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急性心力衰竭患者血清 miRNA-21、MYO、CK-MB 与心功能和预后的关系 *

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摘要 目的：探讨急性心力衰竭患者血清 miRNA-21、肌红蛋白（MYO）、心肌肌酸激酶同工酶（CK-MB）与心功能和预后的关系。**方法：**选择 2018 年 2 月至 2019 年 2 月于我院接诊的 95 例急性心力衰竭患者为研究对象（病例组），另选择同期在我院进行检查的 80 例健康人为对照组，分析两组患者血清 miRNA-21、MYO、CK-MB、左心室射血分数（LVEF）、左心房内径（LAD）、左心室舒张末期内径（LVEd）水平变化情况及和预后相关性。**结果：**病例组患者血清 miRNA-21、MYO、CK-MB 水平显著高于对照组，差异显著（$P<0.05$）；病例组患者 LAD、LVEd 水平显著高于对照组，LVEF 水平显著低于对照组，差异显著（$P<0.05$）；II 级患者血清 miRNA-21、MYO、CK-MB 水平显著低于 III 级、IV 级患者，III 级患者血清 miRNA-21、MYO、CK-MB 水平显著低于 IV 级患者，差异显著（$P<0.05$）；预后良好组患者血清 miRNA-21、MYO、CK-MB 水平显著低于预后不良组，差异显著（$P<0.05$）；Spearman 相关分析显示，血清 miRNA-21、MYO 及 CK-MB 和 LVEF 之间均呈负相关，血清 miRNA-21、MYO 及 CK-MB 和 LAD、LVEd 之间均呈正相关，（$P<0.05$）；Logistic 回归分析结果显示，血清 miRNA-21、MYO 及 CK-MB 及 LVEF、LAD、LVEd 为急性心力衰竭患者预后的影响因素（$P<0.05$）。**结论：**急性心力衰竭患者血清 miRNA-21、MYO、CK-MB 的表达升高，其与心功能和预后密切相关。

关键词：急性心力衰竭；miRNA-21；肌红蛋白；心肌肌酸激酶同工酶；心功能；预后

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Analysis of the Relationship between Serum miRNA-21, MYO, CK-MB and Cardiac Function and Prognosis in Patients with Acute Heart Failure*

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ABSTRACT Objective: To study Analysis of the Relationship between serum miRNA-21, Myoglobin (MYO), myocardial creatine kinase isoenzyme (CK-MB) and cardiac function and prognosis in patients with acute heart failure. **Methods:** 95 patients with acute heart failure admitted to our hospital from February 2018 to February 2019 were selected as the research subjects (case group). In addition, 80 healthy patients who underwent examination in our hospital during the same period were selected as the control group, and the changes of serum miRNA-21, MYO, CK-MB, left ventricular ejection fraction (LVEF), left atrial diameter (LAD), and left ventricular end-diastolic diameter (LVED) levels and their correlation with prognosis were analyzed in 2 groups. **Results:** The levels of serum miRNA-21, MYO and CK-MB in case group were significantly higher than those in control group, and the differences were significant ($P<0.05$). LAD and LVED levels in case group were significantly higher than those in control group, and LVEF levels were significantly lower than those in control group ($P<0.05$). The serum miRNA-21, MYO, CK-MB levels in grade II patients were significantly lower than those in grade III and IV patients, and the serum miRNA-21, MYO, CK-MB levels in grade III patients were significantly lower than those in grade IV patients, the difference was significant ($P<0.05$). The levels of serum miRNA-21, MYO and CK-MB in the good prognosis group were significantly lower than those in the poor prognosis group, with significant differences ($P<0.05$). Spearman correlation analysis showed that serum miRNA-21, MYO, CK-MB and LVEF were negatively correlated, while serum miRNA-21, MYO, CK-MB and LAD and LVEF were positively correlated ($P<0.05$). Logistic regression analysis showed that serum miRNA-21, MYO, CK-MB, LVEF, LAD, LVED were the prognostic factors in patients with acute heart failure ($P<0.05$). **Conclusion:** The expression of miRNA-21, MYO and CK-MB in patients with acute heart failure is increased, which is closely related to cardiac function and prognosis.

Key words: Heart failure; Micrornas-21; Myoglobin; Myocardial creatine kinase isoenzyme; Cardiac function; The prognosis

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前言

急性心力衰竭是由于心脏突然发生结构及功能异常，导致心排出量降低，引起组织灌注量不足的一种生理状态，其中急性心力衰竭可在慢性心衰的基础上起病，发病前患者多合并器质性心血管疾病，常危机患者生命，因此早期、准确评估病情，并给予及时治疗是改善患者预后的关键[1-3]。心力衰竭的发病机制较为复杂，有研究发现其发生与一些基因的表达关系密切[4]。miRNA 为非编码单链 RNA，可调节胚胎发育、细胞增殖和凋亡等过程，在心血管疾病的发生、发展中具有重要价值[5]。有研究指出，miRNA-21 参与调控心肌肥厚及心肌纤维化的病理过程，故 miRNA-21 可能是心力衰竭的潜在标记物之一[6]。MYO 是氧结合蛋白，当心肌受损时，其可从心肌细胞中弥散出来进入血液循环，导致其水平升高；CK-MB 是一种与心肌梗死密切相关的酶类，当心肌梗死中表达较高，被广泛用于心肌梗死的早期诊断中[7,8]。本研究通过观察急性心力衰竭患者血清 miRNA-21、MYO、CK-MB 水平变化，并分析其与心功能和预后的关系。

1 资料与方法

1.1 一般资料

选择 2018 年 2 月至 2019 年 2 月于我院接诊的 95 例急性心力衰竭患者，设为病例组，其中男 47 例，女 48 例，年龄 50~72 岁，平均(62.06±3.61)岁，发病时间 1~5d，平均(2.63±0.61)d，心功能分级：II 级 29 例，III 级 38 例，IV 级 28 例，体质量指数 22~28 kg/m^2，平均(25.52±1.41)kg/m^2。另选择在我院进行检查的 80 例健康人为对照组，年龄 48~71 岁，平均(62.07±3.54)岁，体质量指数 21~27 kg/m^2，平均(25.47±1.35)kg/m^2。两组基线资料差异无统计学意义(P>0.05)，具有可比性。

参照《急性心力衰竭基层诊疗指南》[9]，(1)伴有呼吸困难，踹憋等症状；(2)脑钠肽含量大于 400 ng/L；(3)左室舒张不全。

纳入标准：(1)符合相关诊断标准；(2)能配合治疗；(3)未服用过影响检测药物者；(4)知情同意。排除标准：(1)3 月内使用过激素类药物者；(2)其他病因导致神经病变；(3)呼吸系统疾病者；(4)肝肾功能异常者；(5)依从性较差者；(6)对本次药物过敏者；(7)凝血功能障碍及血液系统病变者。

1.2 方法与评价标准

采集清晨空腹静脉血，血清 miRNA-21、MYO、CK-MB 水平采用酶联免疫吸附法测定；采用超声心动图测量进行 LVEF、LAD、LVEd 测定。

1.3 统计学分析

以 spss18.0 软件包处理，计量资料用均数±标准差($\bar{x}\pm s$)表示，t 检验，相关性分析使用 Spearman 相关系数，影响因素的分析用多因素 Logistic 回归模型，P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组血清 miRNA-21、MYO、CK-MB 水平检查结果比较

病例组患者血清 miRNA-21、MYO、CK-MB 水平显著高于对照组，差异显著(P<0.05)见表 1。

表 1 两组血清 miRNA-21、MYO、CK-MB 水平检查结果比较($\bar{x}\pm s$)

Table 1 Comparison of serum miRNA-21, MYO and CK-MB levels between the two groups($\bar{x}\pm s$)

Groups	n	miRNA-21	MYO(μg/L)	CK-MB(μg/L)
Case group	95	0.82±0.09	120.41±32.31	53.41±20.31
Control group	80	0.34±0.01	21.45±6.32	12.14±6.78
t value		47.436	26.952	17.371
P value		0.000	0.000	0.000

2.2 两组心功能指标水平检查结果比较

病例组患者 LAD、LVEd 水平显著高于对照组，LVEF 水平显著低于对照组，差异显著(P<0.05)见表 2。

表 2 两组心功能指标水平检查结果比较($\bar{x}\pm s$)

Table 2 Comparison of cardiac function index levels between the two groups($\bar{x}\pm s$)

Groups	n	LVEF(%)	LAD(mm)	LVEd(mm)
Case group	95	42.16±5.41	47.24±11.41	57.36±5.47
Control group	80	65.89±5.61	31.01±10.23	44.25±5.31
t value		28.421	9.824	16.006
P value		0.000	0.000	0.000

2.3 不同心功能分级血清 miRNA-21、MYO、CK-MB 水平检查结果比较

II 级患者血清 miRNA-21、MYO、CK-MB 水平显著低于 III 级、IV 级患者，III 级患者血清 miRNA-21、MYO、CK-MB 水平显著低于 IV 级患者，差异显著(P<0.05)见表 3。

2.4 不同预后血清 miRNA-21、MYO、CK-MB 水平检查结果比较

预后良好组患者血清 miRNA-21、MYO、CK-MB 水平显著低于预后不良组，差异显著(P<0.05)见表 4。

2.5 血清 miRNA-21、MYO、CK-MB 与急性心力衰竭患者心功

能的相关性分析

经 Spearman 相关分析显示，血清 miRNA-21、MYO 及 CK-MB 和 LVEF 之间均呈负相关，血清 miRNA-21、MYO 及 CK-MB 和 LAD、LVEd 之间均呈正相关，(P<0.05)，见表 5。

表 3 不同心功能分级血清 miRNA-21、MYO、CK-MB 水平检查结果比较($\bar{x}\pm s$)

Table 3 Comparison of serum miRNA-21, MYO and CK-MB levels in different cardiac function grades($\bar{x}\pm s$)

Groups	n	miRNA-21	MYO(μg/L)	CK-MB(μg/L)
II level	29	0.67±0.08	88.56±30.15	37.58±15.26
III level	38	0.83±0.09	118.56±33.21	50.46±16.15
IV level	28	0.96±0.07	155.91±35.68	73.81±17.12
F value		90.696	140.286	36.767
P value		0.000	0.000	0.000

表 4 不同预后血清 miRNA-21、MYO、CK-MB 水平检查结果比较($\bar{x}\pm s$)

Table 4 Comparison of serum miRNA-21, MYO and CK-MB levels with different prognostic results($\bar{x}\pm s$)

Groups	n	miRNA-21	MYO(μg/L)	CK-MB(μg/L)
Good prognosis group	71	0.71±0.08	92.35±30.67	40.15±20.15
Poor prognosis group	24	1.15±0.09	203.42±39.86	92.64±37.46
t value		22.564	14.177	8.702
P value		0.000	0.000	0.000

表 5 血清 miRNA-21、MYO、CK-MB 与急性心力衰竭患者心功能的相关性分析

Table 5 Correlation analysis of serum miRNA-21, MYO, CK-MB and cardiac function in patients with acute heart failure

Project	LVEF		LAD		LVEd	
	r value	*P* value	*r* value	*P* value	*r* value	*P* value
miRNA-21	-0.884	0.000	0.536	0.000	0.714	0.000
MYO	-0.827	0.000	0.544	0.000	0.669	0.000
CK-MB	-0.684	0.000	0.411	0.000	0.580	0.000

2.6 急性心力衰竭患者预后影响因素的 Logistic 回归分析

以预后为因变量，血清 miRNA-21、MYO 及 CK-MB 及 LVEF、LAD、LVEd 为自变量，进行 Logistic 回归分析，结果显示，血清 miRNA-21、MYO 及 CK-MB 及 LVEF、LAD、LVEd 为急性心力衰竭患者预后的影响因素(P<0.05)，见表 6。

表 6 急性心力衰竭患者预后影响因素的 Logistic 回归分析

Table 6 Logistic regression analysis of prognostic factors in patients with acute heart failure

Variable	Regression coefficient	Wald χ^2	*P* value	ORvalue	95%CI
miRNA-21	1.325	7.568	0.001	2.891	2.007~8.596
MYO	0.854	12.586	0.000	3.114	1.147~5.263
CK-MB	0.964	13.478	0.000	3.157	1.635~7.502
LVEF	1.125	9.586	0.000	5.269	3.899~11.256
LAD	1.026	5.684	0.000	7.425	4.569~16.350
LVEd	0.714	7.892	0.006	3.269	1.875~8.639

3 讨论

心力衰竭是多种心脏疾病发展的终末阶段，是由于心脏负荷加重、神经内分泌功能紊乱等因素所致的心室重构，根据心力衰竭发生的缓急可分为急性心力衰竭和慢性心力衰竭，其中急性心力衰竭是由于急性心肌负荷过重，造成排出量骤减，肺循环充血导致肺水肿并伴组织灌注不足所造成的临床综合征[10-13]。患者可出现呼吸困难、肺水肿等，严重威胁患者的生命，因此早期诊断，及时治疗并在治疗期间实施病情监测，对症状缓解及改善预后有重要作用[14]。目前对于急性心力衰竭的诊断较为完善，但对于治疗效果的观察主要采用心脏彩超检查，但检查效果存在一定局限性，因此，寻找其他评估患者病情的手

段方法成为临床研究热点[15]。

有研究显示,miRNA 参与调节细胞代谢、凋亡等病理过程[16]miRNA 是一类内生的、长度约为 20～24 个核苷酸的小 RNA，在靶基因降解和调控转录后基因表达方面发挥重要作用,在细胞增殖、细胞凋亡等过程中发挥重要作用[17,18]。miRNA-21 是 ERK/MAPK 信号通路关键因子，能通过增强 ERK/MAPK 信号通路活性,诱导心肌细胞纤维化,同时还能活化 DRP1,导致线粒体外膜的断裂,参与细胞凋亡的开始[19,20]。有研究显示,miRNA-21 是心肌重构过程中上调最高的基因之一,能介导心肌肥厚,导致心功能恶化,参与心力衰竭的的发生[21]。相关研究发现,当心脏负荷增加时,miRNA-21 水平升高,从而激活纤维化基因程序,促进心肌细胞纤维化[22]。本研究结果显示,急性心力衰竭患者血清 miRNA-21 水平明显高于健康人群,且预后良好的患者血清 miRNA-21 水平低于预后不良患者,Eremenko A A[23]等研究也显示,miRNA-21 在慢性心力衰竭中呈高表达,与本研究结果相似。提示,血清 miRNA-21 在急性心力衰竭中表达较高,可能参与急性心力衰竭的发展过程。分析其原因可能是因为当发生心力衰竭时钙调蛋白表达增强,导致心肌肥大的产生,使心肌组织中 miRNA-21 表达升高,其释放入血的 miRNA-21 水平也升高，导致心力衰竭患者血清 miRNA-21 升高。

MYO 是一种小分子色素蛋白,主要分布于心肌、骨骼肌内,具有较高的诊断敏感性,当人体出现急性心肌损伤时,MYO 优先释放至血液内,心肌损伤发生 1~3 h 后,其水平大幅增高,于 12 h 内达到峰值[24-26]。CK-MB 是心肌来源的同工酶,是胞液酶的一种,主要存在于心肌细胞内,当心肌受损时,心肌细胞膜的通透性随之改变,血浆中心激酶活性增加,其水平升高,被广泛用于急性心肌梗死的早期诊断中[27,28]。有研究显示,CK-MB 在急性心肌梗死患者中表达升高,参与了急性心肌梗死的发生与发展,且与急性心肌梗死患者冠状动脉狭窄程度关系紧密[29,30]。本研究结果显示，急性心力衰竭患者血清 MYO、CK-MB 水平明显高于健康人群，且预后良好的患者血清 MYO、CK-MB 水平低于预后不良患者,提示,血清 MYO、CK-MB 在急性心力衰竭中表达较高,可能参与急性心力衰竭的发展过程,可作为预测疾病的标志物。分析其原因可能是因为当发生急性心力衰竭时患者出现急性心肌损伤，导致 MYO、CK-MB 大量释放入血液中,使其水平明显升高,从而参与可疾病的发生与发展。

心力衰竭常伴随心功能异常,心功能分级按照心功能受损状况进行的分级,其级别越高,心功能受损程度越重[31,32]。LAD、LVEd 是心功能常用指标,LVEd 是左室舒 bai 张末内径，反映出心脏结构及功能的情况，值越高心功能越差;LVEF 指每搏输出量占心室舒张末期容积的百分比,是评价心脏收缩功能的常用指标,可反映心室的射血功能,是判断心脏功能的主要指标之一,其值越低表明心脏功能越差[33-35]。本研究结果显示,急性心力衰竭患者 LAD、LVEd 水平显著高于健康人,LVEF 水平显著低于健康人群,提示,急性心力衰竭患者心功能较差。本研究进一步分析发现,II 级患者血清 miRNA-21、MYO、CK-MB 水平显著低于 III 级、IV 级患者,III 级患者血清 miRNA-21、MYO、CK-MB 水平显著低于 IV 级患者，且血清 miRNA-21、MYO 及 CK-MB 和 LVEF 之间均呈负相关，血清 miRNA-21、MYO 及 CK-MB 和 LAD、LVEd 之间均呈正相关，提示,miRNA-21、MYO、CK-MB 在反映心功能方面具有一定价值，心功能等级越高，患者血清 miRNA-21、MYO、CK-MB 水平越低心功能越差。本研究进一步多因素 Logistic 回归分析发现,血清 miRNA-21、MYO 及 CK-MB 及 LVEF、LAD、LVEd 为急性心力衰竭患者预后的影响因素，提示，血清 miRNA-21、MYO 及 CK-MB 及 LVEF、LAD、LVEd 为急性心力衰竭不良预后的独立影响因素，临床检查时应注意观察以上指标的水平变化,以降低不良预后的发生。

综上所述，急性心力衰竭患者血清 miRNA-21、MYO、CK-MB 的表达升高,其与心功能和预后密切相关。但本研究时间较短,样本量不足,且未观察治疗前后各指标变化,后期应加大样本量深入研究,为后期临床研究提供依据。

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