

[文章编号] 1671-587X(2024)06-1719-09

DOI:10.13481/j.1671-587X.20240626

慢性心力衰竭患者血清脯氨酸脱氢酶水平与左心收缩功能的 关联性分析

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[摘要] **目的:** 探讨不同射血分数型慢性心力衰竭 (CHF) 患者血清脯氨酸脱氢酶 (ProDH) 水平差异, 阐明 ProDH 水平对心功能的影响。**方法:** 回顾性分析 118 例 CHF 患者的临床资料, 将其分为射血分数减低型心力衰竭组 (HF_rEF) 组 ($n=39$)、射血分数中间值型心力衰竭 (HF_{mr}EF) 组 ($n=42$) 和射血分数保留型心力衰竭组 (HF_pEF) 组 ($n=37$)。收集同期住院的非 CHF 患者 45 例, 作为对照组。收集各组研究对象一般资料, 检测各组研究对象血清中生化指标水平和心脏结构指标, 患者血清中 ProDH 水平与各生化指标的相关性采用 Spearman 相关性分析和点二列相关性分析, HF_rEF 和 HF_{mr}EF 的影响因素采用多因素 Logistic 回归分析。**结果:** 与对照组比较, HF_pEF 组患者 β 受体阻滞剂类药物使用率明显升高 ($P<0.05$); HF_{mr}EF 组男性患者百分率、他汀类药物使用率和 β 受体阻滞剂类药物使用率均明显升高 ($P<0.05$); HF_rEF 组患者年龄和收缩压 (SBP) 均明显降低 ($P<0.05$), 他汀类药物使用率和 β 受体阻滞剂类药物使用率均明显升高 ($P<0.05$)。与 HF_pEF 组比较, HF_{mr}EF 组患者年龄明显降低 ($P<0.05$), 男性患者百分率和他汀类药物使用率均明显升高 ($P<0.05$); HF_rEF 组患者年龄明显降低 ($P<0.05$), 他汀类药物使用率明显升高 ($P<0.05$)。与 HF_{mr}EF 组比较, HF_rEF 组患者 SBP 明显降低 ($P<0.05$)。与对照组比较, HF_pEF 组和 HF_{mr}EF 组患者血清中低密度脂蛋白胆固醇 (LDL-c) 水平均明显降低 ($P<0.05$), N 末端脑利钠肽前体 (NT-proBNP) 水平均明显升高 ($P<0.05$); HF_rEF 组患者血清中肾小球滤过率 (GFR) 和 ProDH 水平均明显降低 ($P<0.05$), 空腹血糖 (FBG) 和 NT-proBNP 水平均明显升高 ($P<0.05$)。与 HF_pEF 组比较, HF_{mr}EF 组患者血清中血红蛋白 (Hb) 水平明显升高 ($P<0.05$); HF_rEF 组患者血清中 NT-proBNP 水平明显升高 ($P<0.05$), ProDH 水平明显降低 ($P<0.05$)。与 HF_{mr}EF 组比较, HF_rEF 组患者血清中 NT-proBNP 水平明显升高 ($P<0.05$)。与对照组比较, HF_pEF 组、HF_{mr}EF 组和 HF_rEF 组患者左心房内径 (LAD) 和左心室舒张早期二尖瓣血流速度 (E) / 二尖瓣环舒张早期运动速度 (Em) 比值均明显升高 ($P<0.05$); HF_{mr}EF 组和 HF_rEF 组患者左心室舒张末期内径 (LVEDD) 均明显升高 ($P<0.05$), 左心室射血分数 (LVEF) 均明显降低 ($P<0.05$); 与 HF_pEF 组比较, HF_{mr}EF 组和 HF_rEF 组患者 LVEDD 均明显升高 ($P<0.05$), LVEF 均明显降低 ($P<0.05$), HF_rEF 组患者 LAD 明显升高 ($P<0.05$)。与 HF_{mr}EF 组比较, HF_rEF 组患者 E/Em 比值明显升高 ($P<0.05$), LVEF 明显降低 ($P<0.05$)。患者血清中 ProDH 水平与 LVEDD 呈负相关关系 ($r=-0.210$, $P=0.007$), 与 LVEF 呈正相关关系 ($r=0.220$, $P=0.005$)。男性和 FBG 水平升高为心脏功能的危险因素, 血清中 GFR 和 ProDH 水平升高为心脏功能的保护因素。**结论:** ProDH 在不同射血分数型 CHF 患者间存在差异, 心功能较差的患者血清 ProDH 水平较低, 较高水平的 ProDH 可能有利于 CHF 患者左心收缩功能的提高。

[关键词] 脯氨酸脱氢酶; 慢性心力衰竭; 射血分数减低型心力衰竭; 射血分数中间值型心力衰竭; 射血分数保留型心力衰竭

[中图分类号] R541.6 **[文献标志码]** A

[收稿日期] 2024-07-17

[基金项目] 河北省卫健委 2024 年政府资助临床医学优秀人才培养项目 (ZF2024004)

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Correlation analysis on serum proline dehydrogenase levels and left ventricular systolic function in patients with chronic heart failure

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ABSTRACT Objective: To discuss the differences in serum proline dehydrogenase (ProDH) levels among chronic heart failure (CHF) patients with different ejection fraction types, and to clarify the effect of ProDH levels on cardiac function. **Methods:** A retrospective analysis of clinical data of 118 CHF patients was conducted. These patients were divided into heart failure with reduced ejection fraction (HFrEF) group ($n=39$), heart failure with mid-range ejection fraction group (HFmrEF) ($n=42$), and heart failure with preserved ejection fraction (HFpEF) group ($n=37$). A total of 45 non-CHF patients hospitalized during the same period were collected as control group. The general data of all the subjects in various groups were collected, and the levels of biochemical indicators and cardiac structure indicators in serum of all the subjects were detected. Spearman correlation analysis and point-biserial correlation analysis were used to analyze the correlation between serum ProDH levels and various biochemical indicators; multivariate Logistic regression analysis was used to analyze the factors influencing HFrEF and HFmrEF. **Results:** Compared with control group, the usage rate of beta-blockers of the patients in HFpEF group was significantly increased ($P<0.05$); in HFmrEF group, the percentage of male patients, the usage rate of statins, and the usage rate of beta-blockers were all significantly increased ($P<0.05$); in HFrEF group, the age and systolic blood pressure (SBP) of the patients were significantly decreased ($P<0.05$), while the usage rates of statins and beta-blockers of the patients were significantly increased ($P<0.05$). Compared with HFpEF group, the age of the patients in HFmrEF group was significantly decreased ($P<0.05$), and the percentage of male patients and the usage rate of statins were significantly increased ($P<0.05$); the age of the patients in the HFrEF group was significantly decreased ($P<0.05$), and the usage rate of statins was significantly increased ($P<0.05$). Compared with HFmrEF group, the SBP of the patients in HFrEF group was significantly decreased ($P<0.05$). Compared with control group, the serum levels of low-density lipoprotein cholesterol (LDL-c) of the patients in HFpEF and HFmrEF groups were significantly decreased ($P<0.05$), while the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) were significantly increased ($P<0.05$); the serum levels of glomerular filtration rate (GFR) and ProDH of the patients in HFrEF group were significantly decreased ($P<0.05$), and the levels of fasting blood glucose (FBG) and NT-proBNP were significantly increased ($P<0.05$). Compared with HFpEF group, the serum hemoglobin (Hb) level of the patients in HFmrEF group was significantly increased ($P<0.05$); the serum NT-proBNP level of the patients in HFrEF group was significantly increased ($P<0.05$), while the ProDH level was significantly decreased ($P<0.05$). Compared with HFmrEF group, the serum NT-proBNP level of the patients in HFrEF group was significantly increased ($P<0.05$). Compared with control group, the left atrial diameter (LAD) and the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/Em) of the patients in HFpEF, HFmrEF, and HFrEF groups were significantly increased ($P<0.05$); the left ventricular end-diastolic diameter (LVEDD) of the patients in HFmrEF and HFrEF groups were significantly increased ($P<0.05$), and the left ventricular ejection fraction (LVEF) were significantly decreased ($P<0.05$). Compared with HFpEF group, the LVEDD of the patients in HFmrEF and HFrEF groups were significantly increased ($P<0.05$), and the LVEF were

significantly decreased ($P < 0.05$); the LAD of the patients in HFrEF group was significantly increased ($P < 0.05$). Compared with HFmrEF group, the E/Em ratio of the patients in HFrEF group was significantly increased ($P < 0.05$), and the LVEF was significantly decreased ($P < 0.05$). The serum ProDH levels of the patients were negatively correlated with LVEDD ($r = -0.210$, $P = 0.007$) and positively correlated with LVEF ($r = 0.220$, $P = 0.005$). Male and elevated FBG levels were the risk factors for cardiac function, while the increasing serum GFR and ProDH levels were the protective factors for cardiac function. **Conclusion:** There are differences in ProDH levels among the CHF patients with different ejection fraction types. The patients with poorer cardiac function have lower serum ProDH levels, and higher ProDH levels may be beneficial for improving the left ventricular systolic function in the CHF patients.

KEYWORDS Proline dehydrogenase; Chronic heart failure; Heart failure with reduced ejection fraction; Heart failure with mid-range ejection fraction; Heart failure with preserved ejection fraction

心力衰竭是由于心脏结构和功能异常导致射血和(或)充盈能力受损以致不能满足机体供血的一种临床综合征。随着人口老龄化加快,慢性心力衰竭(chronic heart failure, CHF)的发病率逐年升高。我国CHF患病率为1.3%,患病人数约为890万例,其中射血分数减低型心力衰竭(heart failure with reduced ejection fraction, HFrEF)、射血分数中间值型心力衰竭(heart failure with mid-range ejection fraction, HFmrEF)和射血分数保留型心力衰竭(heart failure with preserved ejection fraction, HFpEF)分别占40.2%、21.8%和38.0%^[1]。脯氨酸脱氢酶(proline dehydrogenase, ProDH)是催化脯氨酸分解代谢第一步的酶,ProDH介导的脯氨酸代谢轴对于调节各种生物功能至关重要。ProDH广泛存在于生物体中,ProDH与真核生物血管生成、基因表达调节、嘌呤生物合成、细胞氧化还原状态和细胞凋亡及增殖等有关^[2-3]。ProDH为催化脯氨酸分解代谢的关键酶,研究^[4]发现:应用乙酰化的脯氨酸治疗急性心肌梗死小鼠,可减少小鼠心室扩张、改善心脏功能、减少心脏纤维化并增加心肌毛细血管密度。研究^[5]显示:急性心肌梗死小鼠应用脯氨酸治疗后心脏射血分数升高,心肌梗死面积和心肌纤维化减少。除此之外,脯氨酸还可缓解心肌梗死诱导的氧化应激。既往关于ProDH的研究^[5]主要集中于其对癌症代谢的影响,而有关ProDH对心脏功能影响的研究较少。本研究探讨不同射血分数型CHF患者ProDH的差异,并阐明ProDH水平对心功能的影响,为CHF的治疗提供潜在新靶点。

1 资料与方法

1.1 研究对象 回顾性分析2023年4月1日—2023年11月30日河北省人民医院老年心血管内科收治的118例CHF患者的临床资料。CHF患者诊断标准参考《中国慢性心力衰竭和治疗指南2018》^[6],其中男性患者75例,女性患者43例,年龄30~92岁。依据《中国慢性心力衰竭和治疗指南2018》^[6]将CHF患者分为HFrEF组($n=39$)、HFmrEF组($n=42$)和HFpEF组($n=37$)。CHF患者纳入标准:①有心力衰竭症状和(或)体征;②HFrEF组患者左心室射血分数(left ventricular ejection fraction, LVEF) $< 40\%$, HFmrEF组患者 $40\% \leq \text{LVEF} < 50\%$, HFpEF组患者 $\text{LVEF} \geq 50\%$;③HFmrEF组和HFpEF组患者N末端脑利钠肽前体(N-terminal brain natriuretic peptide precursor, NT-proBNP) $\geq 125 \text{ ng} \cdot \text{L}^{-1}$ 并存在左心室肥厚和(或)左心房扩大或心脏舒张功能异常。本研究采用二元Logistic回归分析14个影响因素,HFrEF组和对照组研究对象总人数不应 < 70 人,故选择同期于河北省人民医院住院的45例非CHF患者作为对照组,其中男性21例,女性24例,年龄56~84岁。非CHF患者纳入标准:①无心力衰竭症状或体征;②心动超声图未提示心脏结构和(或)功能异常, $\text{LVEF} > 50\%$;③NT-proBNP $< 125 \text{ ng} \cdot \text{L}^{-1}$ 。排除标准:①存在恶性肿瘤性疾病者;②肝肾功能不全者;③患有自身免疫性疾病、感染性疾病和传染性疾病者;④患有先天性心脏病者;⑤存在急性心力衰竭和急性心肌梗死者;⑥临床资料不全者。本研究符合医学伦理学要求,已通过河北省人民医院伦理委员会批准,伦理审

查编号:(2022)科研伦审第(24)号。

1.2 一般资料收集 收集所有入组研究对象的一般资料,包括年龄、性别、基础疾病史(2型糖尿病和高血压)、用药史[他汀类药物、血管紧张素转化酶抑制剂(angiotensin-converting enzyme inhibitor, ACEI)/血管紧张素受体阻滞剂(angiotensin receptor blocker, ARB)类药物和 β 受体阻滞剂类药物]。收集各组研究对象入院当日收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)和体质量指数(body mass index, BMI)。

1.3 生化指标水平检测 所有研究对象空腹8 h后由专业人员采集肘部静脉血,送至检验科,采用AU5800全自动生化分析仪测定各组研究对象血清中白蛋白(albumin, Alb)、丙氨酸氨基转移酶(alanine aminotransferase, ALT)、天门冬氨酸氨基转移酶(aspartate aminotransferase, AST)、肌酸激酶同工酶(creatinine kinase-MB, CK-MB)、钠(natrium, Na)、低密度脂蛋白胆固醇(low density lipoprotein-cholesterol, LDL-c)和空腹血糖(fasting blood glucose, FBG)水平及肾小球滤过率(glomerular filtration rate, GFR)。采用SysmexXN-3000血液分析仪检测各组研究对象血清中血红蛋白(hemoglobin, Hb)和血小板(platelet, PLT)等生化指标水平。采用电化学发光法测定各组研究对象血清中NT-proBNP水平,试剂盒购自罗氏诊断产品(上海)有限公司。采用酶联免疫吸附试验(enzyme linked immunosorbent assay, ELISA)法检测各组研究对象血清中ProDH水平,试剂盒购自北京盒子生工科技有限公司。

1.4 心脏结构指标检测 由超声科专业医师采用彩色多普勒超声诊断仪(型号:PHILIPSQ7)检测各组研究对象心脏结构指标,包括左心房内径(left atrium diameter, LAD)、室间隔厚度(interventricular septal thickness, IVST)、左心室后壁厚度(left ventricle posterior wall thickness, LVPWT)、左心室舒张末期内径(left ventricular end-diastolic diameter, LVEDD)、左心室舒张早期二尖瓣血流速度(early diastolic transmitral flow velocity, E)、二尖瓣环舒张早期运动速度(early diastolic mitral annular velocity, Em)和LVEF。

1.5 统计学分析 采用SPSS 25.0统计软件进行

统计学分析。各组研究对象年龄和血清中Alb水平符合正态分布,以 $\bar{x}\pm s$ 表示,多组间样本均数比较采用单因素方差分析,组间样本均数两两比较采用LSD-*t*检验。各组研究对象血清中ALT、AST、CK-MB、Na、GFR、LDL-c、FBG、Hb、PLT、NT-proBNP和ProDH水平及SBP、DBP、BMI、LAD、IVST、LVPWT、LVEDD、E/Em比值和LVEF等计量资料不符合正态分布,以 $M(P_{25}, P_{75})$ 表示,多组间样本均数比较采用Kruskal-Wallis *H*秩和检验,组间样本均数两两比较采用Bonferroni法。各组研究对象性别、基础疾病史和用药史为计数资料,采用例数(%)表示,多组间比较采用 χ^2 检验,组间两两比较采用Bonferroni调整法。患者血清中ProDH水平与年龄、SBP、GFR、LAD、LVEDD、E/Em比值和LVEF及血清中LDL-c、FBG、Hb和NT-proBNP水平的相关性采用Spearman相关性分析,血清中ProDH水平与性别的相关性采用点二列相关性分析,采用多因素Logistic回归分析HFpEF和HFmrEF的影响因素。以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 各组研究对象一般资料 与对照组比较, HFpEF组患者 β 受体阻滞剂类药物使用率明显升高($P<0.05$); HFmrEF组男性患者百分率、他汀类药物使用率和 β 受体阻滞剂类药物使用率均明显升高($P<0.05$); HFrfEF组患者年龄和SBP均明显降低($P<0.05$),他汀类药物使用率和 β 受体阻滞剂类药物使用率均明显升高($P<0.05$)。与HFpEF组比较, HFmrEF组患者年龄明显降低($P<0.05$),男性患者百分率和他汀类药物使用率均明显升高($P<0.05$); HFrfEF组患者年龄明显降低($P<0.05$),他汀类药物使用率明显升高($P<0.05$)。与HFmrEF组比较, HFrfEF组患者SBP明显降低($P<0.05$)。见表1。

2.2 各组研究对象血清中生化指标水平 与对照组比较, HFpEF组和HFmrEF患者血清中LDL-c水平均明显降低($P<0.05$), NT-proBNP水平均明显升高($P<0.05$); HFrfEF组患者血清中GFR和ProDH水平均明显降低($P<0.05$), FBG和NT-proBNP水平均明显升高($P<0.05$)。与HFpEF组比较, HFmrEF组患者血清中Hb水平明显升高($P<0.05$), HFrfEF组患者血清中

NT-proBNP 水平明显升高 ($P < 0.05$), ProDH 水平明显降低 ($P < 0.05$)。与 HFmrEF 组比较, HFrEF 组患者血清中 NT-proBNP 水平明显升高 ($P < 0.05$)。见表 2。

表 1 各组研究对象一般资料
Tab. 1 General informations of subjects in various groups

Group	<i>n</i>	Age(year)	Male($\eta/\%$)	SBP(P/mmHg)	DBP(P/mmHg)	BMI(kg·m ⁻²)
Control	45	67.6±6.0	21(46.7)	139(122, 156)	79(71, 90)	25.39(23.24, 26.61)
HFpEF	37	68.6±12.2	16(43.2)	138(114, 158)	72(67, 91)	25.39(21.60, 28.19)
HFmrEF	42	63.4±10.7 [△]	32(76.2) ^{*△}	137(124, 154)	79(72, 90)	25.50(22.97, 28.65)
HFrEF	39	62.4±12.4 ^{*△}	27(69.2)	119(109, 141) ^{*#}	80(70, 90)	24.22(22.13, 29.30)
$\chi^2/F/H$		3.421	13.434	10.823	2.193	0.979
<i>P</i>		0.021	0.004	0.013	0.533	0.806

Group	Diabetes ($\eta/\%$)	Hypertension ($\eta/\%$)	Statins ($\eta/\%$)	ACEI/ARB($\eta/\%$)	Beta-blockers ($\eta/\%$)
Control	13(28.9)	30(66.7)	5(11.1)	11(24.4)	7(15.6)
HFpEF	13(35.1)	27(73.0)	12(32.4)	10(27.0)	18(48.6) [*]
HFmrEF	18(42.9)	26(61.9)	23(54.8) ^{*△}	17(40.5)	22(52.4) [*]
HFrEF	18(46.2)	22(56.4)	22(56.4) ^{*△}	15(38.5)	22(56.4) [*]
$\chi^2/F/H$	3.234	2.487	24.906	3.685	18.725
<i>P</i>	0.357	0.478	<0.01	0.298	<0.01

* $P < 0.05$ vs control group; [△] $P < 0.05$ vs HFpEF group; [#] $P < 0.05$ vs HFmrEF group.

表 2 各组研究对象血清中生化指标水平
Tab. 2 Levels of biochemical indicators in serum of subjects in various groups

Group	<i>n</i>	Alb[$\rho_B/(g \cdot L^{-1})$]	ALT[$\lambda_B/(U \cdot L^{-1})$]	AST[$\lambda_B/(U \cdot L^{-1})$]	CK-MB[$\rho_B/(mg \cdot L^{-1})$]
Control	45	40.38±3.50	16.10(11.50, 23.70)	20.10(16.40, 25.20)	13.30(11.90, 15.00)
HFpEF	37	38.62±3.53	17.70(11.40, 29.20)	21.30(18.40, 31.80)	14.40(11.90, 16.60)
HFmrEF	42	39.45±4.23	19.60(12.50, 24.20)	19.10(17.10, 27.40)	13.10(11.10, 15.20)
HFrEF	39	39.07±4.27	20.00(13.80, 32.85)	20.70(17.65, 31.80)	11.40(8.30, 15.15)
<i>H/F</i>		1.537	3.381	2.517	6.870
<i>P</i>		0.207	0.337	0.472	0.076

Group	Na[$c_B/(mmol \cdot L^{-1})$]	GFR(mL·min ⁻¹)	LDL-c[$c_B/(mmol \cdot L^{-1})$]	FBG[$c_B/(mmol \cdot L^{-1})$]
Control	141.00(139.00, 142.00)	90.76(86.29, 96.41)	3.12(2.44, 3.46)	5.17(4.63, 5.46)
HFpEF	140.00(136.00, 141.00)	84.79(71.01, 93.82)	2.38(1.85, 2.84) [*]	5.50(4.85, 6.44)
HFmrEF	141.00(139.00, 142.00)	88.24(67.16, 95.19)	2.10(1.64, 2.88) [*]	5.63(4.77, 7.19)
HFrEF	140.00(138.00, 142.00)	75.27(63.18, 93.29) [*]	2.46(1.87, 3.20)	5.76(5.29, 7.69) [*]
<i>H/F</i>	7.055	8.215	14.785	11.511
<i>P</i>	0.070	0.042	0.002	0.009

Group	Hb[$\rho_B/(g \cdot L^{-1})$]	PLT($\times 10^9 L^{-1}$)	NT-proBNP[$\rho_B/(ng \cdot L^{-1})$]	ProDH[$\rho_B/(ng \cdot L^{-1})$]
Control	135(129, 144)	219(188, 266)	63.58(60.00, 74.62)	3.67(1.33, 9.67)
HFpEF	127(118, 142)	193(164, 251)	980.00(527.50, 1 963.50) [*]	4.00(2.00, 7.00)
HFmrEF	140(130, 148) [△]	202(176, 244)	876.00(366.50, 3 962.50) [*]	2.22(1.22, 5.22)
HFrEF	135(123, 146)	211(168, 233)	4 323.00(1 684.00, 8 357.00) ^{*△#}	1.22(0.56, 2.56) ^{*△}
<i>H/F</i>	9.186	5.414	107.624	13.784
<i>P</i>	0.027	0.144	<0.01	0.003

* $P < 0.05$ vs control group; [△] $P < 0.05$ vs HFpEF group; [#] $P < 0.05$ vs HFmrEF group.

2.3 各组研究对象心脏结构指标 与对照组比较, HFpEF组、HFmrEF组和HFrEF组患者LAD和E/Em比值均明显升高($P<0.05$), HFmrEF组和HFrEF组患者LVEDD均明显升高($P<0.05$), LVEF均明显降低($P<0.05$)。与HFpEF组比较, HFmrEF组和HFrEF组患者LVEDD均明显升高($P<0.05$), LVEF均明显降低($P<0.05$), HFrEF组

患者LAD明显升高($P<0.05$)。与HFmrEF组比较, HFrEF组患者E/Em比值明显升高($P<0.05$), LVEF明显降低($P<0.05$)。见表3。

2.4 患者血清中ProDH水平与各生化指标的相关性 患者血清中ProDH水平与LVEDD呈负相关关系($r=-0.210$, $P=0.007$), 与LVEF呈正相关关系($r=0.220$, $P=0.005$)。见表4。

表3 各组研究对象心脏彩超指标

Tab. 3 Cardiac ultrasound indicators of subjects in various groups

[M(P25, P75)]

Group	n	LAD(l/mm)	IVST(l/mm)	LVPWT(l/mm)	LVEDD(l/mm)	E/Em(m·s ⁻¹)	LVEF(η/%)
Control	45	36(34, 39)	10(9, 10)	9(9, 10)	46(43, 48)	9.75(7.68, 11.75)	64(61, 68)
HFpEF	39	42(38, 45)*	10(9, 11)	10(9, 10)	47(43, 50)	15.19(13.55, 22.35)*	61(56, 65)
HFmrEF	42	43(40, 46)*	10(9, 11)	10(9, 10)	55(52, 59)* [△]	12.74(10.33, 18.33)*	44(43, 47)* [△]
HFrEF	37	47(42, 50)* [△]	9(8, 10)	9(8, 10)	61(55, 68)* [△]	21.11(15.48, 28.75)* [#]	33(30, 36)* ^{△#}
H/F		66.576	5.702	4.765	87.620	65.312	139.556
P		<0.01	0.127	0.190	<0.01	<0.001	<0.01

* $P<0.05$ vs control group; [△] $P<0.05$ vs HFpEF group; [#] $P<0.05$ vs HFmrEF group.

表4 患者血清中ProDH水平与各生化指标的相关性

Tab. 4 Correlations between ProDH levels and various biochemical indicators in serum of patients

Factor	Age	Gender	SBP	GFR	LDL-c	FBG	Hb	NT-proBNP	LAD	LVEDD	E/Em	LVEF
r	-0.089	0.008	0.028	0.015	-0.078	-0.065	-0.018	-0.133	-0.119	-0.210	-0.066	0.220
P	0.261	0.923	0.724	0.852	0.320	0.409	0.819	0.091	0.129	0.007	0.403	0.005

2.5 HFrEF和HFmrEF的影响因素 以是否发生HFrEF和HFmrEF作为因变量, HFrEF组和HFmrEF组赋值为1, HFpEF组和对照组赋值为0, 以年龄、性别(男性为1, 女性为0)、SBP、是否服用他汀类药物(服用为1, 未服用为0)、是否服用β受体阻滞剂类药物(服用为1, 未服用为0)、血清中CK-MB、Na、GFR、LDL-C、FBG、Hb和ProDH水平作为自变量。Logistic回归分析结果显示: 男性和FBG水平升高为心脏功能的危险因素, 血清中GFR和ProDH水平升高为心脏功能的保护因素。见表5。

3 讨论

心脏是人体的高耗能器官, 维持正常心肌收缩的能量主要来源于线粒体氧化磷酸化和糖酵解。心肌细胞可利用多种能量底物, 包括脂肪酸、葡萄糖、酮体和氨基酸等。生理状态下, 心肌细胞线粒体利用脂肪酸为其提供大部分能量, 其次为葡萄糖。当发生心力衰竭时, 心肌细胞利用脂肪酸和葡萄糖的能力降低, 部分酮体和氨基酸可作为心肌能

量代谢的补充底物。脯氨酸为人体的一种非必需氨基酸, 细胞内高浓度的脯氨酸已被证实有益于细胞生存^[7]。

ProDH是催化脯氨酸分解代谢第一步的酶, ProDH与线粒体氧化呼吸链复合体II共同定位于线粒体内膜上, 通过黄素腺嘌呤二核苷酸(flavin adenine dinucleotide, FAD)将电子转移至呼吸链中的细胞色素C^[8]。ProDH催化脯氨酸转化为1-吡咯啉-5-羧酸盐(1-pyrroline-5-carboxylate, PC5), 在此过程中, 伴随着电子转移, 产生腺嘌呤核苷三磷酸(adenosine triphosphate, ATP)及活性氧^[9]。TANNER等^[10]研究发现: 胞质溶胶中的P5C还原酶会刺激磷酸戊糖途径产生还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)。

研究^[11-13]显示: ProDH可促进机体细胞产生能量, 在急性缺氧和能量不足的情况下, 被AMP依赖的蛋白激酶上调ProDH表达, 支持细胞氧化呼吸并诱导ATP产生, 心肌缺血和缺氧后,

表5 多因素 Logistic 回归分析 HFrEF 和 HFmrEF 的影响因素
Tab. 5 Influencing factors of HFrEF and HFmrEF analyzed by multivariate Logistic regression analysis

Influencing factor	B	SE	Wald	P	OR(95%CI)
Age(year)	-0.085	0.027	9.845	0.002	0.919(0.871—0.969)
Gender	1.260	0.496	6.449	0.011	3.526(1.333—9.327)
SBP(mmHg)	-0.006	0.009	0.405	0.525	0.994(0.977—1.012)
Statins	1.347	0.502	7.211	0.007	3.847(1.439—10.285)
Beta-blockers	0.370	0.484	0.585	0.444	1.448(0.560—3.743)
CK-MB($\mu\text{g}\cdot\text{L}^{-1}$)	-0.104	0.046	5.004	0.025	0.901(0.823—0.987)
Na($\text{mmol}\cdot\text{L}^{-1}$)	0.137	0.077	3.145	0.076	1.146(0.986—1.333)
GFR($\text{mL}\cdot\text{min}^{-1}$)	-0.045	0.013	11.512	0.001	0.956(0.931—0.981)
LDL-c($\text{mL}\cdot\text{min}^{-1}$)	0.197	0.267	0.542	0.462	1.217(0.721—2.054)
FBG($\text{mL}\cdot\text{min}^{-1}$)	0.333	0.136	5.999	0.014	1.395(1.069—1.820)
Hb($\text{g}\cdot\text{L}^{-1}$)	0.023	0.016	2.060	0.151	1.024(0.992—1.057)
ProDH($\text{ng}\cdot\text{L}^{-1}$)	-0.186	0.062	9.067	0.003	0.830(0.736—0.937)

ProDH表达下调。研究^[14]显示：与非缺血性心力衰竭组比较，缺血性心力衰竭组大鼠ProDH表达水平降低，并且随着心肌细胞缺血和缺氧时间的延长，ProDH表达水平逐渐降低。本研究结果显示：与对照组和HFpEF组比较，HFrEF组患者血清中ProDH水平明显降低，提示ProDH有利于为心肌细胞提供能量，终末期心力衰竭患者心肌能量相对匮乏。ProDH与病理性心脏重塑存在相关性，本研究结果显示：患者血清中ProDH水平与LVEDD呈负相关关系，与LVEF呈正相关关系，提示ProDH在心脏重塑中可能具有保护作用，ProDH对心功能有益。研究^[15]显示：特异性ProDH基因敲除的小鼠左心室易发生代偿性扩张，且小鼠表现出更高的心脏质量，而心脏特异性过表达ProDH的小鼠LVEF有所改善，与本研究结果一致。

心肌细胞死亡是心力衰竭的主要病理机制，过度的DNA损伤导致心肌细胞死亡，因此DNA修复对保障心肌细胞基因组稳定性和细胞活性至关重要^[16]。ProDH介导的脯氨酸分解代谢与磷酸戊糖途径耦联，支持核苷酸的生物合成，ProDH表达下调可能会影响心肌细胞DNA生物合成和细胞增殖^[17]。研究^[18]发现：与正常细胞比较，ProDH表达下调的细胞DNA生物合成明显降低。当心肌细胞损伤严重时，心肌细胞会启动保护性自噬机制，该机制的保护作用表现为去除受损或错误折叠的蛋白质和细胞器。研究^[19-20]表明：促进心肌细胞自噬是治疗心力衰竭的一种潜在策略，ProDH在催化脯氨酸的过程中会产生活性氧，在肿瘤的生长中

具有一定作用，ProDH通过活性氧依赖的保护性自噬促进细胞存活。因此，ProDH在心脏的保护性自噬中可能也发挥一定作用，但仍有待进一步研究。本研究结果显示：ProDH是心脏功能的保护性因素，随着ProDH水平升高，患者患HFrEF和HFmrEF的风险降低，较高水平的ProDH可能有利于CHF患者左心收缩功能的提高。

本研究结果显示：男性是HFrEF和HFmrEF的危险因素，与对照组和HFpEF组比较，HFmrEF组男性患者百分率明显升高。研究^[21]发现：女性经常患有HFpEF，男性则更有可能患HFrEF，女性患者心脏更有可能出现向心性重塑，而少有出现离心性肥大。原因可能是男性易患冠状动脉疾病和大血管疾病，而女性易患微血管疾病和血管内皮炎症^[22]。当LVEF<40%时，不同性别患者患病差异较小，当LVEF接近正常值时，不同性别患者患病差异增大^[23]，与本研究结果相似。GFR升高是心脏功能的保护因素，FBG水平升高是心脏功能的危险因素。本研究结果显示：与对照组比较，HFrEF组患者GFR明显降低，FBG水平明显升高。研究^[24]显示：肾功能障碍患者血浆儿茶酚胺水平升高，肾素-血管紧张素-醛固酮系统激活，体内水钠潴留增加，导致心脏负荷增加。此外，高水平的血管紧张素促进心脏重塑和纤维化过程^[25]。研究^[26]发现：较高的FBG变异性与较高的心力衰竭发病风险独立相关，这可能是由于高糖环境易引起心血管系统损害，进一步导致心力衰竭的发生。因此，对于CHF患者，维持较高的肾功

能和积极控制血糖可能有利于延缓心力衰竭的进展。

综上所述, ProDH在不同射血分数型CHF患者间存在差异, 心功能较差的患者血清中ProDH水平较低, 较高水平的ProDH可能有利于CHF患者左心收缩功能的提高。

利益冲突声明:

所有作者声明不存在利益冲突。

作者贡献声明:

杨凯同参与数据收集、统计学分析和论文撰写, 和丽丽参与研究设计和论文撰写指导, 左庆娟参与论文撰写指导, 于鑫伟参与数据收集和统计学分析, 郭艺芳参与论文审校。

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