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伊伐布雷定对慢性心力衰竭患者血浆桥接整合因子 1 含量的影响 *

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摘要 目的:探讨伊伐布雷定对慢性心力衰竭(chronic heart failure,CHF)患者血浆中桥接整合因子 1(bridging integrator 1,Bin1)的影响。**方法:**收集左室射血分数(left ventricular ejection fraction,LVEF)小于 40%的 CHF 患者 40 例,分为伊伐布雷定组 20 例,常规治疗组 20 例;选择 23 例同期体检且年龄、性别与实验组无统计学差异者作为对照组。入选对象采集清晨空腹静脉血,CHF 患者于治疗 30 天后再次采集空腹静脉血。测定血浆 Bin1 和 NT-proBNP 浓度,心脏彩超检测 LVEF、左室舒张末期内径(end-diastolic diameter of left ventricle,LVEDd)、E 峰、A 峰及 E/A 比值。**结果:**CHF 患者血浆 Bin1 浓度 (1047.85± 304.82 pg/mL) 较对照组(1248.84± 238.04 pg/mL)显著降低,差异有统计学意义(P<0.05)。CHF 患者血浆 Bin1 浓度与 LVEF 呈正相关(r=0.567,P<0.05),与 LVEDd (r=-0.332,P<0.05)、NT-proBNP 呈负相关 (r=-0.509,P<0.05)。伊伐布雷定组治疗后 Bin1 浓度较治疗前升高 (△ 234.98± 267.18 pg/mL),常规治疗组治疗后 Bin1 浓度较治疗前升高(△ 34.87± 66.89 pg/mL),伊伐布雷定组治疗前后血浆 Bin1 浓度变化常规治疗组更明显,差异具有统计学意义(P<0.05)。**结论:**CHF 患者血中 Bin1 浓度显著降低,与心功不全程度相关;伊伐布雷定可升高 CHF 患者血浆 Bin1 浓度,可能对改善衰竭心肌兴奋收缩耦联、提高心肌收缩力有益。

关键词:伊伐布雷定;桥接整合因子 1;兴奋收缩耦联;心力衰竭

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Effect of Ivabradine on the Plasma Bridging Integrator 1 Level of Patients with Chronic Heart Failure*

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ABSTRACT Objective: To discuss the effect of ivabradine on the plasma level of bridging integrator 1 (Bin1) in patients with chronic heart failure (CHF). **Methods:** 40 cases of CHF patients with left ventricular ejection fraction (LVEF) <40% and 23 healthy people were enrolled in this study. CHF patients were divided into the ivabradine group (n=20) and conventional therapy group (n=20). The concentration of Bin1 and N-terminal pro-brain natriuretic peptide (NT-proBNP), the changes of cardiac function related parameters were measured and compared between different groups. After 30 days of treatment, all the above-mentioned index were measured in the ivabradine group and conventional therapy group again. **Results:** Compared with the healthy control group, the concentration of plasma Bin1 was significantly decreased in the CHF group (1248.84± 238.04 pg/mL vs. 1047.85± 304.82 pg/mL, P<0.05). The concentration of plasma Bin1 in the CHF group was positively correlated with the LVEF (r=0.567, P<0.05), and negatively correlated with the LVEDd (r=-0.332, P<0.05) and NT-proBNP (r=-0.509, P<0.05). After treatment with ivbradine, the concentration of Bin1 was increased by (△ 234.98± 267.18 pg/mL). While after conventional therapy, the concentration of Bin1 was only increased by (△ 34.87± 66.89 pg/mL). There was significant difference in the changes of Bin1 concentrations between the ivbradine and conventional therapy groups (P<0.05). **Conclusions:** The level of Bin1 in CHF patients was significantly decreased and was positively correlated with cardiac function. Ivabradine could increase the plasma level of Bin1 in patients with CHF, it is beneficial to improve the cardiac excitation-contraction coupling and increase the myocardial contraction.

Key words: Ivabradine; Bridging integrator 1; Excitation-contraction coupling; Chronic heart failure

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前言

慢性心力衰竭(chronic heart failure,CHF)是由多种心血管疾病导致的心脏结构和（或）功能异常，进而损害心室充盈和(或)射血功能,以致不能满足机体供血需求的一种综合征[1,2]。随着我国老龄化人口的快速增长,HF 的发病率和死亡率均居高

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不下[3]。目前的治疗方法虽能降低 HF 患者死亡率,但患者 5 年生存率仍维持在较低水平[4-6]。

心脏正常搏动依赖于心肌细胞搏动的协调性。T 管系统是一种高度特异化且广泛分布的亚细胞结构，含有丰富的 L- 钙通道,参与介导心肌兴奋收缩耦联,从而保证心脏收缩的同步性和协调性[7-9]。研究表明桥接整合因子 1(bridging integrator 1,Bin1)是双联蛋白(Bin/Amphiphy/Rvs,BAR)结构域超家族中的一员,参与 T 管系统的形成及稳定,并且对 L 型钙通道 Cav1.2 起到锚定作用[10,11]。CHF 患者 Bin1 表达显著降低,T 管完整性受损,L 型钙通道数量减少,进而影响心肌细胞兴奋收缩耦联,是衰竭心肌收缩力下降的主要原因[12]。

伊伐布雷定是窦房结起搏电流(If 电流)特异性抑制剂,可降低心率,显著改善 CHF 患者预后[13,14]。此外,动物实验表明伊伐布雷定能够逆转心室重构并且改善兴奋收缩耦联[15]。本研究主要探讨了伊伐布雷定对 CHF 患者血浆 Bin1 含量的影响,旨在进一步探析其治疗 CHF 的相关机制。

1 材料与方法

1.1 入选对象

选取 2016 年 8 月 -2017 年 1 月在哈尔滨医科大学附属第一医院内科危重症病房就诊的 CHF 患者 40 例(男性 27 例,女性 13 例)作为 CHF 组,并将 CHF 患者分为常规治疗组(20 例)和伊伐布雷定组(20 例,常规治疗 + 伊伐布雷定)。从同期体检人群中选择 23 例年龄、性别匹配者作为对照组。

纳入标准:(1)NYHA 心功能分级 III-IV 级,确诊为 CHF 的患者;(2)超声心动图提示 LVEF<40 %;(3)患者及其家属签署知情同意书,并经医院伦理委员会通过。

排除标准:(1)对伊伐布雷定活性成份或任何一种辅料过敏;(2)严重低血压(<90/50 mmHg);(3)窦房传导阻滞;(4)治疗前静息心率小于 70 次 / 分;(5)病窦综合征;(6)二度和三度房室传导阻滞;(7)应用细胞色素 P450-3A4 抑制剂;(8)重度肝功能不全。

1.2 实验方法

1.2.1 标本采集 所有入选对象采集清晨空腹静脉血 5mL,于 4℃离心 20 分钟(4000 rpm),取上清液(血浆),移入 2 mL EP 管,置于 -80℃低温冰箱保存待测。所有 CHF 患者治疗 30 天后再次采集空腹静脉血,处理及保存方法同上。

1.2.2 Bin1 及 NT-proBNP 水平的测定 采用酶联免疫吸附法(ELISA)检测,试剂盒购自上海恒远生物科技有限公司,操作严格按照说明书进行。NT-proBNP 采用全自动生化分析仪检测,操作由我院核医学科检验医师完成。

1.2.3 心脏彩超检查 用 PHILIPS CX50 型彩色多普勒超声心动仪和 1-5MHz 探头检测患者左室舒张末期内径 (LVEDD)和左室射血分数(LVEF)。取心尖四腔切面水平测量舒张早期二尖瓣血流峰值(E)、舒张晚期二尖瓣血流速度峰值(A),计算 E/A值。

1.3 统计学处理

应用 SPSS20.0 软件包进行统计学分析计量资料以均数± 标准差表示,两组间比较采用 t 检验,不服从正态分布的应用秩和检验。计数资料用例数(百分比)表示,组间比较采用 x^2 检验。相关性分析采用 Pearson 相关分析。以 P<0.05 为差异有统计学意义。

2 结果

2.1 对照组与 CHF 组相关指标的比较

CHF 患者血清肌酐水平较健康对照组显著升高(P<0.05),但未达到严重肾功能不全,两组其它临床资料比较无显著差异(P>0.05)。CHF 组患者 E 峰、E/A 比值、LVEF 和血浆 Bin1 含量较对照组显著降低(P<0.05),LVEDd 及血浆 NT-proBNP 水平均明显高于对照组(P<0.05),见表 1。

表 1 对照组和心衰组患者相关指标的比较

Table 1 Comparison of the related indicators between control group and heart failure group

	Control group (n=23)	Heart failure group (n=40)
Clinical characteristics		
Male (n)	13	27
Heart rate (bpm)	73.04± 9.99	92.10± 13.49*
Fasting glucose (mmol/L)	6.32± 1.80	6.40± 3.67
Serum creatinine (umol/L)	65.61± 13.24	100.70± 66.00*
ALT (U/L)	27.67± 19.68	20.22± 15.45
AST (U/L)	25.36± 11.59	24.58± 10.91
TG (mmol/L)	1.68± 0.89	1.47± 0.69
CHOL (mmol/L)	5.02± 1.16	4.44± 1.18
Echocardiography parameters		
E peak (m/s)	1.10± 0.42	0.68± 0.18*
A peak (m/s)	0.79± 0.27	0.82± 0.16
E/A	1.56± 1.05	0.84± 0.20*
LVEDd (mm)	46.74± 3.41	68.00± 10.38*
LVEF (%)	65.70± 4.76	24.65± 8.25*

Biomarkers		
NT-proBNP (pg/mL)	64.70± 20.47	6483.84± 7527.77**
Bin1 (pg/mL)	1248.84± 238.04	1047.85± 304.82*

Note: compared with control group, *P<0.05, **P<0.01.

2.2 CHF 患者血浆 Bin1 含量与 NT-proBNP、LVEDd 及 LVEF 的相关性分析

CHF 患者血浆 Bin1 含量与 NT-proBNP 水平、LVEDd 均呈显著负相关(P<0.05),而与 LVEF 呈显著正相关(P<0.05)。见表 2。

表 2 CHF 患者血浆 Bin1 水平与 NT-proBNP、LVEDd、LVEF 的相关性分析

Table 2 Correlative analysis of plasma Bin1 level with the NT-proBNP, LVEDd and LVEF of CHF patients

	r	P
NT-proBNP (pg/mL)	-0.509	<0.05
LVEDd (mm)	-0.332	<0.05
LVEF (%)	0.567	<0.05

2.3 伊伐布雷定组与常规治疗组患者的相关指标比较

治疗前,伊伐布雷定组与常规治疗组基线资料、心脏彩超相关指标、Bin1 含量及 NT-proBNP 水平比较均无显著差异(P>0.05),见表 3。治疗 30 天后,伊伐布雷定组患者心率下降较常规治疗组更为显著,而血浆 Bin1 含量显著升高,差异有统计学意义(P<0.05),见表 4。

表 3 常规治疗组与伊伐布雷定组治疗前相关指标的比较

Table 3 Comparison of the related indicators between the conventional therapy group and ivabradine group before treatment

	Conventional therapy group (n=20)	Ivabradine group (n=20)
Clinical characteristics		
Male (n)	4	14
Heart rate (bpm)	88.25± 12.79	95.95 ± 13.38
Fasting glucose (mmol/L)	6.31± 3.84	6.44± 3. 61
Serum creatinine (umol/L)	94.7± 40.59	106.06± 85.14
ALT (U/L)	17.91± 10.33	23.03± 19.43
AST (U/L)	23.45± 10.00	25.71± 11.91
TG (mmol/L)	1.69± 0.71	1.31± 0.60
CHOL (mmol/L)	4.77± 1.32	4.11± 0.92
Echocardiography parameters		
LVEDd (mm)	70.5± 10.85	65.50± 9.51
LVEF (%)	24.85± 8.63	24.45± 8.06
Biomarkers		
NT-proBNP (pg/ml)	6080.28± 6245.15	6887.41± 8773.39
Bin1 (pg/ml)	1073.37± 301.94	1022.33± 313.34

表 4 常规治疗组及伊伐布雷定组治疗前后指标变化的比较

Table 4 Comparison of thechanges of the related indicators between the conventional therapy group and ivabradine group before and after treatment

	Conventional therapy group (n=20)	Ivabradine group (n=20)
Δ Heart failure (bpm)	-10.95± 10.85	-34.7± 12.02*
Δ LVEDd (mm)	-1.20± 3.36	-2.45± 4.11
Δ LVEF (%)	6.50± 6.62	7.95± 6.93
Δ NT-proBNP (pg/ml)	-3048.03± 3374.46	-4213.07± 4340.77
Δ Bin1 (pg/ml)	34.87± 66.89	234.98± 267.18*

Note: compared with Ivabradine group, *P<0.05.

3 讨论

维持机体正常血运循环需要心脏规律的正常收缩和舒张。T 管是肌膜向心肌细胞中 " 内陷 " 而延续的膜结构。T 管系统是一种特殊的膜管道网络,包裹在肌纤维束表面,在心肌兴奋收缩耦联及兴奋收缩的同步性中发挥重要作用。T 管密集有序的排列是维持心肌纤维同步兴奋的主要因素[16]。T 管膜上含有丰富的 L 型钙通道,心肌细胞兴奋时钙通道开放,钙离子内流并引起 T 管附近肌浆网释放大量钙离子到胞质,与肌钙蛋白结合并引发收缩运动[17]。

Bin1 又被称为 Amphiphysin 2,是 BAR 结构域超家族的一员,是维持 T 管结构的重要蛋白之一[18,19]。同时,Bin1 作为锚定蛋白介导 L 型钙通道定位于 T 管膜上，参与细胞兴奋收缩偶联发生。研究显示 Bin1 基因敲除后细胞 T 管发育受损,同时 T 管膜上 L 型钙通道 Cav1.2 发生定位错误,钙瞬变减少,最终影响细胞兴奋收缩耦联发生,导致心肌收缩力下降[11,12]。CHF 患者常因心肌收缩力下降而出现各种临床症状[20]。本研究结果显示 CHF 患者血浆 Bin1 含量较健康人群显著降低，且与心衰严重程度相关，提示 Bin1 水平降低可能是 CHF 患者发生心肌重构、收缩力下降的原因之一。

正常情况下,窦房结细胞自律性最高,是引导整个心脏兴奋和搏动的 " 司令官 "。窦房结 If 电流是由超极化激活的内向电流,引起细胞产生 4 期自动去极化进而产生起搏作用,因此也被称为起搏电流[21]。伊伐布雷定是窦房结 If 电流特异性抑制剂,能够控制窦房结内的自发舒张去极化和调节心率,因此该药物可以降低静息及运动时的心率,同时无负性肌力和负性传导作用[22,23]。心率是决定心肌耗氧量主要因素之一,HF 时可出现代偿性心率增快。静息心率可作为无心房颤动 CHF 患者的预后独立预测因子，并且与是否接受β 受体阻滞剂治疗及 LVEF 无关[24,25]。降低静息心率可作为射血分数减低 CHF 患者的治疗靶点[14,26]。SHIFT 等研究表明应用伊伐布雷定 CHF 患者心率控制在 70 次 / 分以下能显著降低死亡率和再住院率[14,27]。此外,较低的心率会减少心脏做功,从而降低心肌耗氧量。冠状动脉是在心脏舒张期灌注，心率的减慢能够延长舒张期时限,从而延长了心肌的灌注时间。据此,伊伐布雷定还具有抗心绞痛作用[28,29]。

前期研究证实伊伐布雷定能够逆转心室重构、维持细胞 T 管密度并稳定 L 型钙通道电流[15]。本研究将 CHF 患者分为伊伐布雷定治疗组和常规治疗组,治疗 30 天后,伊伐布雷定组患者静息心率显著下降,血浆 Bin1 含量显著增加。因此,我们推测伊伐布雷定可能通过上调 Bin1 发挥上述作用，进而改善心肌兴奋收缩耦联,提高心肌收缩力。SHIFT 研究中国亚组数据分析显示，应用伊伐布雷定可改善中国 CHF 患者临床预后和心功能[30]。本研究结果显示应用伊伐布雷定治疗 30 天后,患者 LVEF、LVEDd 和 NT-proBNP 也略有改善，但无统计学差异,这可能与本研究观察时间较短有关。长期应用伊伐布雷定是否能有显著改善仍有待进一步研究。

综上所述,CHF 患者血中 Bin1 浓度显著降低,与心功不全程度相关;伊伐布雷定可升高 CHF 患者血浆 Bin1 浓度,对改善衰竭心肌兴奋收缩耦联、提高心肌收缩力有益。

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