖诱导的 RAW264.7 细胞中 miR-181b 与 IL-6 的表达呈负相关^[28],Huo 等人的研究证实 miR-181b 的表达下调与哮喘患者的气道炎症密切相关^[29]。由此可以推测,miR-181b 可能是通过抑制 NF- κ B 信号通路的激活或其他途径,减少炎症因子的分泌,减轻炎症反应对慢性心力衰竭患者心功能造成的损伤,对患者的心功能可起到一定的保护作用^[30]。本研究初步证实了 miR-181b 可能在慢性心力衰竭的疾病进展中起到一定的作用,然而具体的作用机制及 miR-181b 的作用靶点尚不明确,在后续的研究中将建立动物模型,进行更加深入的研究。

综上所述,miR-181b 在冠心病慢性心力衰竭患者血清中呈异常低表达,且表达水平与炎症反应程度和 LVEF 存在一定相关性,提示 miR-181b 可能参与了疾病的发生、发展,然而其

具体的作用机制还有待进一步的探讨。

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